Prescribing Cephalosporins to Penicillin-allergic Patients

a report by
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The American Academy of Pediatrics (AAP) has recently issued practice guidelines for the management of acute bacterial sinusitis. These guidelines recommend specific second- and third-generation cephalosporin antibiotics (cefuroxime, cefpodoxime, and cefdinir) for patients with penicillin allergies, assuming that the penicillin reaction is not severe (anaphylaxis, Stevens-Johnson syndrome, toxic epidermal necrolysis, or drug-induced hypersensitivity syndrome).[1] However, many physicians remain reluctant to prescribe such agents, as rates of cross-sensitivity to cephalosporins among penicillin-allergic patients have been cited as 8% to 18%.[2,3] Nevertheless, the AAP guidelines are evidence-based – they recognize that a lack of consistent data regarding exactly what constitutes an initial penicillin-allergic reaction and subsequent cross-sensitivity to cephalosporins may be preventing many patients from receiving optimal antibiotic therapy.

The presumption of cross-reactivity may stem from early reviews of the literature concerning allergy to first-generation cephalosporins among penicillin-allergic patients. Such reviews[2–4] evaluated samples of first-generation cephalosporins that were contaminated with trace amounts of penicillin,[5,6] and did not accurately define allergy (they included unspecified rashes), therefore they overestimated cross-sensitivity. Anaphylactic reactions were also reported in patients with a penicillin allergy in the years following the introduction of cephaloridine and cephalothin,[7,8] and subsequent *in vitro* testing showed significant cross-reactivity between penicillin and cephaloridine and cephalothin.[9–11] However, the clinical relevance of the *in vitro* cross-reactions was never demonstrated, and skin tests with cephalosporin C among penicillin-sensitive patients failed to confirm any allergic cross-reactivity.[12]

The true risk of an allergic reaction to a cephalosporin among penicillin-allergic patients should take into consideration the possibility of a primary and unrelated cephalosporin allergy. To date, studies have not clearly established the risk attributable to penicillin allergy when an allergic reaction follows cephalosporin treatment.

Types of Immunologically Mediated Reactions

Adverse drug reactions can be categorized by immunological mediators.[13] Immunoglobulin E (IgE)-mediated reactions (type I – immediate hypersensitivity reactions) are the most dangerous – they are the only true allergic reactions. The presence of IgE antibodies in penicillins and cephalosporins is predictive of possible subsequent, immediate, IgE-mediated, allergic hypersensitivity reactions that can range from urticaria to anaphylaxis. However, any patients with detectable IgE antibodies do not display a clinical allergic reaction. After receiving penicillin, most patients produce immunoglobulin G (IgG) and immunoglobulin M (IgM) antibodies, which may cross-react with cephalosporins; however, the presence of these antibodies is not predictive of adverse consequences and does not necessarily predict allergic cross-sensitivity. In fact, type II (IgG-mediated) or III (IgG- or IgM-mediated) reactions are rarely induced by beta-lactam antibiotics, and are not allergic. Similarly, contact dermatitis (type IV or delayed hypersensitivity) reactions and idiopathic reactions are not allergic reactions.

Recommendation

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. Similarly, a cephalosporin may be given to a patient who has experienced a non-IgE-mediated adverse reaction (a type II, III, IV, or idiopathic reaction) to a penicillin. Only IgE-mediated reactions are likely to become more severe with time and result in anaphylaxis. IgE-mediated reactions usually manifest as bronchospasm, angioedema, hypotension, urticaria, or a pruritic rash. If the rash was neither urticarial nor pruritic, then it is unlikely that the rash was IgE-mediated and there is no increased risk of the same rash recurring with repeated courses of the same antibiotic. Elective penicillin skin testing can be used in uncertain cases.

If the patient has a history that is consistent with a severe IgE-mediated reaction to penicillin or ampicillin/

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Table 1: Grouping Penicillins and Cephalosporins According to Chemical Structures of Seven-position Side-chains[25]

Similar structure/ possible cross-reactivity within group			Dissimilar structure/unlikely cross-reactivity	
Related	**Related**	**Related**	**Not related**	**Not related**
Penicillin G	Amoxicillin	Cefotaxime	Cefsulodin	Cefotiam
Cephaloridine	Ampicillin	Ceftizoxime	Cefazolin	Ceftazidime
Cephalothin	Cefaclor	Ceftriaxone	Cefonicid	Cefamandole
Cefoxitin	Cephalexin	Cefpodoxime	Cefotetan	Cephapirin
	Cephradine	Cefpirome	Cefuroxime	Cefixime
	Cefprozil	Cefepime	Cefoperazone	Cefmetazole
	Cefatrizine	Cefetamet	Cefdinir	Ceftibuten
	Cefadroxil	Cefteram		Moxalactam

amoxicillin, then cephalosporins with a similar side-chain should be used with caution (see *Table 1*). Other cephalosporins with different side-chains are no more likely to produce allergic reactions among penicillin- or ampicillin-/amoxicillin-allergic patients than among non-allergic patients.

Use of Skin Testing

Skin testing is an important means of confirming or refuting a history of allergy and of predicting which patients are at risk of developing IgE-mediated drug-reactions. Positive skin tests are approximately 60% predictive of clinical hypersensitivity to penicillins.[14–18] Predictive values for skin testing with cephalosporins are not as well established and the haptens responsible for cephalosporin allergy are not known.

Penicillin skin testing is not predictive of cephalosporin allergy unless the side-chain of the penicillin or ampicillin reagent is similar to that of the cephalosporin under evaluation. Even so, detection of cross-reactive IgE antibodies does not predict a definite clinical reaction. Cephalosporin skin testing may be useful for detecting IgE antibodies to the specific agent used in testing and other cephalosporins with similar side-chains.

Incidence of Penicillin Allergy

When a patient gives a history of penicillin allergy, it is advisable to probe the authenticity of this information. Very often the drug was not actually taken, or a recognized non-immunological adverse event occurred, such as vomiting, diarrhea, or a non-specific rash. The true incidence of penicillin-allergy among patients with that history is likely to be less than 10%.[18–22]

Incidence of Cephalosporin Allergy

Cephalosporins cause allergic or immune-mediated reactions among 1% to 3% of patients.[23] Most allergic reactions are rashes, which occur in 1% to 2.8% of patients.[24] Without the ability to prospectively detect patients with IgE antibodies to penicillin and without the ability to distinguish true IgE immunological reactions from idiopathic reactions among patients who are given cephalosporins, it is impossible to claim increased immune or IgE-mediated reactions to cephalosporins among truly penicillin-allergic (IgE) patients.

A considerable body of evidence has established that the immune response to cephalosporins is more dependent on their side-chain molecular structure than is the case for penicillins.[25] Cephalosporins with side-chains similar to penicillin or ampicillin/amoxicillin (see *Table 1*) are more likely to react with penicillin or ampicillin/amoxicillin, respectively. In contrast, agents such as cefuroxime and cefdinir, which have a dissimilar seven-position side-chain to penicillin and ampicillin/amoxicillin, are highly unlikely to produce a reaction among penicillin- or ampicillin-/amoxicillin-allergic patients. Patients with an allergic reaction to a specific cephalosporin are more likely to react to another cephalosporin with a similar side-chain.

Recommendation

A patient who has experienced an allergic reaction to a specific cephalosporin should probably not receive that cephalosporin again. However, the risk of a drug reaction when a different cephalosporin is administered appears to be very low or non-existent if the side-chains of the drugs are not similar.

Incidence of Cross-reactivity Between Cephalosporins and Penicillins

Penicillins and cephalosporins have similar chemical configurations – both classes are of low molecular weight, are highly substituted, and possess a beta-lactam ring on which antimicrobial activity depends.[26] They differ in that penicillin has a five-membered thiazolidine ring that is replaced with a six-membered dihydrothiazine ring in cephalosporins. Importantly, they also differ in their degradation pattern, as penicillins form a stable penicilloate ring and cephalosporins undergo rapid fragmentation of the beta-lactam and dihydrothiazine rings.[10,27,28] On the basis of these differences in degradation, immunologic cross-reactivity between the beta-lactam rings of these compounds should be minimal. This conclusion is supported by monoclonal antibody analyses[29,30] and clinical studies (see *Table 2*). Numerous studies have reported outcomes in patients with a history of allergy to penicillin, or skin test confirmation of penicillin allergy, and who received cephalosporins (see *Table 2*). Results of these studies indicate that the rate of reaction depends on which generation of cephalosporin is used – first-generation agents demonstrate an increased rate of reaction that is not observed with second- or

Table 2: Proportions of Patients with 'Allergic Reactions' to Cephalosporins, According to Cephalosporin Generation, Penicillin Allergy History, and Penicillin Skin Test Results[25]

Cephalosporin	Penicillin allergy history but no skin testing, number (%)		p	Penicillin skin allergy test confirmed, number (%)		p
	Yes	No		Yes	No	
First-generation (reported attributable)	83/1,043 (7.9)[4,12,31–35]	458/32,885 (1.4)[3,4,31,33–35]	<0.0001	15/138 (10.9)[3,9,36–40]	2/63 (3.2)[3,14]	0.12
Second-generation[b]	11/585 (1.9)	112/675 (1.7)	0.82	5/269 (1.9)[36–38]	6/497 (1.2)	0.69
Third-generation[b]	5/772 (0.6)[23,41,42]	77/5,452 (1.4)[41]	0.12	2/259 (0.8)[38,39]	7/497 (1.4)	0.68

a. The term 'allergic reaction' is used as applied in each study, but review indicates that a proportion of the reactions were not allergic. These values are therefore likely to be over-estimates.
b. Data included in each calculation from the author's unpublished prospective case series, with history and skin-testing techniques as described by Pichichero et al.[19]

third-generation agents. This increased incidence of allergic reactions to cephalosporins among penicillin-allergic patients, attributable to cross-reactive antibodies, appears to be dependent on whether the chemical side-chain of the cephalosporin is similar to that of penicillin or amoxicillin. When considering the information in *Table 2*, it should be remembered that there is a three-fold increased coincidental risk of adverse reactions to unrelated drugs among penicillin-allergic patients.[17] For the agents endorsed by the AAP for sinusitis (cefuroxime, cefpodoxime, and cefdinir), the risk is negligible. Few studies have been conducted to evaluate cross-reactivity with penicillin among cephalosporin-allergic patients. Results of available studies indicate that less than 20% of cephalosporin-allergic patients react to skin tests with classic penicillin determinants, but most have positive responses to other cephalosporins with the same or similar chain structure (see *Table 1*).[5,43,44]

Anaphylaxis

The incidence of anaphylaxis with penicillins is low – approximately 0.004% to 0.015%.[20] Data concerning cephalosporins are more limited, but anaphylaxis also appears uncommon with these agents (0.0001% to 0.1%).[24] There is no evidence of an increased risk of anaphylaxis with cephalosporins among penicillin-allergic patients.[23]

Conclusion

Coincidental allergic reactions to cephalosporins occur among penicillin/amoxicillin-allergic patients. A predictable, immunological causal link for allergic reactions may occur with early-generation cephalosporins, but has no evidence base for most second- or third-generation agents. ■

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