ASCIA Consensus Statement for Assessment of Suspected Allergy to Cephalosporin Antibiotics

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For patient or carer support contact Allergy & Anaphylaxis Australia or Allergy New Zealand.

This document has been developed by the ASCIA Drug Allergy Committee to assist medical practitioners with an interest and experience in the management of immediate drug allergy to antibiotics in the cephalosporin family.

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Note: The Cefalexin allergy high risk assessment flowchart (previously Appendix 4) is currently under review.

Acronymns and abbreviations

ADR	Adverse drug reaction
AERD	Aspirin-exacerbated respiratory disease
Bioisosterism	Similar 3D and steric properties
BL	Beta-lactam antibiotics
Cephalosporins	Cefaclor, Cephalexin, Cefuroxime
DPT	Drug Provocation Test
IDT	Intradermal Testing
IgE	Immunoglobulin E
Side Chains	Thiophene and benzene
SPT	Skin Prick Testing

Background

This Consensus Statement provides guidance for the testing of immunoglobulin E (IgE)-mediated allergy in people with the label of cephalosporin allergy in Australia and New Zealand. It is adjunct to the ASCIA consensus statement for the assessment of patients with suspected penicillin allergy.

Beta-lactam (BL) antibiotics contain a shared beta-lactam ring and are made up of two major classes, penicillins and cephalosporins. In Australia and New Zealand there are also three minor classes: carbapenems, monobactams and clavams (see supplemental Figure 1 in Appendix 1). Allergy to a cephalosporin is frequently reported in the community and in hospitalised patients.

Based on past studies, a significant proportion of these patients with an allergy to a cephalosporin will tolerate the culprit medication after appropriate assessment. While 1-3% of cephalosporin exposed patients develop cutaneous reactions, anaphylaxis is considered to be rare at <0.1%, except when seen in the context of perioperative anaphylaxis (Romano et al., 2005). Just as for penicillin allergy, de-labelling is likely to reduce patient morbidity and mortality, microbial resistance to antibiotics and economic costs associated with prolonged hospital stays (Solensky, 2014).

The majority of patients with immediate allergy to a cephalosporin have IgE directed against side chains and not the BL ring (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, 2010).

The implication of this is that in the vast majority of cases, allergy to a particular cephalosporin does not confer a risk of cross-reactive allergy to other cephalosporins (in the absence of side chain identity or similarity). Wherever possible the specific cephalosporin drug which was associated with the reaction (the index drug) should be recorded and the generic term “cephalosporin allergy” should be avoided.

The most common allergy in Australia is to cefalexin due to its widespread use in the community. Cefalexin is an aminocephalosporin which shares an identical R_1 side chain with ceclor (ceclor has limited availability in Australia and New Zealand) and the aminopenicillin ampicillin (limited availability in Australia, not available in New Zealand). The R_1 side chain of cefalexin also has significant similarity to the R_1 side chain of amoxicillin. Currently, the level of crossreactivity between cefalexin and amoxicillin is unclear, therefore tolerance of amoxicillin cannot be assumed in subjects with confirmed cefalexin allergy. Testing strategies for cefalexin are addressed later.

There is an apparent increase of allergy to cephalosporins in Australia and New Zealand, particularly cefazolin allergy in perioperative settings. IgE-mediated allergy to cefazolin is now thought to be one of the leading causes of perioperative anaphylaxis in Australia and New Zealand, due to its abundant use before procedures.

As cefazolin is usually given with other anaesthetic medications perioperatively, cefazolin allergy is commonly assessed by an anaesthetic allergy clinic to make the initial diagnosis. Patients with confirmed cefazolin allergy are then referred to an immunologist to make recommendations, in regards to the tolerance of other cephalosporins and BL antibiotics. Management of cefazolin allergy is addressed later within this document.

Skin testing and oral challenge (drug provocation testing) with the drug of interest should always be performed in a setting where anaphylaxis can be treated.

Perioperative anaphylaxis with cefazolin

All patients with a record of perioperative anaphylaxis should be tested for all potential culprit agents, including antibiotics, used in the perioperative setting. In the majority of centres in Australia and New Zealand, the antibiotic used perioperatively is cefazolin. Testing for perioperative anaphylaxis within three to six months after the event is suggested.

If cefazolin allergy has been confirmed by skin testing, several approaches (listed below) may be pursued. There is increasing evidence that confirmed cefazolin allergy is unlikely to be associated with an allergy to other cephalosporins or beta-lactams (BL) antibiotics, indicating that the use of other cephalosporins or BL antibiotics without any further testing may be safe. However, anecdotal cases of BL or cephalosporin ring allergy in patients with cefazolin allergy have been described. It is difficult to say if this is due to true cross-reactivity or co-reactivity.

Valid approaches that may be considered based of the experience of the drug allergy specialist are:

- Penicillin/beta-lactam skin testing → if negative → two dose oral cephalosporin challenge; if negative → safe to have all penicillins and cephalosporins except for cefazolin. This approach should be used for all patients who, in addition to cefazolin allergy, also have a history of a reaction to another beta-lactam antibiotic.
- Cephalosporin skin testing → if negative → two dose oral cephalosporin challenge; if negative → safe to have all penicillins and cephalosporins except for cefazolin.
- Two-dose oral cephalosporin challenge → if negative → safe to have all penicillins and cephalosporins except for cefazolin.

Currently this expert group recommends at a minimum a two dose oral cephalosporin challenge (e.g. cefalexin or cefuroxime) before further use of all cephalosporins (except forcefazolin (which needs to be avoided life long).

If skin testing to other beta-lactams or cephalosporins is positive, or the oral cephalosporin challenge is not tolerated, further beta-lactam allergy testing is recommended before the use of further penicillins or cephalosporins. Carbapenems can be given with caution and monobactams are safe.

Note: If no culprit agent can be found for the perioperative anaphylaxis by skin testing, and cefazolin remains a likely agent of causing the reaction, any of the three approaches listed above are recommended, and continuing to avoid cefazolin.

Assessment of cefalexin allergy

To test for cefalexin allergy, testing for cross reactivity with aminopenicillins should be performed. This includes Amoxicllin (Australia and New Zealand); and Ampicillin (Australia). For cefalexin challenge please see the algorithm (appendix 3).

This algorithm suggests a direct two dose cephalexin challenges for patients with a history of a benign rash. A benign rash is defined as a transient morbilliform or maculopapular rash that may be mildly pruritic and is not associated with other symptoms.

Skin testing is required when there is a history of an IgE-mediated reaction which typically manifests with one or more of the following: urticaria, angioedema, rhinitis, conjunctivitis, bronchospasm, hypotension and anaphylactic shock.

Management of allergies of other cephalosporins

In patients with low pre-test probability of IgE-mediated allergy to cephalosporins, testing will exclude allergy in most cases.

In patients with high pre-test probability of IgE-mediated allergy to a cephalosporin, the aim may be:

- Confirmation of the diagnosis.
- Exclusion of the diagnosis.
- Finding suitable alternative BLs.

Patients with a distant history of a benign rash to a cephalosporin may be considered low risk. A **benign rash** is defined as a transient morbilliform or maculopapular rash that may be mildly pruritic and is not associated with other symptoms.

A history of an **IgE-mediated reaction** which typically manifests with one or more of the following: immediate urticaria (within one to two hours after taking the drug), angioedema, rhinitis, conjunctivitis, bronchospasm, hypotension and anaphylactic shock, is considered high risk and requires skin testing.

People with IgE-mediated allergy to a cephalosporin can be further subdivided into:

- Patients allergic to both cephalosporins and penicillins due to BL ring allergy (very rare).
- Patients allergic to cephalosporin determinants but not to penicillin determinants.
- Patients selectively allergic to particular cephalosporin(s) and/or other BLs with similar R_1 side chains but can tolerate other BLs.

The flow charts (figures 1 and 2) are designed to cater for these possibilities. Examples at the extreme end of low and high pre-test probability are provided for guidance. The testing algorithm should be adjusted as per the clinical need. If allergy to a particular antibiotic is considered highly likely (in the absence of testing) or is confirmed by testing, desensitisation may allow temporary tolerance of the antibiotic in a situation where the antibiotic is strongly indicated to treat an episode of infection. This requires an appropriate validated desensitisation protocol, administered in a hospital setting with input and supervision from a clinical immunology/allergy specialist.

The following editable template pre-clinic questionnaire is provided to facilitate assessment and the triage of patients referred to a drug allergy clinic:

https://allergy.org.au/members/ascia-drug-allergy-pre-clinic-information-template

The following issues are not addressed and are beyond the scope of this document:

- Non-IgE mediated allergy to a cephalosporin.
- Minimal reference to penicillins has been included as this is addressed in the ASCIA consensus statement for the assessment of patients with immediate (IgE-mediated) penicillin allergy.
- The determination of pre-test probability of IgE-mediated allergy to a cephalosporin- this is based on clinical experience.
- Exclusion criteria for testing.

Common scenarios for testing for allergy to a cephalosporin

- Reaction in the distant past (five or more years) with little or no patient recall, little or no contemporaneous information.
- Reaction in the recent past (less than five years) with non-immediate and no dangerous features identified.
- Reaction in the recent past with immediate anaphylactic or dangerous features. If a causal relationship to a cephalosporin is clear, more extensive beta lactam skin testing should be considered to clarify the nature of the cross-reactivity.
- Reaction in the recent past with immediate anaphylactic or dangerous features, but causal connection to a cephalosporin is not clear (other potential culprits), proceed to sIgE testing before skin test and challenge.

Common indications for cephalosporin testing in patients with a cephalosporin allergy label:

- Patients who have frequent infections with requirement for antibiotics several times per year.
- Patients who have infections for which cephalosporins are the most appropriate antibiotic.
- Patients who are allergic or intolerant to other antibiotics in addition to a cephalosporin in whom the choice is narrowing.
- Patients with immunodeficiency, bronchiectasis or other risk factors for infections requiring antibiotic use.

Skin testing protocol for cephalosporin allergy

- There is less data on the diagnostic validity of skin testing (skin prick testing and intradermal) for cephalosporin allergy than penicillin allergy.
- Skin testing is recommended for patients with a high pre-test probability of cephalosporin allergy.
- ASCIA information regarding the technical aspects of skin prick testing is available at https://www.allergy.org.au/hp//papers/skin-prick-testing
- Solutions used for skin prick testing (SPT) and intradermal testing (IDT) should not exceed non-irritant concentrations (see Table 1) (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, 2010, Brockow, 2013).
- Unlike penicillins, cephalosporins are available in **either** oral **or** parenteral formulations. The latter are more readily suited to skin testing. Oral (solid) cephalosporins (cefaclor, cephalexin, cefuroxime) may be solublised for skin testing but such testing has not been validated.
- The diagnostic utility of skin testing to cephalosporins is less well established as compared to skin testing to penicillins. Sensitivity varies considerably (between 30-70%) and only the native molecule (not determinant) testing is available for cephalosporins. Further studies are required to clarify this issue (Blanca, 2009).
- Histamine is to be used as a positive control for skin prick testing, and morphine can be used as a positive control for IDT. Relevant negative test controls must be included.
- As a minimum the panel should include ceftriaxone, cefazolin and the culprit cephalosporin, if available. Cefazolin may be substituted with cefalothin if this is more commonly used in the local setting. Further testing with penicillins is also encouraged to assess for cross-reactivity as detailed above (for penicillins skin testing, see the ASCIA Penicillin Consensus Statement).
- IDT for penicillins can precipitate anaphylaxis and may precipitate anaphylaxis with cepahalosporins (Torres, 2001). Therefore, in those with high pre-test probability of IgE-mediated cephalosporin allergy, commencing IDT at 1:10 or 1:100 dilution is recommended**.**
- If penicillins are in the testing panel, beware of cross reactivity (see circled in Supplemental Figure 1 in Appendix 1). Tables 1 and 2 in Appendix 2 (Joint Task Force on Practice Parameters et al., 2010, Romano & Caubet, 2014).
    - Cephalexin, cefaclor and ampicillin have identical R_1 side chains.
    - Amoxicillin has a similar but not identical R_1 side chain to ampicillin, cephalexin and cefaclor.
- The same intradermal testing protocol may be used for delayed reading reactions at 48-72 hours for the assessment of T cell mediated cephalosporin hypersensitivity.
- Testing is more likely to be positive if performed within six months of the reaction (Romano et al., 2014).

Table 1: Suggested non-irritating test concentrations for cephalosporins

Drug*	SPT Dilution	IDT Minimum concentration	IDT Maximum concentration
Cefazolin	1-2mg/ml	1mg/ml	20mg/ml
Ceftriaxone	1mg/ml	1mg/ml	20mg/ml
Cefotaxime	2mg/ml	1mg/ml	20mg/ml
Ceftazidime	2mg/ml	1mg/ml	20mg/ml
Other cephalosporins	2mg/ml*	1mg/ml	20mg/ml*

Table based on data from Joint Task Force on Practice Parameters et al.; 2010, and Brockow et al, 2013.

* European guidelines recommend 2mg/ml for all cephalosporins.

Note: For penicillin skin prick test concentrations included in the examples below, please see the ASCIA Penicillin Consensus protocol document.

Oral challenge in low pre-test probability patients

In patients with a low pre-test probability of an IgE-mediated to a cephalosporin, the aim is to exclude cephalosporin allergy.

In cases where the clinical history does not match an IgE-mediated cephalosporin allergy (e.g. benign rash** in a paediatric population), performing an oral challenge without SPT and IDT is likely to be safe, Caubet et al., 2011).

****** In the context of drug allergy a benign rash is a transient morbilliform or maculopapular rash that may be mildly pruritic and is not associated with other symptoms. Features indicating a more serious reaction include immediate onset urticaria, erythroderma, and constitutional symptoms such as fever, sore throat, malaise, arthralgia, lymphadenopathy, cough with facial or mucous membrane involvement, skin tenderness or blistering such as purpura or desquamation.

The choice of cephalosporin for oral challenge or drug provocation test (DPT):

- Performing DPT with the culprit drug should be considered if the culprit drug is known and is the most effective way of removing a cephalosporin allergy label.
- When the culprit cephalosporin is unknown (less common for cephalosporins compared with penicillins), e.g. distant reaction, but known to be an oral cephalosporin, ASCIA suggests:
    - **Cefaclor or cephalexin**. These are the most frequently prescribed cephalosporins in the community and the prevalence of cefaclor and cephalexin allergy is also high in Australia and New Zealand (unpublished data).
    - If necessary, a second challenge to **cefuroxime** could be performed to confirm tolerance of all currently available oral cephalosporins.
- If an IV cephalosporin was implicated, but the culprit cephalosporin is truly unknown (uncommon situation), then the above challenges could be performed to at least confirm tolerance of oral cephalosporins.
- Challenge protocol:
    - Graded challenges can be performed as a three-dose challenge (1/100, 1/10, full dose) of full treatment dose; two-dose challenge (1/10, full dose); or single-dose challenge. In children, the daily treatment dose should not be exceeded. The recommended time interval between doses is a minimum of 30 minutes, and the patient should be observed for two hours after the last dose.
    - A one or two-dose challenge is adequate to assess IgE-mediated allergy.
    - A longer treatment course (e.g. three to seven days) of the relevant cephalosporin may be required to adequately exclude delayed-type hypersensitivity.

In order to administer a fractionated dose (1:10, 1:100) a liquid (suspension) form of cephalexin or cefaclor is commonly used. The standard preparation is 100ml at a concentration of 250mg/5ml for cephalexin, so the full adult dose is 10ml twice a day (or 5ml four times a day). Fractionated doses are 0.1ml, 1.0ml, and 10ml. Therefore, after the first set of provocation doses, it is convenient to provide the patient with the remainder of the bottle which is sufficient for a three day challenge.

Example

Assessment of a patient with a history of mild non-pruritic rash after cephalexin in the setting of a viral infection:

- **Perform DPT (skip SPT/IDT)** to oral cephalexin 50mg (or 1/10th of the full dose) and after 30 minutes, 500mg (or 9/10th of the full dose) stat and observe for two hours.
- **Optional: if oral challenge is negative,** continue cephalexin 500mg BD for three to seven days to assess for delayed type cephalexin hypersensitivity.

Testing of intermediate/high pre-test probability patients

True IgE-mediated cephalosporin allergy holds the risk for anaphylaxis or death and assessment of an appropriate algorithm for a patient may need to be individualised. It is advisable to refer such patients to a specialised drug allergy centre for further testing.

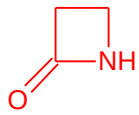
In patients with high pre-test probability of IgE-mediated allergy to a cephalosporin, the aim is to either confirm the culprit cephalosporin and/or find an alternative cephalosporin.

- Use of SPT, IDT and DPT must be assessed against the clinical need to confirm a diagnosis of antibiotic allergy, the risk of a reaction and the effect on clinical management.
- The choice of an ideal alternative BL antibiotic is driven by a number of factors including clinical need, pharmacological and antimicrobial properties of the cephalosporin and potential cross-reactivity between BL antibiotics. Ideally this choice should be made in multidisciplinary consultation with the infectious disease and treating team.
- In cases of severe reaction to cephalosporin, it may be prudent to initially perform IDT with lower concentrations (1:10, 1:100 or 1:1,000 dilutions of the standard IDT reagent) [10]. Perform IDT with gradually increasing concentrations until there is the appearance of a positive skin response, or until the standard testing concentration is reached.

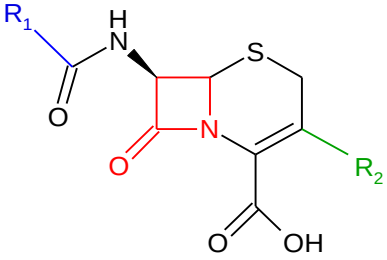
In most cases, if it is deemed necessary to test for allergy to a cephalosporin, skin testing should be followed by DPT (oral or IV) since the validity of skin testing is not established. A graded challenge is recommended with the choice of cephalosporin dependent on the clinical indications for testing.

In patients with a very high likelihood of true allergy but negative testing results, the possibility of resensitisation should be considered and repeat testing with skin testing +/- rechallenge is indicated (Blanca et al., 2009).

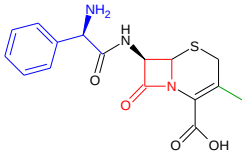
Appendix 1 – Core structures of cephalosporin



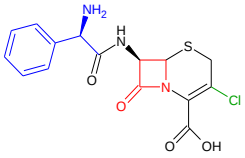
B-lactam ring



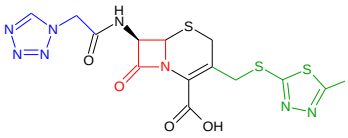
Cephalosporin core



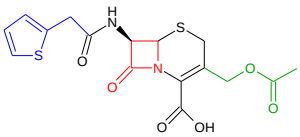
Cefaclor



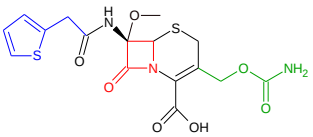
Cefalexin



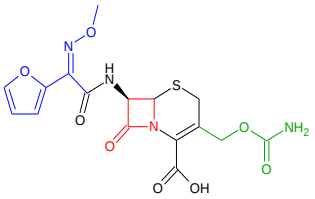
Cefazolin



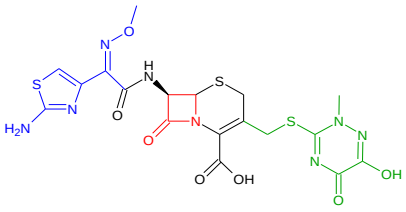
Cefalotin



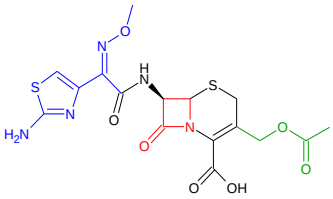
Cefoxitin



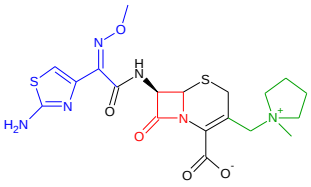
Cefuroxime



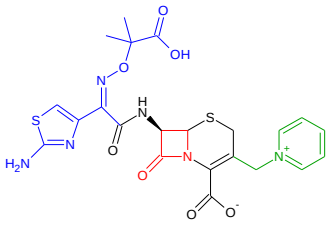
Ceftriaxone



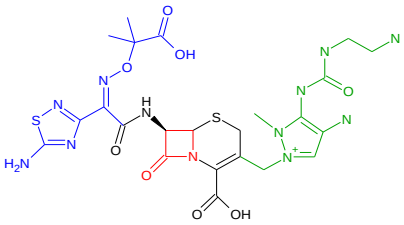
Cefotaxime



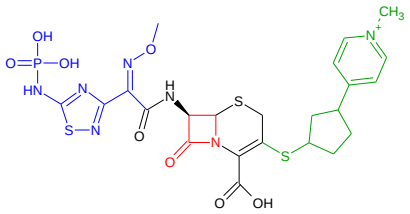
Cefepime



Ceftazidime



Ceftolozane



Ceftaroline

Supplemental Figure 1. Core structures of cephalosporin along with drugs available in Australia and New Zealand (as at 31/08/2017 according to TGA, www.tga.gov.au, and Medisafe, www.medsafe.govt.nz) showing the diversity of the R_1 and R_2 side chains.

Appendix 2 – Cephalosporins with with a R_1 side chain

Table 1: Cephalosporins with a R_1 side chain similar/identical to other β-lactam antibiotics

Groups with shared R_1-side chains		
	Identical	**Similar**
Group A	Ceftriaxone Cefotaxime Cefepime	Cefuroxime* Ceftazidime Ceftolozane Ceftaroline Whilst similar, each of the above side chains are unique.
Group B	Cefaclor Cefalexin Ampicillin	Amoxicillin
Group C1	Cefazolin	
Group C2	Cefalothin** Cefoxitin	Penicillin G**
Group C3	Ceftazidime Aztreonam	Ceftolozane (see also Group A)

* Branch chain moiety (methoxyiminio group) is identical to other Group A cephalosporins, but not whole R_1 side chain.

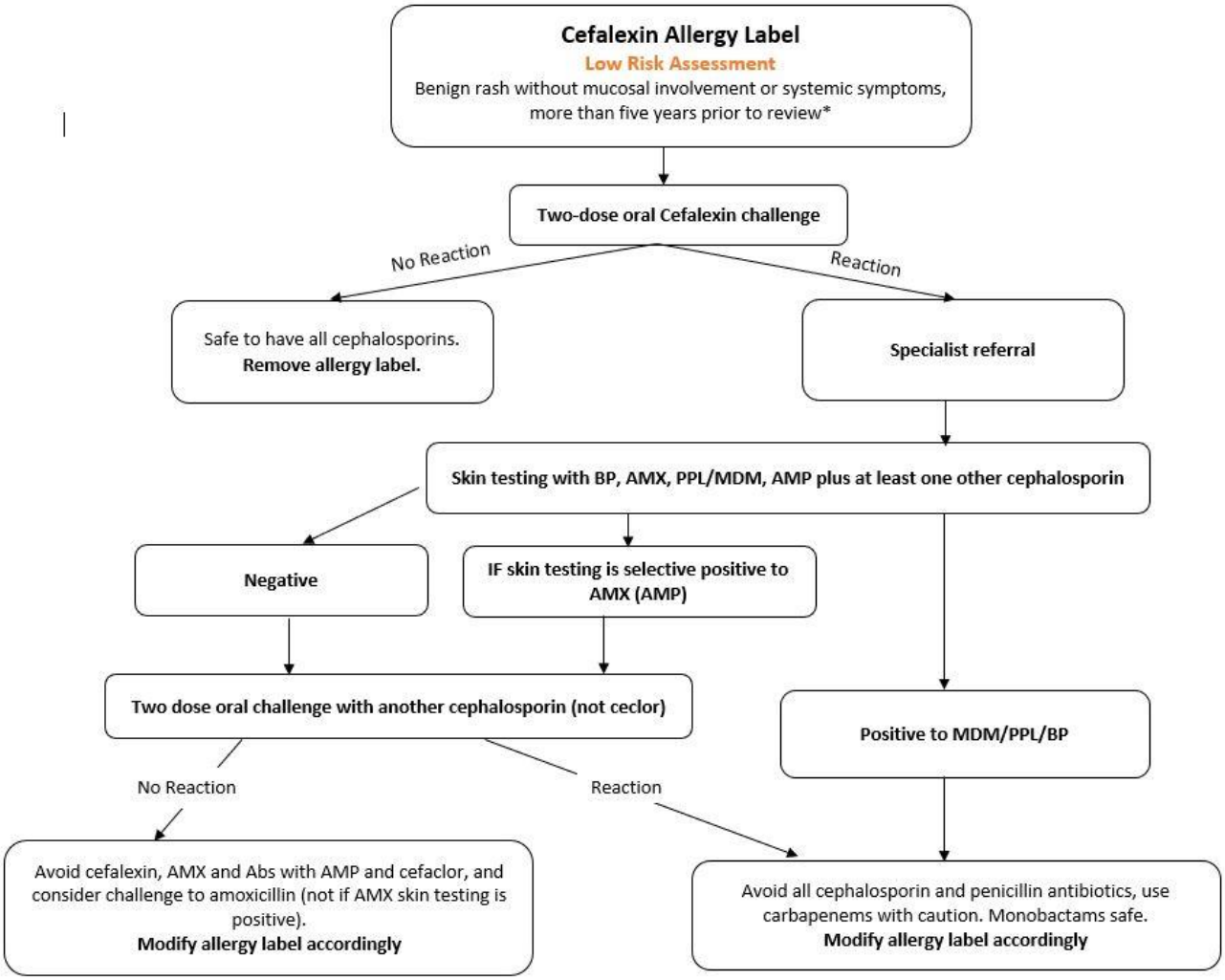
** Cross-reactivity between cefalothin and penicillin G has been attributed to either: the common methylene group in their R_1 side chains or the bioisosterism (similar 3D and steric properties) of the side chains (thiophene and benzene, respectively) Ref – Hasdenteufel *Curr Clin Pharmacol* 2012, Zhao et al. *Clin Exp Allergy,* 2002.

Groups A and B as per Romano et al.,2005.

Table 2: Groups of β-lactam antibiotics with identical R2-side chains

Groups with shared R2-side chains	
	Identical
Group A	Cefotaxime Cefalothin
Group B	Cefuroxime Cefoxitin

Appendix 3 - Cefalexin allergy low risk assessment



* Refer to assessment of cefalexin allergy, page 3.

Appendix 4: Drug allergy testing examples

Example 1

Assessment of a patient who has a **well-documented history** of anaphylaxis to cephalexin within ten minutes of drug exposure (either recently e.g. two months ago or remotely).

Note: Cephalexin should be avoided lifelong (along with cefaclor and ampicillin due to identical shared R_1 side chain +/- amoxycillin). The aim of assessment is to determine tolerance of other BLs, including those with cross-reactive R_1 side chains.

- **Perform SPT:**
  - Histamine (Positive control)
  - Normal Saline (Negative control)
  - Diater PPL® Neat
  - Diater MDM® Neat
  - AMX 20mg/ml
  - BP 10,000 UI/ml (6mg/ml)
  - Ceftriaxone 1mg/ml
  - Cefazolin 1-2mg/ml

- **If SPT is not done, then perform IDT at 1/10 dilutions:**
  - 1:10 diluted Diater PPL®
  - 1:10 diluted Diater MDM® (1:10)
  - AMX 2mg/ml
  - BP 1,000 UI/ml (0.6mg/ml)
  - Ceftriaxone 1mg/ml
  - Cefazolin 1mg/ml

- **If SPT or IDT at 1:10 dilutions is negative, perform IDT to:**
  - Diater PPL® Neat
  - Diater MDM® Neat
  - AMX 20mg/ml
  - BP 10,000 UI/ml (6mg/ml)
  -
  - Ceftriaxone 10mg/ml
  - Cefazolin 10mg/ml

- **If final concentration IDT is negative, perform DPT with three-dose or two-dose cefuroxime challenge:**
  - Give cefuroxime 2.5mg (or 1/100th; optional) and observe for 30-90 minutes.
  - If negative, give cefuroxime 25mg (or 1/10th) and observe for 30-90 minutes.
  - If negative, give cefuroxime 250mg (or full dose) and observe for two hours.

- **At a subsequent visit, perform DPT with three-dose AMX challenge:**
  - Give AMX 2.5mg (or 1/100th) and observe for 30-90 minutes.
  - If negative, give AMX 25mg (or 1/10th) and observe for 30-90 minutes.
  - If negative, give AMX 250mg (or 9/10th) and observe for two hours.

Example 2

Assessment of a patient who had a likely anaphylaxis to cefazolin within 15 minutes after drug exposure in the peri-operative setting two months ago. Other anaesthetic drugs, given contemparoneously, were previously tested and not found to be the cause of the reaction.

Note: Cefazolin should be avoided lifelong. Aim to undertake skin testing within three to six months of reaction. The aim of assessment is to confirm tolerance of other BLs and confirmation of the cefazolin allergy by skin testing.

Once an antibiotic is positive by skin testing, omit the antibiotic from the panel for the next step.

- **Perform SPT:**
  - Histamine (Positive control)
  - Normal Saline (Negative control)
  - Diater PPL® Neat
  - Diater MDM® Neat
  - AMX 20mg/ml
  - BP 10,000 UI/ml (6mg/ml)
  - Ceftriaxone 10mg/ml
  - Cefazolin 10mg/ml

- **If SPT is not done, then perform IDT at 1:10 dilutions:**
  - Diater PPL® 1:10
  - Diater MDM® 1:10
  - Cefazolin 1mg/ml (1:10)
  - AMX 2mg/ml (1:10)
  - BP 1,000 UI/ml (0.6mg/ml) (1:10)
  - Ceftriaxone 1mg/ml (1:10)
- **If prior IDT is negative, perform IDT to:**
  - 1:10 diluted Diater® PPL Neat
  - 1:10 diluted Diater® MDM Neat
  - AMX 20mg/ml
  - BP 10,000 UI/ml (6mg/ml)
  - Ceftriaxone 10mg/ml
  - Cefazolin 10mg/ml
- **If skin test is positive to cefazolin and final concentration IDT against the other antibiotics are negative, perform DPT with two-dose cephalexin challenge:**
  - Give cefalexin 25mg (or 1/10th) and observe for 30-90 minutes.
  - If negative, give cefalexin 250mg (or 9/10th) and observe for two hours.

If all skin testing is negative to cefazolin we recommend still to continue to avoid cefazolin, and to perform a cefalexin challenge as described above. We would not recommend rechallenge to cefazolin.

Cefazolin has a unique R_1 side chain and as such it is likely that the patient will have an allergy to this BL alone. However, anaphylaxis to amoxicillin challenge has been observed in patients with a history of cefazolin anaphylaxis. At present, insufficient data exists to definitively confirm tolerance of other cephalosporins in the absence of additional challenge.

Example 3

Assessment of a patient who has a history of possible anaphylaxis to cefalexin 20 years ago (e.g. history less clear/not well documented).

- **Perform SPT:**
  - Histamine (Positive control)
  - Normal Saline (Negative control)
  - Diater PPL® Neat
  - Diater MDM® Neat
  - AMX 20mg/ml
  - BP 10,000 UI/ml (6mg/ml)
  - Ceftriaxone 10mg/ml
  - Cefazolin 10mg/ml
- **If SPT is not done, then perform IDT at 1:10 dilutions:**
  - 1:10 diluted Diater PPL®
  - 1:10 diluted Diater MDM®
  - Cefazolin 1mg/ml (1:10)
  - AMX 2mg/ml
  - BP 1,000 UI/ml (0.6mg/ml)
  - Ceftriaxone 1mg/ml
- **If SPT or IDT at 1:10 is negative, perform IDT to:**
  - Diater® PPL Neat
  - Diater® MDM Neat
  - AMX 20mg/ml
  - BP 10,000 UI/ml (6mg/ml)
  - Ceftriaxone 10mg/ml
  - Cefazolin 10mg/ml
- **If final concentration IDT is negative, perform DPT with three-dose cephalexin challenge:**
  - Give cefalexin 2.5mg (or 1/100th; optional) and observe for 30-90 minutes.
  - If negative, give cefalexin 25mg (or 1/10th) and observe for 30-90 minutes
  - If negative, give cefalexin 250mg (or in children 9/10th) and observe for 30-90 minutes
- **At a subsequent visit (independent of the outcome of the cefalexin challenge), perform DPT with 1 or 2 dose amoxicillin challenge:**
  - Give amoxicillin 25mg (or 1/10th) and observe for 30-90 minutes.
  - If negative, give amoxicillin 250mg (or 9/10th) and observe for two hours.

If cefalexin challenge is positive, cefaclor and ampicillin should also be strictly avoided.

If both challenges are positive, amoxycillin, cefaclor and ampicillin should be strictly avoided. The patient should then be booked in for a 2 or 3 dose penicillin VK challenge to assess for tolerance of other beta-lactam antibiotics, which do not have a similar or identical side chain to cephalexin.

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