Approach to Cephalosporin Allergy

Immediate Hypersensitivity Reactions

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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

- Carbopenems
- Cephamycins
- Monobactams
- Clavams
- Penicillins
  - Aminopenicillins
  - Carboxypenicillins
  - 1st generation
  - 2nd generation
  - 3rd generation
  - 4th generation
  - 5th generation

Structure of cephalosporins

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

Core structure, with R1 and R2 variable groups.

Core structure, where "R" is the variable group.

6-membered dihydrothiazine ring

5-membered Thiazolidine ring
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.

<table>
<thead>
<tr>
<th>Generations</th>
<th>First generation</th>
<th>Second generation</th>
<th>Third generation</th>
<th>Fourth generation</th>
<th>Fifth generation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefadroxil</td>
<td>Cefaclor</td>
<td>Cefdinir</td>
<td>Ceftaroline</td>
<td>Ceferoline</td>
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<td>Cefazidine</td>
<td>Cefamandole</td>
<td>Cefditoren</td>
<td>Ceftazidime</td>
<td>Ceftobidine</td>
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<td>Cefuroxime</td>
<td>Cefmetazole</td>
<td>Cefotaxime</td>
<td>Ceftazolin</td>
<td>Ceftobutin</td>
<td></td>
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<tr>
<td>Cephalixin</td>
<td>Cefminox</td>
<td>Cefotin</td>
<td>Ceftizone</td>
<td>Ceftizol</td>
<td></td>
</tr>
<tr>
<td>Cephaloglycin</td>
<td>Cefonicid</td>
<td>Cefuroxime</td>
<td>Ceftazolin</td>
<td>Cefepoxide</td>
<td></td>
</tr>
<tr>
<td>Cephaloridine</td>
<td>Cefetan</td>
<td>Cefuroxime</td>
<td>Ceftazolin</td>
<td>Cefpirome</td>
<td></td>
</tr>
<tr>
<td>Cephalothin</td>
<td>Cefotiam</td>
<td>Cefuroxime</td>
<td>Ceftazolin</td>
<td>Cefpirome</td>
<td></td>
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<tr>
<td>Cephamycin</td>
<td>Cefotikin</td>
<td>Cefuroxime</td>
<td>Ceftazolin</td>
<td>Cefpirome</td>
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<tr>
<td>Cephamidine</td>
<td>Cefpodoxime</td>
<td>Cefuroxime</td>
<td>Ceftazolin</td>
<td>Cefpirome</td>
<td></td>
</tr>
<tr>
<td>Cephamide</td>
<td>Loracarbef</td>
<td></td>
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</tr>
</tbody>
</table>

Spectrum of activity

<table>
<thead>
<tr>
<th>Generations</th>
<th>First generation</th>
<th>Second generation</th>
<th>Third generation</th>
<th>Fourth generation</th>
<th>Fifth generation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-positive</td>
<td>Good</td>
<td>Poor</td>
<td>Good</td>
<td>Excellent</td>
<td>Good</td>
</tr>
<tr>
<td>Gram-negative</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cocci coverage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- 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.

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.

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

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.


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.

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

- 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

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.

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.

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.

<table>
<thead>
<tr>
<th>Study</th>
<th>Publication Details</th>
<th>Findings</th>
</tr>
</thead>
</table>
- Found that 2mg/mL injectable cephalosporins diluted in normal saline, was non-irritating to the skin. |
- 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.
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:


  - 69.7% (53/76 subjects), only adults (Romano A, et al. Diagnosing immediate reactions to cephalosporins. Clin Exp Allergy 2005;35: 1234-)


*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 EAACI 2016

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

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.

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 2 years 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
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

<table>
<thead>
<tr>
<th>Negative predictive value</th>
<th>Positive predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Not known.</td>
<td>• Has not been precisely defined.</td>
</tr>
<tr>
<td>• 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.</td>
<td>• Would require administering the drug to large numbers of skin test positive patients to confirm their reactivity.</td>
</tr>
<tr>
<td>• A negative result should not be interpreted as proof that allergy is not present.</td>
<td></td>
</tr>
<tr>
<td>• Negative skin test should be followed up with drug provocation test.</td>
<td></td>
</tr>
</tbody>
</table>

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.

  - 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.
### IV and Oral Drug Provocation Protocols

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Time from start of DPT</th>
<th>Cumulative dose reached (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IV</strong> Cefazolin by infusion (same protocol as for ceftriaxone)</td>
<td>1 hr</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>2 hr</td>
<td>500</td>
</tr>
<tr>
<td></td>
<td>Subsequent rate as per pharmacy guidelines to complete cumulative dose of 1000 mg</td>
<td></td>
</tr>
<tr>
<td><strong>PO</strong> Cefuroxime 125mg/5mL syrup</td>
<td>0 hr</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>1 hr</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>1 hr 15 min</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>1 hr 30 min</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>1 hr 45 min</td>
<td>155</td>
</tr>
<tr>
<td></td>
<td>2 hr</td>
<td>315</td>
</tr>
<tr>
<td></td>
<td>2 hr 15 min</td>
<td>500</td>
</tr>
<tr>
<td></td>
<td>Then continue usual dosing if required for treatment of infection</td>
<td></td>
</tr>
</tbody>
</table>

Total time to reach cumulative dose of 500mg: 2hr if IV DPT; 2hrs 15 mins if oral DPT
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

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
Tan Tock Seng Hospital, Singapore

<table>
<thead>
<tr>
<th>Year</th>
<th>Total no of desensitization</th>
<th>Rapid desensitization</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>2009</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>2010</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>2011</td>
<td>18</td>
<td>3</td>
</tr>
<tr>
<td>2012</td>
<td>33</td>
<td>7</td>
</tr>
<tr>
<td>2013 (to Nov)</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>TOTAL</td>
<td>96</td>
<td>18</td>
</tr>
</tbody>
</table>

### Drug Analysis

<table>
<thead>
<tr>
<th>Drug</th>
<th>No of rapid desensitization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>1</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>1</td>
</tr>
<tr>
<td>Piperacillin/Tazobactam</td>
<td>1</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>4</td>
</tr>
<tr>
<td>Cefoxitin</td>
<td>1</td>
</tr>
<tr>
<td>Cefepime</td>
<td>1</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>1</td>
</tr>
<tr>
<td>Imipenem</td>
<td>1</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>3</td>
</tr>
<tr>
<td>Clarithromycin(oral)</td>
<td>1</td>
</tr>
<tr>
<td>Bactrim</td>
<td>1</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>2</td>
</tr>
</tbody>
</table>

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.