

Is there a 10% cross-sensitivity between penicillins and cephalosporins?

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Date prepared: 11th October 2018

Background

Penicillins are among the most useful and frequently prescribed antibiotics (1). However, as with all medicines they can cause adverse reactions. These include allergic reactions ranging from mild rash to life threatening anaphylaxis (2).

According to standard reference texts, penicillin allergy is common, occurring in 1 – 10% of those taking the drug (1, 2). Life threatening problems are much rarer, with anaphylactic reactions occurring in up to 0.05% of treated patients and a fatal outcome in about 5 – 10 % of treated patients (3).

The cephalosporins are broad-spectrum antibiotics with similar pharmacology to penicillins (4). The incidence of reported adverse reactions due to cephalosporin antibiotics range from 1% to 10% (5). These reactions are mainly rashes, eosinophilia, fever, gastrointestinal symptoms, haematological manifestations and phlebitis (5). Anaphylaxis is rare (1:1,000 to 1:10,000) (6).

It is commonly taught that approximately 10% of patients who are allergic to penicillin will have an adverse reaction to cephalosporins (7, 8). The chemical structure is similar between cephalosporins and penicillins in the form of a common beta-lactam ring which allows potential for allergic cross-reactivity. Additionally, some cephalosporins and penicillins share identical side chains which are another source of potential cross-reactivity (9). This potential cross-reactivity has important therapeutic implications because many serious infections are best treated with cephalosporins as first line therapy (7).

However, within the medical literature this quoted cross-allergy risk of 10% has been questioned (1, 10-15). The widely cited rate of 10% cross-sensitivity to cephalosporins among penicillin allergic patients appears to be based on data collected and reviewed in the 1960s and 1970s and results of in vitro (immunological) tests that were not supported by clinical skin tests in penicillin-sensitive patients (15).

Reviews which reported allergic reactions in 7.7% and 8.1%, respectively, of “penicillin allergic” patients included the first generation cephalosporins cephaloridine, cephalexin, cephalothin and cefazolin, and the second generation agent cefamandole. These rates provided the 10% estimate of risk of allergic reactions to cephalosporins in patients allergic to penicillin (15-19).

Answer

A meta-analysis published in 2007 identified reasons why a 10% cross-sensitivity between penicillins and cephalosporins may be an overestimate (15). These include:

- Studies conducted have not taken into consideration the coincidental 3-fold increased risk of adverse reactions to any unrelated drugs in penicillin allergic patients (note that this does not mean you can divide the quoted cross-reactivity figures by 3 as a certain proportion of patients will still cross-react. Whether these patients are hypersensitive is incidental because it cannot be predicted in advance).
- Studies have loosely defined allergy, including reports of patients with unspecified rashes in their analyses.
- Before 1980, first generation cephalosporins were produced by the cephalosporium mould, later shown to be contaminated with trace amounts of penicillin.

In addition to the reasons above, the side chain molecular structure of the cephalosporins has been identified as an important determinant of the immune response (19). Cephalosporins bearing a side chain similar to benzylpenicillin are possibly more likely to cross-react with penicillin (19) but this conclusion is based on limited data (9).

A review of pooled data from six studies involving a total of 2,387 patients with reported penicillin allergy and 44,897 with no such history showed the risk of cross reactivity was related to cephalosporin generation and, correspondingly, to side chain configuration. Meta-analysis showed an odds ratio of an allergic reaction to any cephalosporin in subjects with penicillin or amoxicillin allergy by history alone was increased (4% of patients with a history of penicillin allergy reacted vs. 1.4% of patients with no previous history of penicillin allergy, OR = 2.63; 95% CI = 2.11 to 3.28; $P < 0.00001$). The first generation cephalosporins and cefamandole (not licensed in the UK) share a chemical side chain similar to penicillin or amoxicillin. Meta-analysis of pooled data from four studies showed that the odds ratio of an allergic reaction to a first generation cephalosporin (plus cefamandole) in penicillin-allergic patients was increased (7.6% of patients with a history of penicillin allergy reacted vs. 1.4% of patients with no previous history of penicillin allergy, OR = 4.79; 95% CI = 3.71 to 6.17; $P < 0.00001$). Second and third generation cephalosporins generally have different side chains from penicillin and amoxicillin, and these agents were not associated with any increase in the risk of cross-reactivity in penicillin (15, 19).

Cross allergy of three first generation cephalosporins was subjected to meta-analysis when there were at least two studies that reported results. An increased rate of an allergic reaction to cephalothin (OR = 2.5; 95% CI = 1.13 to 4.42; $P = 0.02$), cephaloridine (OR = 8.74; 95% CI = 5.95 to 12.84; $P < 0.00001$), and cephalexin (OR = 5.78; 95% CI = 3.62 to 9.21; $P < 0.00001$) was calculated (15).

The rationale above is supported by guidelines for the management of acute otitis media and acute sinusitis published by the American Academy of Paediatrics (AAP). These recommend the use of specific second and third generation cephalosporins (cefuroxime, cefpodoxime and cefdinir) in penicillin allergic patients provided that the penicillin reaction was not severe (urticaria or anaphylaxis) or a "Type 1" allergy (20, 21). 'Type 1' allergy, or immediate reaction, is often associated with the systemic manifestations of anaphylaxis, such as diffuse erythema, pruritis, urticaria, angioedema, bronchospasm, laryngeal oedema, hyperperistalsis, hypotension, or cardiac arrhythmias, either alone or in combination. The allergy is classed as an IgE-mediated reaction (19, 22).

It is extremely important that when patients state they have a history of penicillin allergy, the authenticity of this information should be probed. A retrospective cohort study involving 11,872 patients and conducted in one US hospital found that having a documented allergy in the patient's medical record to any antimicrobial was associated with an increased length of hospital stay. On average this was found to be 1.21 days (unadjusted) and 1.16 days (adjusted for covariates) longer for patients with a documented antimicrobial allergy compared with those patients without a documented allergy. Patients with a documented antimicrobial allergy also had a significantly higher intensive care unit admission rate (17.52% vs. 12.02%, adjusted OR 1.42; 95% CI 1.21 – 1.67); received more than one antimicrobial (62.24% vs 50.58%, adjusted OR 1.51; 95% CI 1.33 – 1.70); and a higher mortality rate during their hospital stay (5.1% vs. 3.4%, adjusted OR 1.52, 95% CI 1.16 – 2.00) compared with those patients without a documented allergy (23).

The information necessary for an allergy history is provided in table 1 (22, 24, 25). Very often the drug was not actually taken, patients cannot recall their allergic response or a recognised non-immunologic side effect, e.g. vomiting, diarrhoea, or a non-specific rash occurred instead (19, 23). It is therefore accepted that many patients who present with a history of penicillin allergy have not had an immunological reaction to penicillin (23).

Detailed description of the reaction, including symptoms, severity, duration	History of other antibiotics taken since the reaction and outcome
Route of drug administration and duration of therapy	Presence of a medical alert bracelet
Interval between initiation of therapy and reaction (timing of onset)	Whether skin testing has ever been performed (and if so, the results)
What happened when the antibiotic was stopped; did the reaction require treatment?	Consideration of possible causes of the reaction (antibiotic, other drugs, disease)
How long ago the reaction occurred (patient's age at time of reaction)	

The following recommendations are taken from American publications which include a meta-analysis and clinical practice guideline for prescribing cephalosporins in patients with a penicillin allergy (8, 18).

Non-IgE-Mediated Reaction

An IgE mediated reaction manifests as bronchospasm, angioedema, hypotension, urticaria, or a pruritic rash. If the rash is nonurticarial and nonpruritic, then it is almost certain that the rash is not IgE mediated and the risk of recurrence of the same rash with repeated courses of the same antibiotic is not increased. In uncertain cases, elective penicillin skin testing is advisable (19). However, there are a number of limitations associated with such testing, e.g. commercially available allergens used may not reflect the exact chemical structure of the antibiotic, but this discussion is outside the scope of this review.

If a patient has experienced a reaction to a penicillin or cephalosporin that was not IgE mediated and was not serious, it is safe to administer repeated courses of that antibiotic and related antibiotics. Only IgE mediated reactions are likely to become more severe with time and to result in anaphylaxis (8, 19).

IgE-Mediated Reaction

Penicillin G

If the patient has a history that is consistent with a severe, IgE mediated reaction to Penicillin G, then cephalosporins with a similar 7-position side chain on the beta-lactam ring should be avoided. These include cefoxitin and cephalothin, both of which are not licensed in the UK (4, 8, 19).

Amoxicillin/Ampicillin

If the allergic reaction followed administration of ampicillin or amoxicillin, then cephalosporins with a similar side chain should be avoided. These include cefaclor, cefradine, cefalexin and cefadroxil (8, 19, 26).

Reviews of the evidence suggest that other cephalosporins with different side chains are unlikely to produce allergic reactions among penicillin- or amoxicillin allergic patients compared to non-allergic patients. These might include cefuroxime, cefixime, ceftriaxone and ceftazidime amongst others (8, 19, 26).

Reviews of the evidence in 2005 and 2014 to support the AAP recommendations for prescribing cephalosporins in patients allergic to penicillin with sinusitis or otitis media, concluded coincidental allergic reactions to cephalosporins occur among penicillin/amoxicillin allergic patients (19, 27). The

authors suggest that a predictable, immunologically causal link for allergic reactions may occur with first generation cephalosporins (0.5% increased attributable risk) but most second- and third-generation agents are unlikely to be associated with cross-reactivity based on differences in their chemical structures compared to penicillins and early cephalosporins (19). Anaphylaxis from cephalosporins is rare. There is no evidence of an increased risk of anaphylaxis to cephalosporins in penicillin allergic patients (27).

More recent literature reviews have concluded that the overall cross-reactivity rate for penicillin allergic patients is approximately 1% when using first-generation cephalosporins or cephalosporins with similar R1 side chains (e.g. cefaclor, cefadroxil, cephalexin, cephadrine). First and second generation cephalosporins with different R1 side chains can be given. For penicillin-allergic patients, third or fourth-generation cephalosporins or cephalosporins with dissimilar side chains than the offending penicillin can be used as they carry a negligible risk of cross allergy (28). A further review published in 2014 states that the average cross-reactivity rate between penicillins and cephalosporins was 4.32%, with the rates being less than 1% for the third- and fourth-generation cephalosporins (29). This review also states that around 2% of patients with positive penicillin skin tests will react to cephalosporins, which may include anaphylaxis.

The information contained in the 56th and subsequent editions of the BNF now states that the hypersensitivity rate between penicillins and cephalosporins is 0.5% - 6.5% (4, 30). In the UK, there is not a document similar to the AAP review recommending specific cephalosporin antibiotics for penicillin allergic patients with sinusitis or otitis media. Therefore, the latest prescribing information or specialist advice should always be consulted when considering the potential use of cephalosporin antibiotics in patients allergic to penicillin antibiotics.

Summary

- It is commonly taught that approximately 10% of patients who are allergic to penicillin will have an adverse reaction to cephalosporins. However, within the medical literature this quoted cross-allergy risk of 10% has been questioned.
- The widely cited rate of 10% cross-sensitivity to cephalosporins among penicillin allergic patients appears to be based on data collected and reviewed in the 1960s and 1970s and results of in vitro (immunological) tests that were not supported by clinical skin tests in penicillin-sensitive patients.
- A meta-analysis published in 2007 identified the reasons why a 10% cross-sensitivity between penicillins and cephalosporins may be an overestimate.
- The American Academy of Paediatrics (AAP) recommends prescribing cephalosporins in patients allergic to penicillin for sinusitis or otitis media. A review of the evidence to support the recommendation concluded coincidental allergic reactions to cephalosporins occur among penicillin/amoxicillin allergic patients. The authors suggest that a predictable, immunologically causal link for allergic reactions may occur with first generation cephalosporins (0.5% increased attributable risk) but most second- and third-generation agents are unlikely to be associated with cross-reactivity based on differences in their chemical structures compared to penicillins and early cephalosporins.
- The information contained in the 56th and subsequent editions of the BNF now states that the hypersensitivity rate between penicillins and cephalosporins is 0.5% - 6.5%. In the UK, there is not a document similar to the AAP review recommending specific cephalosporin antibiotics for penicillin allergic patients with sinusitis or otitis media. Therefore, the latest prescribing information or specialist advice should always be consulted when considering the potential use of cephalosporin antibiotics in patients allergic to penicillin antibiotics.

Limitations

The lists of cephalosporins provided as examples are not exhaustive. This does not take into account local guidelines for prescribing antibiotics in patients who are allergic to penicillin.

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10/09/2018

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Date of check

24/10/18

Search strategy

- In-house Databases including British National Formulary, Martindale, AHFS DI, The Infectious Diseases Manual, Principles and Practice of Infectious Diseases
- Embase: "(exp CROSS ALLERGY/) AND ((exp DRUG HYPERSENSITIVITY/) AND (exp PENICILLIN DERIVATIVE/)) [Limit to: Human and Publication Year 2016-2018]"; "((exp PENICILLIN DERIVATIVE/) OR (exp CEPHALOSPORIN DERIVATIVE/)) AND (exp CROSS ALLERGY/)" [Limit to: Human and Publication Year 2016-2018]
- Medline: "((exp CROSS REACTIONS/) AND ((exp PENICILLINS/) OR (exp CEPHALOSPORINS/))) [Limit to: Humans and Publication Year 2016-2018]"