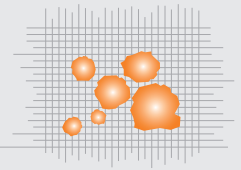


Cephalosporins for people with penicillin allergy?

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Cross-allergy between penicillins and cephalosporins

Interpretation of the literature regarding any cross-allergy between penicillins and cephalosporins is fraught with difficulty. The main issues in the literature concern the definition of the type of allergy, that drug allergies are heterogeneous and multifactorial, and that there has been little or no account taken of the generation of cephalosporin.

Definition of the type of allergy

- Only 80–90% of those with a history of penicillin allergy have a true allergy (see Table 1). Others have experienced a delayed hypersensitivity or 'adverse drug reaction' rather than a Type 1, IgE-mediated allergic response.^{1–6}
- It can be difficult to distinguish between IgE- and non-IgE-mediated hypersensitivity, especially the delayed T-cell-mediated reactions.^{4,5}
- Few people have a 'penicillin allergy' confirmed by skin test.
- For older people the allergy or hypersensitivity may have been due to an impurity in the earlier penicillin products.
- Early cephalosporins contained trace amounts of penicillin, leading to an over-estimate of the cross-hypersensitivity reactions.

Drug allergies are heterogeneous and multifactorial

- For penicillins, an IgE-mediated allergy is most likely to be due to the side chain,^{3,4} but there may be other determinants, such as the β -lactam ring or an unknown hapten. This influences the cross-hypersensitivity rates and predictability.

- People who have a hypersensitivity to penicillin are three times more likely to be hypersensitive to any medicine.⁶ For example, one study found that the people with penicillin hypersensitivity (no IgE/skin testing done) were as likely to have a hypersensitivity reaction to a sulphonamide as to a cephalosporin.²

The generation of cephalosporin is not usually taken into account

- The greatest cross-hypersensitivity appears to be with first generation cephalosporins, less with second generation cephalosporins and there appears to be negligible cross-hypersensitivity with third and fourth generation cephalosporins—but a person may have a hypersensitivity to any cephalosporin independent of any hypersensitivity to penicillin.^{4,6}
- In general practice, oral antibiotics are predominantly used and the oral cephalosporins currently available are first- and second-generation cephalosporins. Ceftriaxone, the once-daily injection, is a third-generation cephalosporin. Hospitals are more likely to use third- and fourth-generation intravenous cephalosporins.

Revised rate of cross-hypersensitivity

The most reliable way to estimate the cross-hypersensitivity rate is to consider studies where IgE testing was undertaken to confirm a true penicillin allergy, and checked for a cross-reaction against a range of cephalosporins. Skin testing for allergy is not perfect, but is currently the best method available for determining IgE-mediated reactions. Using this methodology, cross-hypersensitivity rates range from 4 to 11%, but are dependent on the generation of cephalosporin.^{2,6,9,10}

KEY POINTS

Cross-hypersensitivity ranges from 4 to 11% but is dependent on the generation of cephalosporin, with first-generation cephalosporins having the highest risk.

NUGGETS of KNOWLEDGE provides succinct summaries of pharmaceutical evidence about treatment of common conditions presenting in primary care and possible adverse drug reactions.

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Table 1. Drug hypersensitivity is classified as four types^{12–14}

Type I	Type I is IgE mediated and is 'allergic'. It is an immediate reaction with anaphylaxis, angioedema, urticaria and bronchospasm. The drug or drug metabolite reacts with IgE bound to the surface of the mast cells and leads to the activation, degranulation and release of mast cell-like vasoactive mediators like histamine and tryptase. Non-IgE-mediated are generally but not always delayed, occurring after 72 hours. The reactions are haemolytic anaemia, interstitial nephritis, thrombocytopenia, serum sickness, drug fever, morbilliform eruptions, erythema multiforme, maculopapular exanthema, delayed urticaria, Stevens Johnson syndrome and toxic epidermal necrolysis.
Type II	Type II reactions involve IgG antibodies.
Type III	Type III reactions involve IgG or IgM antibodies.
Type IV	Type IV reactions are T-cell dependent.

Risk mitigation strategies

- Is it clinically equivalent to use an alternative antibiotic?
- If the description of the hypersensitivity suggests an immediate and/or severe reaction, do a skin penicillin sensitivity test to confirm whether the hypersensitivity is IgE mediated.
- If the 'allergy' is to penicillin, then caution is required with cephaloridine, cephalothin, cephmandol⁶ and cefoxitin (similar side chains). Cefuroxime, cefpodoxime, and cefdinir carry less risk.^{1,10}
- If the 'allergy' is to amoxicillin, then caution is required with cephalexin, cephadrine, cefaclor, cefatrizine, cefadroxil and cefprozil.^{1,10}
- Be aware that some people are allergic to cephalosporins and not penicillin.
- A negative skin test may not have identified a minor determinant.
- Before the risk for an immediate reaction can be ruled out, and regardless of skin test results, patients should receive a graded challenge of the drug in question in settings with readily available emergency medical support.¹¹

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