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Cephalosporin Administration to Patients With a History of Penicillin Allergy

Adverse Reactions to Drugs, Biologicals and Latex Committee

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INTRODUCTION

Penicillins and cephalosporins share a common beta-lactam ring structure, and hence the potential for IgE-mediated allergic cross-reactivity. Allergic cross-reactivity between penicillins and cephalosporins potentially may also occur due to presence of identical or similar R-group side chains, in which case IgE is directed against the side chain, rather the core beta-lactam structure. This work group report will address the administration of cephalosporins in patients with a history of penicillin allergy. First, published data will be reviewed regarding 1) cephalosporin challenges of patients with a history of penicillin allergy (without preceding skin testing or *in vitro* testing), and 2) cephalosporin challenges of patients proven to have a type I allergy to penicillins (via positive penicillin skin test, *in vitro* test or challenge). Secondly, recommendations on cephalosporin administration to patients with a history of penicillin allergy

will be presented. Unless specifically noted, the term ‘penicillin allergy’ will be used to indicate an allergy to one or more of the penicillin-class antibiotics, not just to penicillin itself.

The following discussion includes references, in certain clinical situations, to performing cephalosporin graded challenges in patients with a history of penicillin allergy. It should be noted that a comparison establishing increased safety by administering cephalosporins via graded challenge vs full administration has not been done. Additionally, there is no single standard method for graded challenges regarding starting dose and number of steps. For formal evaluation of specific allergies to penicillins and cephalosporins, patients should seek advice from an allergist/immunologist.

CEPHALOSPORIN CHALLENGES OF PATIENTS WITH HISTORY OF PENICILLIN ALLERGY WITHOUT PRECEDING ALLERGY TESTING

Table 1 summarizes results of five published retrospective studies in which patients with a history of penicillin allergy were treated with cephalosporins without preceding penicillin allergy testing (skin testing or *in vitro* testing). In the two older studies from the 1970’s,^{1,2} no information was provided on the nature of the cephalosporin reactions. In the Goodman et al study, a patient with a history of penicillin allergy was assumed to have had a reaction because hydrocortisone and diphenhydramine were administered after induction of spinal anesthesia. However, there was no record of symptoms or signs of an allergic reaction. Since the patient was on chronic corticosteroid treatment, an alternate explanation is that the hydrocortisone served as a stress dose and the antihistamine may have been given as a sedative.³ In the Daulat et al study, the only cephalosporin reaction in a patient with a history of penicillin allergy was worsening of eczema after several days of treatment, and this is not consistent with an IgE-mediated mechanism.⁴ In the Fonacier study, most of the 7 reported cephalosporin reactions

were consistent with a possible IgE-mediated mechanism.⁵ However, in addition to the 83 reported patients with a history of penicillin allergy who were treated with cephalosporin, there were 103 other patients who did not return their surveys. If none of the remaining 103 patients developed a reaction to cephalosporins, the reaction rate would have been reduced to 7/186, or 3.8%.

Retrospective studies evaluating cephalosporin reactions in patients with a history of penicillin allergy have many limitations:

- The vast majority of patients were probably not penicillin-allergic at time of treatment with cephalosporins, since only about 10% of all patients who report a history of penicillin allergy are penicillin skin test-positive.⁶⁻⁸
- Since these were ‘real world’ studies, there was probably a selection bias in deciding which patients with a history of penicillin allergy were given cephalosporins instead of non-beta-lactam antibiotics. Physicians were probably less likely to treat with cephalosporins if patients had more severe or recent penicillin reaction histories. In some cases, pharmacists intervened to prevent patients with severe penicillin allergy histories from receiving cephalosporins.⁴
- Cephalosporins produced prior to 1980 are known to have been contaminated with trace amounts of penicillin,⁹ which means that some reactions to cephalosporins in patients with a history of penicillin allergy (in the two studies from the 1970’s) may have been due to penicillin instead.
- None of these retrospective studies included a control group of patients, such as individuals with a history of penicillin allergy who were treated with a non-beta-lactam antibiotic. It is known that patients who have reacted to one drug are more likely to react

to another unrelated drug.¹⁰⁻¹² One would expect an increased rate of reactions to all classes of antibiotics in patients with a history of penicillin allergy. Consequently, some patients with a history of penicillin allergy who reacted to cephalosporins may have manifested a second unrelated allergy due to their underlying multiple drug allergy syndrome. Using the United Kingdom General Practice Research Database, Apter et al evaluated the incidence of allergic-like events to cephalosporins and sulfonamides in patients with a previous documented penicillin allergic-like event.¹³ They found that the relative risk for an allergic-like event was elevated for both cephalosporins (10.1, CI 7.4-13.8) and sulfonamides (7.2, 3.8-13.5).¹³

CEPHALOSPORIN CHALLENGES IN PENICILLIN SKIN TEST-POSITIVE PATIENTS

Table 2 summarizes reports in which patients with positive penicillin skin tests (to major and minor penicillin determinants) were challenged with cephalosporins. Prior to cephalosporin administration, some investigators also performed cephalosporin skin testing and administered cephalosporins only if those tests were negative.¹⁴⁻¹⁷ In most studies, no cephalosporin skin testing was performed. Since the positive predictive value of cephalosporin skin testing is unclear, it is unknown whether patients who were excluded from receiving cephalosporins by virtue of positive cephalosporin skin testing would have reacted to the antibiotic.

The overall reaction rate to cephalosporins in penicillin skin test-positive patients is 3.4%; the reaction rate since 1980 is 2.0% (Table 2). Most of the reactions were to 1st and 2nd generation cephalosporins, and two potential mechanisms may account for this observation. First, early 1st and 2nd generation cephalosporins may have been contaminated with trace amounts of penicillin, whereas 3rd generation cephalosporins, which did not exist prior to 1980, would not be subject to this possible bias. Secondly, earlier generation cephalosporins contain

R1 group side chains that are similar in structure to benzylpenicillin, which was the main penicillin used at that time (rather than semisynthetic penicillins). Therefore, some penicillin-allergic patients may have reacted to cephalosporins by virtue of cross-reacting IgE antibodies directed at the R group side chains, rather than IgE directed at the core beta-lactam portion of the molecule. Side chain-specific reactions suggest that penicillin-allergic patients who react to cephalosporins with similar side chains would be able to tolerate cephalosporins with dissimilar side chains, but there are no data to prove this theory.

Two studies (Miranda et al and Sastre et al) have formally evaluated clinical cross-reactivity between a penicillin-class antibiotic and a cephalosporin that share identical R group side chains.^{18,19} In these studies, patients proven to be selectively allergic to amoxicillin (i.e., not reactive to penicillin) were challenged in open fashion with cefadroxil. The R group side chain of amoxicillin is identical to the R1 group side chain of cefadroxil. In the Miranda et al study, 8/21 (38%) amoxicillin-allergic patients reacted to cefadroxil, and in the Sastre et al study, 2/16 (12%) of patients reacted to cefadroxil.^{18,19} These data indicate that clinical cross-reactivity between penicillins and cephalosporins that share identical R group side chains is higher than the overall clinical cross-reactivity observed in penicillin skin test-positive patients (which is 3.4%, as described above). It is unknown whether data on cross-reactivity between penicillins and cephalosporins with identical R group side chains can be extrapolated to penicillins and cephalosporins that share similar (but not identical) side chains. There are no analogous studies evaluating cross-reactivity of penicillins/cephalosporins with similar R group side chains.

Studies of penicillin skin test-positive patients challenged with cephalosporins are subject to fewer limitations than if penicillin allergy is based on history alone, but potential limitations include:

- Cephalosporin challenges were generally carried out in open fashion, rather than single or double-blinded. Therefore, while negative cephalosporin challenges unequivocally proved the absence of an IgE-mediated allergy, some ‘positive’ challenges may not be indicative of truly allergic reactions. Patients with a history of allergic drug reactions are susceptible to manifesting a nocebo effect (untoward reaction following administration of an inert substance). For example, reactions to placebo occurred in 27% of 600 patients with a history of drug allergy during single-blinded drug challenges, and they included objective findings such as hypotension, rashes and respiratory abnormalities.²⁰ As a result, positive drug challenges, such as with cephalosporins in penicillin skin test-positive patients, must be interpreted with caution.
- There were no control groups of patients to account for possible multiple drug allergy syndrome. Examples of potential control groups are 1) penicillin skin test-positive patients challenged with a non-beta-lactam antibiotic and 2) patients with a confirmed allergy to a non-beta-lactam antibiotic challenged with cephalosporins.

RECOMMENDATIONS – IF PENICILLIN SKIN TESTING IS UNAVAILABLE

Validated penicillin skin test reagents are presently commercially unavailable in the United States. Additionally, even if the full set of reagents comes to market, situations may arise in which penicillin skin testing is not feasible. Such examples include rural settings without a nearby allergist/immunologist or urgent need for antibiotics in a hospital setting. Without the availability of validated penicillin skin test reagents, it is difficult to determine, based on history alone, whether patients have an IgE-mediated allergy to penicillins. Overall, about 10% of patients who report a history of penicillin allergy are penicillin skin test-positive.⁶⁻⁸ Therefore, the vast majority of patients with a history of penicillin allergy who are treated with

cephalosporins are not at risk of an allergic reaction on the basis of cross-reactivity with penicillins. However, the rate of positive penicillin skin tests is influenced by the type of reaction history and by how much time has elapsed since the reaction occurred. As a result, patients who are more likely to be truly penicillin-allergic may be at increased risk of a cephalosporin reaction by virtue of cross-reacting IgE antibodies.

Daulat et al and Goodman et al are the 2 most informative studies of cephalosporin administration to patients with a history of penicillin allergy.^{3,4} They contain large sample sizes, their results are not confounded by possible presence of trace amounts of penicillin in cephalosporins, the cephalosporin reactions are based on chart review rather than patient recall, and they clearly delineate the cephalosporin reactions.^{3,4} Out of a combined 906 patients with a history of penicillin allergy treated with mostly intravenous 1st generation cephalosporins, there was one questionable IgE-mediated reaction. Patients with severe penicillin allergy reaction histories were likely not treated with cephalosporins and hence not included in these studies.

From this information, it is reasonable to conclude that among all-comers with a history of penicillin allergy, if one excludes patients with more severe reaction histories, there is an extremely low chance of developing cephalosporin-induced allergic reactions. There are no absolute criteria of what constitutes a previous "severe" penicillin reaction, but presumably a history of anaphylaxis should be considered as such. Also, more recent penicillin reactions probably indicate a higher likelihood of IgE-mediated penicillin allergy than distant reactions, since penicillin-specific IgE antibodies are known to wane over time.²¹ When a decision to initiate cephalosporin therapy in a patient with a history of penicillin allergy is based on the reaction history, clinician should consider and weigh the benefit of treatment against the risk of inducing a potential reaction. The treating physician may also choose to administer the first

cephalosporin dose via graded challenge, rather than as a single full dose. The most typical method of performing such a graded challenge is to administer 1/10 of the full dose, followed an hour later by the full dose. A formal comparison establishing increased safety by administering medications, such as cephalosporins, via graded challenge vs full administration has not been done.

Consideration may be given to performing cephalosporin skin testing in patients with a history of penicillin allergy prior to cephalosporin administration. However, positive and negative predictive values of cephalosporin skin testing are uncertain. One study reported no cephalosporin reactions (100% negative predictive value) in a large group of penicillin-allergic patients who underwent skin testing with cephalosporins (2 mg/ml concentration).¹⁴ There are descriptions of IgE-mediated reactions in such patients despite negative cephalosporin skin testing.²² Additionally, cephalosporin skin testing concentrations are not standardized; intradermal cephalosporin skin testing (which should only follow a negative prick/puncture test) has been reported using concentrations ranging from 1 mg/cc to 100 mg/cc.^{14-16,22-25} Because of this, it is not possible to recommend a single cephalosporin skin test concentration.

Limited data indicate 12-38% clinical cross-reactivity rate between a penicillin and cephalosporin with identical R group side chains (see Table 3).^{18,19} Therefore, if identity of the penicillin responsible for a patient's reaction is known, then cephalosporins that share the same R group side chain should be avoided. For example, patients who report reactions to amoxicillin should avoid cefadroxil, cefprozil, and cefatrizine. Similarly, patients with a history of allergy to ampicillin should avoid cephalixin, cefaclor, cephadrine, cephaloglycin, and loracarbef.

RECOMMENDATIONS – IF PENICILLIN SKIN TESTING IS AVAILABLE

Patients found to be negative on penicillin skin testing are not at increased risk of allergic reactions to cephalosporins and no special precautions need to be undertaken. However, some penicillin skin test-negative patients may still react to cephalosporins due to R group side chain-specific IgE antibodies or due to multiple drug allergy syndrome. *In vitro* tests for penicillin allergy are less sensitive and have poorer negative predictive value than penicillin skin testing.^{26,27} For this reason, patients with negative *in vitro* tests for penicillin allergy are more likely to be penicillin-allergic than penicillin skin test-negative patients. As a result, patients with negative *in vitro* tests for penicillin allergy may be at higher risk of reacting to cephalosporins compared to penicillin skin test-negative patients. Therefore, additional caution should be exercised when patients with negative *in vitro* tests for penicillin allergy are treated with cephalosporins.

Overall, penicillin skin test-positive patients reacted to cephalosporins 3.4% of the time, according to the published literature (Table 2). Limitations of these studies include potential contamination of cephalosporins with penicillin prior to 1980, lack of blinding of challenges, and lack of inclusion of control groups. Based on more limited data, 12-38% of patients selectively allergic to amoxicillin (i.e., able to tolerate penicillin) reacted to a cephalosporin with an identical R1 group side chain (cefadroxil).^{18,19}

Because of an increased chance of experiencing allergic reactions, patients found to be positive on penicillin skin testing should either avoid cephalosporins or receive them cautiously, via graded challenge or rapid desensitization. The approach to patients with positive *in vitro* tests for penicillin allergy is identical to that of penicillin skin test-positive patients. Unlike desensitization, a graded challenge does not modify the immune response, but rather is a more cautious method of administration of the drug. A typical method of performing oral

cephalosporin graded challenge is to administer 1/10 the full dose, followed an hour later by the full dose. Since antibiotic administration via a parenteral route is probably more likely to cause severe IgE-mediated reactions than oral administration, more caution should be exercised during parental graded challenge. In this case, 1/1000 the full dose, 1/10 the full dose, and the full dose are administered in hourly intervals under observation. While graded challenge is commonly recommended, a formal comparison of the safety of administering medications, such as cephalosporins, via graded challenge vs full administration has not been done. Also, since in clinical practice graded challenge is largely reserved for low risk patients, who are unlikely to react anyway, it remains to be established as to whether it offers any advantage over slowed initial administration under direct observation. Rapid desensitization with cephalosporins has been described using protocols analogous to penicillin desensitization,²⁸⁻³¹ and it can be accomplished orally or intravenously.

Cephalosporin skin testing of penicillin skin test-positive patients may be considered prior to treatment with cephalosporins.¹⁴⁻¹⁷ However, positive and negative predictive values of cephalosporin skin testing are uncertain. One study reported no cephalosporin reactions (100% negative predictive value) in a large group of penicillin-allergic patients who underwent skin testing with cephalosporins (2 mg/ml concentration).¹⁴ If cephalosporin skin testing is negative, the cephalosporin should be administered via 2-step graded challenge, as described previously. If cephalosporin skin testing is positive, the cephalosporin should be avoided or administered via rapid desensitization.

Patients who are found to have a positive skin test to amoxicillin, ampicillin or another semisynthetic penicillin should avoid cephalosporins with identical side chains (Table 3). Therefore, patients skin test-positive to amoxicillin should avoid cefadroxil, cefprozil, and

cefatrizine. Similarly, patients skin test-positive to ampicillin should avoid cephalexin, cefaclor, cephadrine, cephaloglycin, and loracarbef. If treatment with these cephalosporin is necessary, it should be administered via rapid desensitization.

ROLE OF PENICILLIN SKIN TESTING IN PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY PRIOR TO CEPHALOSPORIN ADMINISTRATION

At the present time, penicilloyl polylysine (Pre Pen) is commercially unavailable in the US, and therefore fully valid penicillin skin testing cannot be performed. When a full set of penicillin skin test reagents becomes available, ideally all patients with a history of penicillin reactions consistent with a possible IgE-mediated reaction should be evaluated by an allergist/immunologist.³² An evaluation for penicillin allergy is negative in most individuals, has been found to be cost effective, and decreases use of broad spectrum antibiotics (such as fluoroquinolones and vancomycin), which are associated with more potential toxicity and antibiotic resistance.^{8,33-38} By virtue of a negative evaluation for penicillin allergy, most patients with a history of penicillin allergy are able to receive cephalosporins without an elevated risk of reactions.

RECOMMENDATIONS FOR FUTURE RESEARCH

The question of allergic cross-reactivity between penicillins and cephalosporins does not yet have unequivocal answers. Additional research is needed to clarify uncertainties brought up in this practice paper. Ideally, future studies will be constructed using better scientific method, such as incorporating 1) prospective design, 2) blinding of drug challenges, 3) placebo challenges, and 4) control/comparison groups. Additionally, to allow for larger sample sizes, collaborative efforts among different centers should be encouraged.

The following are examples of types of possible protocols that will serve to advance knowledge of penicillin/cephalosporin cross-reactivity.

- Reaction rates in patients with a history of penicillin allergy (no skin testing), determined by double blind administration of:
 - 1st generation cephalosporins
 - 2nd generation cephalosporins
 - 3rd generation cephalosporins
 - Macrolide or sulfonamide antibiotic
 - Placebo
- Cephalosporin reaction rates (determined by double blind administration) in patients (no skin testing):
 - With a history of penicillin allergy
 - With a history of sulfonamide or macrolide allergy
 - Without a history of drug allergy
- Reaction rates in patients who are skin test-positive to core penicillin antigens (penicilloyl polylysine, minor determinants), determined by double blind administration of:
 - 1st generation cephalosporins
 - 2nd generation cephalosporins
 - 3rd generation cephalosporins
 - Macrolide or sulfonamide antibiotic
 - Placebo
- Reaction rates in patients skin test-positive to only amoxicillin or ampicillin (not to other penicillin antigens), determined by double blind administration of:

- Cephalosporins with identical side chains (such as cefadroxil for amoxicillin-allergic patients and cefaclor for ampicillin-allergic patients)
- Cephalosporins with dissimilar side chains
- Macrolide or sulfonamide antibiotic
- Placebo

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Table 1. Summary of studies of cephalosporin challenges in patients with a history of penicillin (pcn) allergy without preceding penicillin allergy testing

Cephalosporin Reaction Rate

Reference	History of pcn allergy	No history of pcn allergy	Cephalosporins administered
Dash CH	25/324 (7.7%)	140/17,216 (0.8%)	Cephalexin and cephaloridine
Petz LD	57/701 (8.1%)	285/15,007 (1.9%)	Cephalexin, cephaloridine, cephalothin, cefazolin and cefamandole
Goodman EJ	1/300 (0.3%)	1/2,431 (0.04%)	Cefazolin (in all but one patient)
Daulat SB	1/606 (0.17%)	15/22,664 (0.07%)	1 st generation (42%), 2 nd generation (21%), 3 rd /4 th generation (37%)
Fonacier L	7/83 (8.4%)	Not reported	1 st generation (59%), 2 nd generation (8.4%), 3 rd generation (25%), 4 th generation (7%)

Table 2. Summary of penicillin skin test-positive patients challenged with cephalosporins, excluding those patients skin test-positive to only amoxicillin or ampicillin (and not to major and/or minor penicillin determinants)

Cephalosporins

Reference	# of patients	# of reactions	Skin testing	Comment
Girard JP (1968)	23	2 (8.7%)	No	Both reactions to cephaloridine
Assem ESK (1974)	3	3 (100%)	No	All reactions to cephaloridine
Warrington RJ (1978)	3	0	Yes	
Solley GO (1982)	27	0	No	
Saxon A (1987)	62	1 (1.6%)	No	Cephalosporin not noted
Blanca M (1989)	16	2 (12.5%)	No	Both reactions to cefamandole
Shepherd GM (1993)	9	0	No	
Audicana M (1994)	12	0	Yes	
Pichichero ME (1998)	39	2 (5.1%)	No	Reaction to cefaclor and unknown agent
Novalbos A (2001)	23	0	Yes	
Macy E (2002)	42	1 (2.4%)	No	Reaction to cefixime
Romano A (2004)	75	0	Yes	
Greenberger PA (2005)	6	0	No	
Park MA	37	2 (5.4%)	No	Cephalosporins not noted
Total	377	12 (3.4%)		

Table 3. List of penicillins and cephalosporins that share identical R-group side chains

<u>Ampicillin</u>	<u>Amoxicillin</u>
Cefaclor	Cefadroxil
Cephalexin	Cefprozil
Cephradine	Cefatrizine
Cephaloglycin	
Loracarbef	