

Approach to Cephalosporin Allergy

Immediate Hypersensitivity Reactions

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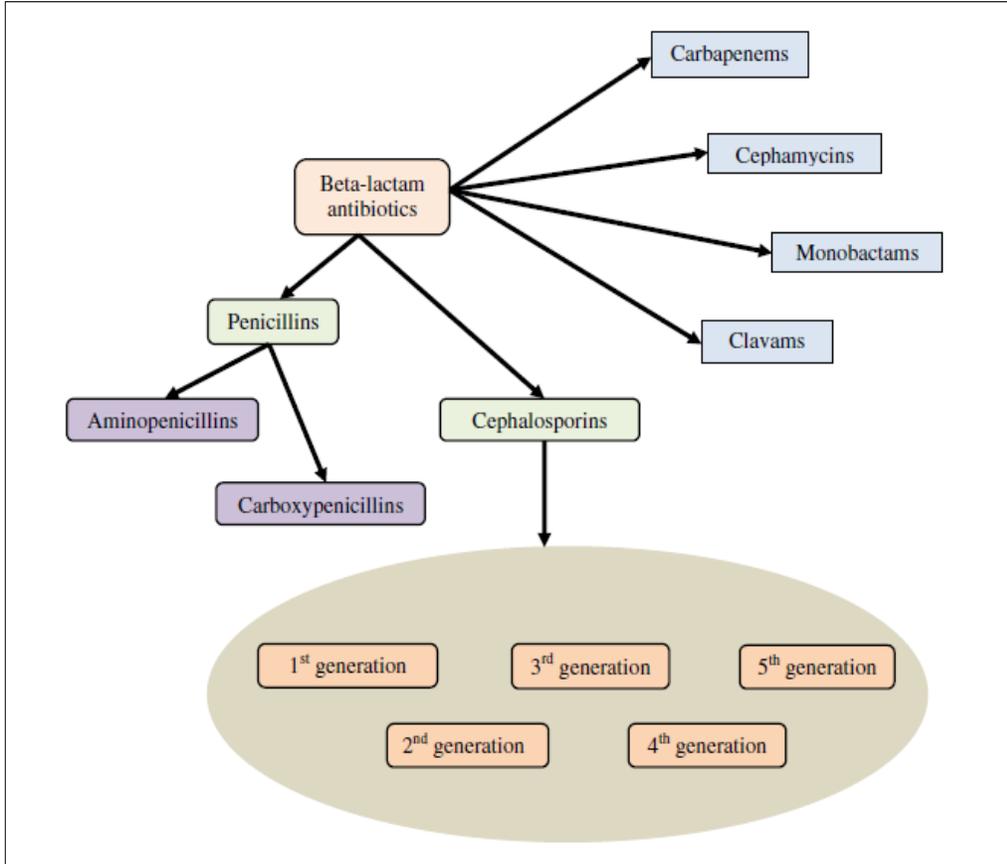
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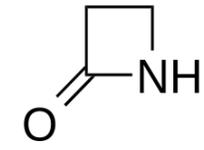
Cephalosporins

- Are β -lactam antibiotics.
- Are commonly prescribed, both in family practice and in hospitals.
- Can cause a range of allergic reactions including IgE-mediated reactions (immediate hypersensitivity reactions) with manifestations that may include urticaria, angioedema, rhinitis, bronchospasm, and hypotension.

Classification of beta-lactam antibiotics

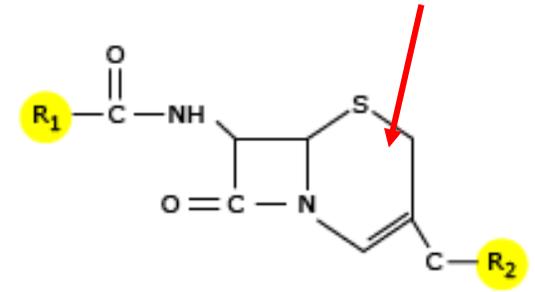


Structure of cephalosporins



Core structure of cephalosporins contains a four-membered beta-lactam ring.

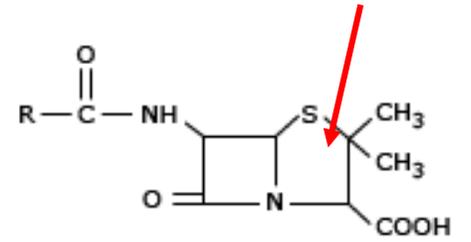
6-membered dihydrothiazine ring



Cephalosporins

Core structure, with R1 and R2 variable groups.

5-membered Thiazolidine ring



Penicillins

Core structure, where "R" is the variable group

Table 1 Classification of Cephalosporins and Spectrum of Activity [2]

<u>First generation</u>	<u>Second generation</u>	<u>Third generation</u>	<u>Fourth generation</u>	<u>Fifth generation</u>
Cefadroxil	Cefaclor	Cefdinir	Cefepime	Ceftaroline
Cefatrizine	Cefamandole	Cefditoren		
Cefazolin	Cefmetazole	Cefetamet		
Cephalexin	Cefminox	Cefixime		
Cephaloglycin	Cefonicid	Cefmenoxime		
Cephaloridine	Cefotetan	Cefodizime		
Cephalothin	Cefotiam	Cefoperazone		
Cephapirin	Cefoxitin	Cefotaxime		
Cephradine	Cefprozil	Cefpiramide		
	Cefuroxime	Cefpodoxime		
	Loracarbef	Cefsulodin		
		Ceftazidime		
		Ceftibuten		
		Ceftizoxime		
		Ceftriaxone		
		Moxolactam		
<u>Spectrum of activity</u>	Gram-positive cocci coverage	Gram-negative cocci coverage		
First generation	Good	Poor		
Second generation	Poor	Good		
Third generation	Poor	Excellent		
Fourth generation	Good	Excellent		
Fifth generation	Good	Excellent		

Generations of cephalosporins

- First-generation produced by chemically or enzymatically modifying R1 site of the basic cephalosporin structure.
- Subsequent generations are synthetically produced.
- Second-generation and subsequent generations have modification at R1 and R2 sites.
- Substitution at R sites provide variation in spectrum of activity against different bacteria species and longer duration of action.

Allergenic determinants of cephalosporins

- Allergenic determinants are not yet completely known.
- A cephalosporin determinant, cephalosporyl, is derived from nucleophilic disruption of the β -lactam ring, is unstable and undergoes multiple fragmentations of the dihydrothiazine ring, breaking into several pieces while preserving the R1 and R2 side chains.
- Mayorga C, Torres MJ, Blanca M. N Engl J Med. 2002;346:380-381

IgE antibodies in subjects with cephalosporin allergy

Can identify a range of antigenic determinants, including

- A portion of a side chain to a full side chain.
- Combination of a side chain with part of the β -lactam ring.
- The whole cephalosporin compound.

- Harle DG, Baldo BA. Drugs as allergens: an immunoassay for detecting IgE antibodies to cephalosporins. *Int Arch Allergy Appl Immunol*. 1990;92.

- Pham NH, Baldo BA. β -Lactam drug allergens: fine structural recognition patterns of cephalosporin-reactive IgE antibodies. *J Mol Recognit*. 1996;9.

- Venemalm L. Pyrazinone conjugates as potential cephalosporin allergens. *Bioorg Med Chem Lett*. 2001;11.

- Zhao Z, Baldo BA, Rimmer J. β -Lactam allergenic determinants: fine structural recognition of a cross-reacting determinant on benzylpenicillin and cephalothin. *Clin Exp Allergy*. 2002;32.

- Sanchez-Sancho F, Perez-Inestrosa E, Suau R, et al. Synthesis, characterization and immunochemical evaluation of cephalosporin antigenic determinants. *J Mol Recognit*. 2003;16.

Cross-reactivity between cephalosporins

- Cephalosporin allergy does not cross all generations of the antibiotic class.
- Cross-reactivity among cephalosporins arises from whether their R1 and/or R2 side chains are structurally similar and not the β -lactam ring.
- Selective reactivity to the culprit cephalosporin can also occur and it may then be a reaction to the whole drug molecule or a unique R2 side chain.

Groups of β -lactam antibiotics with identical or similar side chains

Groups with an identical R1-side chain						
Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7
Amoxicillin	Ampicillin	Ceftriaxone	Cefoxitin	Cefamandole	Ceftazidime	Cefepime
Cefadroxil	Cefaclor	Cefotaxime	Cephaloridine	Cefonicid	Aztreonam	Cefotaxime
Cefprozil	Cephalexin	Cefpodoxime	Cephalothin			Ceftriaxone
Cefatrizine	Cephradine	Cefditoren				
	Cephaloglycin	Ceftizoxime				
	Loracarbef	Cefmenoxime				

Groups with a similar R1-side chain					
Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Penicillin	Cefaclor	Cefuroxime	Ceftazidime	Ceftazidime	Ceftazidime
Cephalothin	Cefadroxil	Cefotaxime	Ceftriaxone	Cefotaxime	Cefepime
Cephalodrine					
Cefoxitin					

Groups with an identical R2-side chain					
Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Cephalexin	Cefotaxime	Cefuroxime	Cefotetan	Cefaclor	Ceftibuten
Cefadroxil	Cephalothin	Cefoxitin	Cefamandole	Loracarbef	Ceftizoxime
Cephradine	Cephaloglycin		Cefmetazole		
	Cephapirin		Cefpiramide		

Groups with a similar R2-side chain	
Group 1	Group 2
Cefdinir	Ceftazidime
Cefixime	Cefsulodin

Can cephalosporin be prescribed to a patient with cephalosporin allergy?

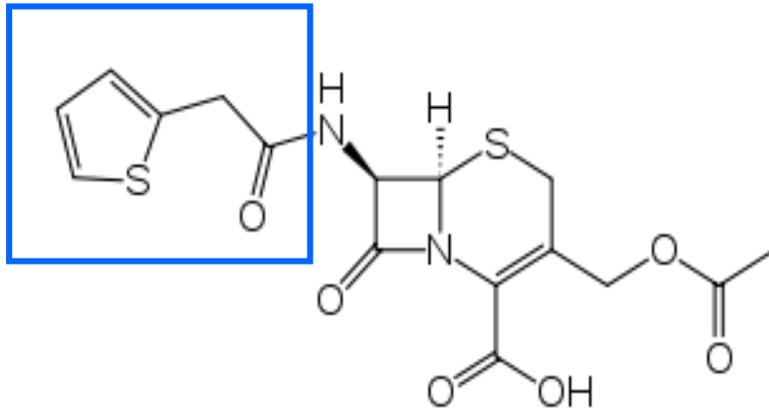
- Yes.
 - Choose cephalosporin belonging to another group with different side chains for skin testing and drug provocation test before administration.
 - As selective cephalosporin hypersensitivity has been reported, when the need arises, treat with a cephalosporin of the same group which is negative on both skin testing and drug provocation test.
-
- Gueant J, Gueant-Rodriguez R, Viola M, Valluzzi R, Romano A. IgE-mediated hypersensitivity to cephalosporins. *Curr Pharm Des* 2006;12.
 - Tuyls S, Breynaert C, Schrijvers R. Subgroups in cephalosporin allergy, making a patient-tailored approach redundant? *J Allergy Clin Immunol* 2016;137.

Penicillin - Cephalosporin cross-reactivity

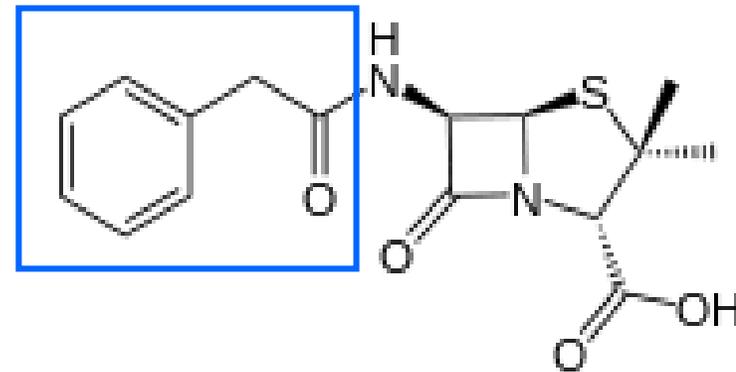
- Late 1960s and early 1970s: reports of cross-reactivity rates of 8-18%.
- Cephalosporins produced between mid-1960s to mid-1980s had minor contamination by penicillin - may explain most reports of cross-allergy.
- Recent studies report risk of cephalosporin allergy of 1-2% in patients with penicillin allergy.
- Cross-reactivity between penicillin and cephalosporin arises from identical or similar side chains rather than the β lactam ring.
- However, not all structurally related side chains will have cross-reactivity to penicillin because compounds with dissimilar structures yet similar 3-D electronic and steric properties might result in cross-reactivity (Miranda A, et al. J Allergy Clin Immunol. 1996; Hasdenteufel F, et al. Curr Clin Pharmacol. 2012; Zhao Z, Baldo BA, Rimmer J. Clin Exp Allergy. 2002;32:1644-1650).

Example of similar side chain cross-reaction

- Cephalothin and cephaloridine (used in 1980s) - share similar side chains with benzylpenicillin

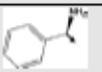
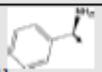
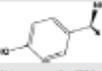
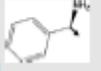
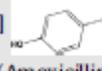
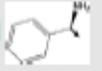
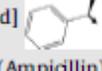


Cephalothin



Penicillin G

Structural similarities of cephalosporins to penicillin derivatives

100% Identical R1 side chain	Similar R1 structural components
Cefaclor [Second]  (Ampicillin)	Cefamandole [Second] 
Cefadroxil [First]  (Amoxicillin)	Cefonicid [Second] 
Cefatrizine [First]  (Amoxicillin)	
Cefprozil [Second]  (Amoxicillin)	
Cephalexin [First]  (Ampicillin)	
Cephaloglycin [First]  (Ampicillin)	
Loracarbef [Second]  (Ampicillin)	

Pichichero ME, Zagursky R. Ann Allergy Asthma Immunol 2014;112:404-412

- Penicillin derivatives whose R side chain is 100% identical to the cephalosporin R1 side chain is shown in parentheses.
- These drugs are either known to elicit an allergic reaction in penicillin allergic patients or, due to their similarity to the penicillin derivative, suggested to be avoided in patients with known allergies to those penicillins.

References

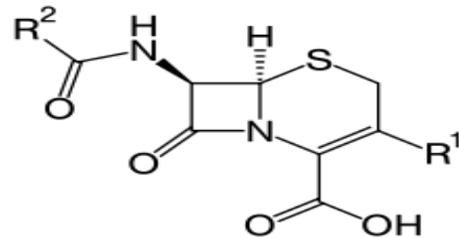
- Pichichero ME. A review of evidence supporting the American Academy of Pediatrics recommendation for prescribing cephalosporin antibiotics for penicillin-allergic patients. Pediatrics. 2005
- Campagna JD, Bond MC, Schabelman E, Hayes BD. The use of cephalosporins in penicillin-allergic patients: a literature review. J Emerg Med. 2012
- Pichichero ME. Evidence supporting the use of cephalosporin antibiotics in penicillin-allergic patients. Pediatr Asthma Allergy Immunol. 2005.
- Dickson SD, Salazar KC. Diagnosis and management of immediate hypersensitivity reactions to cephalosporins. Clin Rev Allergy Immunol. 2013.

Possibility also of co-occurrence of allergy to drugs and not drug cross-reactivity

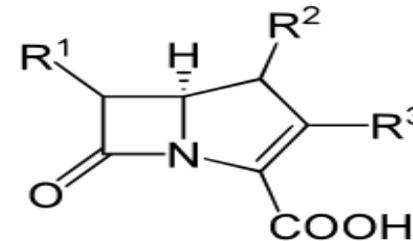
- Occurrence of an allergic reaction to a cephalosporin in a penicillin-allergic patient does not prove causality because it may be completely coincidental.
- There is a 3-fold increased coincidental risk of adverse reactions to unrelated drugs among penicillin-allergic patients.

Cross reactivity with Carbapenems

- Clinical cross-reactivity between carbapenems and cephalosporins appears to be rare.



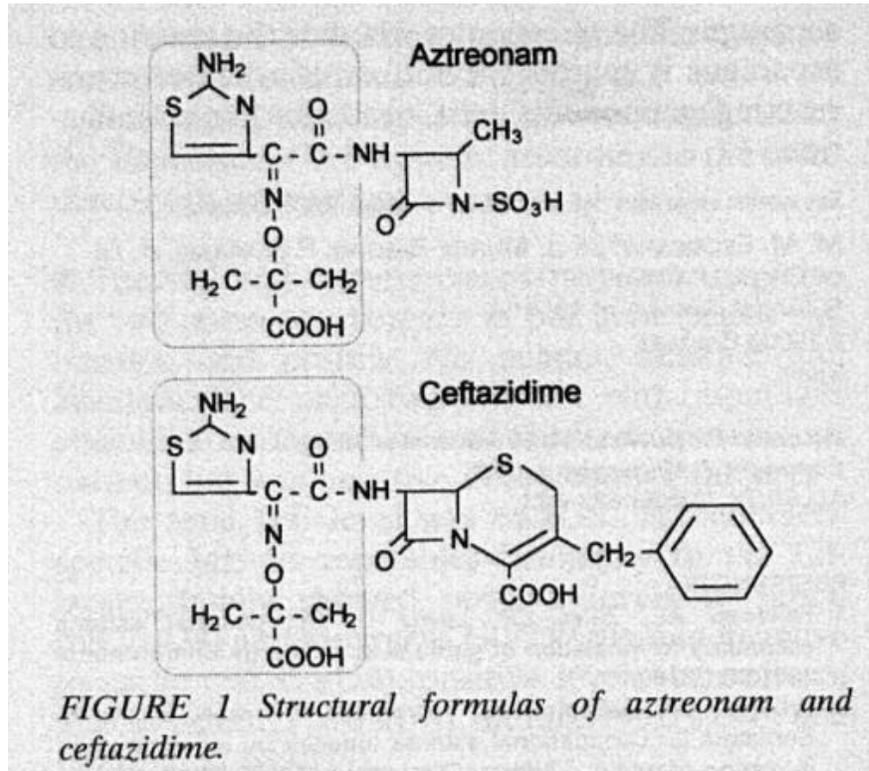
Core structure of cephalosporin



Core structure of carbapenem

- Romano A, et al. IgE-mediated hypersensitivity to cephalosporins: cross-reactivity and tolerability of penicillins, monobactams, and carbapenems. *J Allergy Clin Immunol* 2010;126:994-9.

Cross reactivity with Monobactams



- Monobactams do not have cross-allergy with most cephalosporins.
- An exception is aztreonam cross-reaction with ceftazidime because both drugs share an identical side chain.

Saxon A, Hassner A, Swabb EA, et al. Lack of cross-reactivity between aztreonam, a monobactam antibiotic and penicillin in penicillin-allergic subjects. *J Infect Dis* 1984; 149

Adkinson NF, Jr. Immunogenicity and cross-allergenicity of aztreonam. *Am J Med* 1990; 88:(Suppl 3C)

Frumin J, Gallagher JC. Allergic cross-sensitivity between penicillin, carbapenem, and monobactam antibiotics: what are the chances? *Ann Pharmacother*. 2009;43.

Cephalosporin skin testing: prick and intradermal

- For evaluation of immediate hypersensitivity reactions.
- Reagents recommended to be included in the skin-testing panel:
 - The cephalosporin suspected of causing the reaction.
 - One or more alternative cephalosporins with different R groups from the culprit drug.
 - Penicillin reagents, ampicillin (20 mg/mL) and amoxicillin (20 mg/mL).
- The standard penicillin reagents include:
 - Penicilloyl-polylysine (Pre-Pen) and minor determinant mixtures (MDM).
 - Penicillin G is a minor determinant that can be used at a concentration of 10,000 U/mL when MDM is not available.

Skin test concentrations in evaluation of immediate reactions.

- Romano et al. J Allergy Clin Immunol 1999;104:1113 -
 - Reported a case of IgE-mediated hypersensitivity to ceftriaxone.
 - Found that 2mg/mL injectable cephalosporins diluted in normal saline, was non-irritating to the skin.
- Romano A, et al. J Allergy Clin Immunol 2000;106:1177-
 - Reported that 2mg/mL concentration is sensitive.
 - 30 subjects with history of immediate hypersensitivity to cephalosporins.
 - Skin testing with 6 different injectable cephalosporins using 2 mg/ml concentration diluted in 0.9 % NaCl.
 - Cephalosporin allergy was confirmed in 29 of 30 (96.7%).
- Empedrad et al, J Allergy Clin Immunol 2003;112:629-
 - Reported non-irritating concentrations for different cephalosporins:
 - cefazolin = 33mg/mL
 - cefuroxime, ceftriaxone, cefotaxime, ceftazidime = 10mg/mL
 - Subjects were without history of drug allergy.
 - Dilutions of commercially available intravenous antibiotic solutions was used.

Studies have reported using concentrations of cephalosporins ranging from 0.5mg to 250mg/mL.

A concentration of 2mg/mL for cephalosporins was recommended by the European guidelines.

Torres MJ, et al. Diagnosis of immediate allergic reactions to beta-lactam antibiotics. *Allergy* 2003;58:961-.

Blanca M, et al. Update on the evaluation of hypersensitivity reactions to betalactams. *Allergy* 2009;64:183-.

In its 2013 position paper, the ENDA/EAACI Drug Allergy Interest Group recommended a concentration of 2mg/mL for cephalosporin skin tests.

Brockow K, et al. Skin test concentrations for systemically administered drugs - an ENDA/EAACI Drug Allergy Interest Group position paper. *Allergy* 2013;68:702-

Variable rate of cephalosporin skin test positivity

3 European studies

- Evaluated patients with history of immediate reactions to cephalosporins.
- Rate of positive skin testing with the responsible cephalosporins were:
 - 72.1% (31/43 subjects), only children (Romano A, et al. Diagnosing hypersensitivity reactions to cephalosporins in children. *Pediatrics* 2008;122:521-)
 - 69.7% (53/76 subjects), only adults (Romano A, et al. Diagnosing immediate reactions to cephalosporins. *Clin Exp Allergy* 2005;35: 1234-)
 - 30.7% (39/127 subjects), both children and adults (*Antunez C, et al. Immediate allergic reactions to cephalosporins: evaluation of cross-reactivity with a panel of penicillins and cephalosporins. *J Allergy Clin Immunol* 2006;117:404-)

*Used 2mg/mL for the cephalosporins.

More studies needed to improve the sensitivity of cephalosporin skin test.

Chng HH, et al. Skin testing and drug provocation test in the evaluation of cephalosporin allergy in TTSH. Presented at EAACI2016

Pat	Culprit drug	Reactions	IDT results	DPT results	DPT Drug
1	Cefazolin	Anaphylaxis	ampicillin, MDM 1:1, cefazolin 3mg/mL @1:10	Not done	Not applicable
2	Cefazolin	Anaphylaxis	cefazolin 3mg/mL @1:1	Not done	Not applicable
5	Cefazolin	Anaphylaxis	Negative	Negative	Cefazolin
6	Cefazolin	Anaphylaxis	Negative	Negative	Amoxicillin
7	Cefazolin	Anaphylaxis	Negative	Negative	Cefazolin
8	Cefazolin	? MP rash	Negative	Pruritic, erythematous macules	Cefazolin
9	Cefazolin	Urticaria	Negative	Negative	Cefazolin
10	Cefazolin	Anaphylaxis	Negative	Unwell, giddy, flushing	Cefazolin
11	Cefazolin	Anaphylaxis	Negative	Negative	Cefazolin
12	Cefazolin	Anaphylaxis	Negative	Negative	Cefazolin
13	Cefazolin	Angioedema	Negative	Negative	Cefazolin
3*	Cefuroxime & Amoxicillin/clavulanate	Angioedema	PPL 1:1, MDM1:1, cefazolin 3mg/mL @1:10 (not tested to cefuroxime as it was not available and doctors wanted to use cefazolin)	Not done	Not applicable
14	Cefuroxime	? MP rash	Negative	Negative	Cefuroxime
15	Cefuroxime	Urticaria	Negative	Negative	Augmentin
4	Ceftriaxone	Urticaria	ceftriaxone 3mg/mL @1:1	Not done	Not applicable
16	Ceftriaxone	Urticaria	Negative	Urticaria	Ceftriaxone
17	Ceftriaxone	Anaphylaxis	Negative	Urticaria	Ceftriaxone
18	Ceftriaxone	? MP rash	Negative	Negative	Imipenem
19	Ceftriaxone	Angioedema	Negative	Negative	Augmentin
20	Ceftriaxone	Urticaria	Negative	Negative	Ceftriaxone

Retrospective study
Jan 2006 – Dec 2012

SPT and IDT to:
- penicillin panel and ampicillin
- Cephalosporin **3mg/ml** at 1:100, 1:10, 1:1

18/20 patients had tests within 2years of reaction

Only **4/20** had **positive skin test**

4/12 were **positive on DPT** to the culprit drug to which they were skin test negative

If #6 excluded, **Negative Predictive Value** of **cefazolin** ST is 75% (6/8); when assuming #6 is true negative, NPV is 77.8% (7/9) at best and sensitivity 50% at best.

If #18 & 19 excluded, **Negative Predictive Value** of **ceftriaxone** ST is 33.3% (1/3), when assuming they are true negative, NPV is 60% (3/5) at best and sensitivity 33.3% at best.

Perhaps for certain cephalosporins, skin testing at a higher concentration than 2mg/mL (recommended by ENDA/EAACI) may improve the sensitivity and the negative predictive value.

In our small study using a higher concentration of 3mg/mL, both cefazolin and ceftriaxone skin testing have low sensitivities.

Study on a larger number of patients is needed.

Yoon SY, et al. Validation of the cephalosporin intradermal skin test for predicting immediate hypersensitivity: a prospective study with drug challenge. *Allergy* 2013;68:938-

- Investigated validity of skin tests for predicting immediate hypersensitivity to cephalosporins in subjects with no history of allergy to β -lactam antibiotics.
- Intradermal skin tests (2mg/mL) performed with 4 cephalosporins, one from each generation of cephalosporins, as well as penicillin G.
- 1,421 patients who required a preoperative antibiotic.
- Irrespective of skin test results, each patient received an intravenous challenge dose of one of the tested cephalosporins with careful observation.

Results:

- 74 patients skin test-positive to at least 1 cephalosporin, and none had immediate hypersensitivity on drug challenge. (*5% False positive*)
- 4 patients with negative skin tests developed an immediate hypersensitivity reaction. (*False negative cases*)
- Specifically for ceftriaxone there were 22 cases of false positive skin test and 3 cases of false negative tests.

Predictive value of cephalosporin skin testing

Negative predictive value

- Not known.
- Negative test suggests the patient does not have specific IgE antibodies to the cephalosporin in its native state, but patient could still have IgE against a degradation product-protein complex.
- A negative result should not be interpreted as proof that allergy is not present.
- Negative skin test should be followed up with drug provocation test.

Positive predictive value

- Has not been precisely defined.
- Would require administering the drug to large numbers of skin test positive patients to confirm their reactivity.

Further studies to determine and standardize the concentrations of each cephalosporin in its native state as reagents for skin testing is needed.

Time interval between last reaction and skin testing is relevant

- Possible for tests to become negative over time.
- Interpret negative skin test results in light of the time elapsed since their last exposure to the drug.

- Romano A, et al. **Natural evolution of skin-test sensitivity in patients with IgE-mediated hypersensitivity to cephalosporins.** Allergy 2014;69:806-9.
 - 72 patients with IgE-mediated hypersensitivity to cephalosporins, studied prospectively over 5 years.
 - Allergy tests repeated 1 year later and in case of persistent positivity, 3 and 5 years after the first evaluation.
 - After first evaluation, 2 groups found: Group A (n = 16) positive to both penicillin reagents and cephalosporins, and Group B (n = 56) positive only to cephalosporins.
- Group B further subgrouped: subgroup B1 (n=22) positive to different cephalosporins, including those responsible and subgroup B2 (n=34) positive only to the culprit cephalosporins.
- Seven of 16 subjects in Group A and 38 of 56 in Group B became negative (16 in subgroup B1 and 22 in subgroup B2); 1 was lost to follow-up.

Desensitisation when no available alternative drug

- Desensitization modifies a patient's response to temporarily allow treatment safely.
- It is an option if the specific cephalosporin implicated is needed for a life-threatening infection.
- Oral desensitization should preferably be performed when possible prior to parenteral antibiotic use.

Example:
Ceftriaxone desensitization

Ceftriaxone Dilution:

Solution 1 = 10 mg/1 ml

Solution 2 = 1 mg/1 ml

Solution 3 = 0.1 mg/1 ml

Solution 4 = 0.01 mg/1 ml

Solution 4	0.01mg/ml	Dose	Cummulative dose
1 ml		0.01mg	0.01 mg
2 ml		0.02 mg	0.03 mg
4 ml		0.04 mg	0.07 mg
8 ml		0.08 mg	0.15 mg
Solution 3	0.1 mg/ml	Dose	
1 ml		0.1mg	0.25 mg
2 ml		0.2 mg	0.45 mg
4 ml		0.4 mg	0.85 mg
8 ml		0.8 mg	1.65 mg
Solution 2	1 mg /ml	Dose	
1 ml		1mg	2.65 mg
2 ml		2 mg	4.65 mg
4 ml		4 mg	8.65 mg
8 ml		8 mg	16.65 mg
Solution 1	10 mg /ml	Dose	
1 ml		10 mg	26.65 mg
2 ml		20 mg	46.65 mg
4 ml		40 mg	86.65 mg
8 ml		80 mg	266.65 mg
16 ml *		160 mg	326.65 mg
32 ml *		320 mg	646.65 mg
64 ml *		640 mg	1286.65 mg

After completion of above, wait 30 mins before proceeding to give the full therapeutic dose if more than 1000 mg daily is required.

Rapid desensitization data (2008 – Oct 2013)
 Department of Rheumatology, Allergy &
 Immunology
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Year	Total no of desensitization	Rapid desensitization
2008	2	0
2009	11	2
2010	12	4
2011	18	3
2012	33	7
2013 (to Nov)	20	2
TOTAL	96	18

Drug	No of rapid desensitization
Penicillin	1
Amoxicillin	1
Piperacillin/Tazobactam	1
Ceftriaxone	4
Cefoxitin	1
Cefepime	1
Cefazolin	1
Imipenem	1
Ertapenem	3
Clarithromycin(oral)	1
Bactrim	1
Ciprofloxacin	2

1. No premedication given in all patients.
2. Protocols individualized, follow general principle of incremental dosing, starting very low, usually 14 – 16 steps as in penicillin desensitization protocols.
3. We have not used BWH protocols because of concern with the frequency of breakthrough reactions and the need for premedications.
4. All 18 desensitizations successfully completed without serious breakthrough reactions.

Summary

- Cephalosporin allergy does not cross all generations of the antibiotic class.
- Cross-reactivity among cephalosporins is mostly due to similar side chains.
- Cephalosporin allergic patients who require an alternative cephalosporin may be treated with one with different side-chain determinants.
- Pre-treatment skin testing and drug provocation test with alternative cephalosporins are advised before their administration to subjects with cephalosporin allergy.
- Desensitization is an option if the specific cephalosporin implicated is needed.
- Although variable rates of positivity are obtained in skin testing at current recommended concentration, and its predictive values not fully established, skin testing is still clinically useful within limitations.
- Cross-reactivity between penicillin and cephalosporin is due to side chain similarity rather than the β lactam ring.
- Cross-reactivity between cephalosporin and carbapenem or monobactam is rare.