CHANGE PAGE

In patients allergic to penicillin, consider second and third generation cephalosporins for life threatening infections

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The clinical problem

Many patients claim to be allergic to penicillin. For those confirmed as being truly allergic (type 1 allergy, with features of urticaria, pruritic rash, etc), the cited overall rate of 10% cross reactivity between penicillin and cephalosporins is an overestimate.¹ For life threatening infections in which a non-cephalosporin antibiotic would be suboptimal, consider giving a second or third generation cephalosporin: ceftriaxone, cefotaxime, cefuroxime, ceftazidime, as clinically appropriate.

The evidence for change

The term “allergy” is often applied incorrectly by both patients and doctors to any adverse reaction that occurs during treatment with penicillins, and many “adverse effects” are clearly intolerances—for example, nausea, diarrhoea, and vomiting.¹ Many patients who claim to be allergic to penicillin do not have a true (type 1) allergy. Type 1 allergy is defined by a skin test but is clinically recognisable by features of urticaria, laryngeal oedema, bronchospasm, hypotension, or local swelling within 72 hours of administration, or development of a pruritic rash (even after 72 hours). The true incidence of penicillin allergy among such patients is in the region of 7-23% (based on skin prick testing in case series of 776 and 726 patients^{2 3}). The risk of anaphylaxis with cephalosporins is low, between 0.1% and 0.0001% based on a retrospective analysis of toxicity data from 210 clinical trials involving 2539 patients receiving ceftazidime and on postmarketing surveillance data.^{4 5}

The frequently cited figure of 10% cross reactivity between penicillin and cephalosporins seems to be based on data from systematic reviews undertaken in the 1970s of 17 540⁶ and 15 708 patients which examined allergy to cephalosporins among patients allergic to penicillin and non-allergic patients.^{7 8} These reviews overestimate the true rate of cross reactivity because until 1982, compounds related to penicillin had been produced commercially by using the cephalosporium mould and the cephalosporins included in the analyses were contaminated with penicillin.⁹ Additionally, patients with a penicillin allergy seem to have three times the risk of adverse reactions to other drugs¹⁰—a factor not accounted for in these reviews. Furthermore, the definition of allergy in the reviews was imprecise and included cases of cross sensitivity (not true allergy). These methodological limitations have resulted in an overestimation of cross reactivity between penicillin and cephalosporins generally.

A narrative review that showed a lack of cross reactivity between second and third generation cephalosporins and penicillins¹ is endorsed by a meta-analysis that pooled data from six studies of 2387 patients with reported

penicillin allergy and 44897 with no such history and showed the risk of cross reactivity was related to cephalosporin generation.¹¹ It found an odds ratio of 4.79 (95% confidence interval 3.71 to 6.17) for an allergic reaction to a first generation cephalosporin or cefamandole in patients allergic to penicillin and odds ratios of 1.13 (0.61 to 2.12) and 0.45 (0.18 to 1.13) for second and third generation cephalosporins, respectively.

Thus, first generation cephalosporins with a chemical side chain similar to penicillin have the potential for cross reactivity, but the attributable risk is closer to 0.5% than 10%. Second and third generation cephalosporins, such as ceftriaxone, cefotaxime, cefuroxime, and ceftazidime, are unlikely to be associated with cross reactivity as they have different side chains to penicillin.

Barriers to change

Cross reactivity between penicillin and cephalosporins of 10% is widely quoted, and the problem is compounded by a poor understanding of the clinical assessment of drug allergy and its implication for prescribing. Fear of litigation promotes a “safety first” approach which, although appropriate in many circumstances, may not include an assessment of the likely risks of withholding effective drug treatment.

How should we change our practice?

All patients reporting allergy to penicillin should be questioned to determine the likelihood of true allergy, and assessed as to whether their symptoms are consistent with a type 1 allergic reaction. Patients with no evidence of type 1 allergy to penicillin may be treated with any cephalosporin for infections of any severity.

Patients who have had symptoms suggesting type 1 allergy to penicillin should avoid all cephalosporins for mild or moderate infections when a suitable alternative antibiotic exists. In life threatening infections, when use of a non-cephalosporin antibiotic would be suboptimal, consider giving, under observation, a second or third generation cephalosporin with a different side chain to the penicillin under suspicion.

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Evidence for change

We searched Medline (1966 to present), EMBASE (1980 to present), and the Cochrane Library to identify published randomised controlled trials and systematic reviews that assessed the potential for cross reactivity between penicillins and cephalosporins. We also reviewed reference lists of selected articles to identify relevant published evidence.

KEY POINTS

True penicillin allergy occurs in 7-23% of patients who give a history of penicillin allergy

The frequently cited figure of 10% cross reactivity between penicillin and cephalosporins is an overestimate

Cross reactivity between penicillins and second and third generation cephalosporins is low and may be lower than the cross reactivity between penicillins and unrelated antibiotics

Anaphylaxis with cephalosporins is rare (0.1-0.0001%)

In life threatening infections consider using second and third generation cephalosporins even in patients with a history of penicillin allergy