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Diagnosis and Management of Immediate Hypersensitivity Reactions to Cephalosporins

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Abstract Cephalosporins are one of the most commonly prescribed classes of antibiotics. Immediate IgE-mediated hypersensitivity reactions have been reported with use of a specific cephalosporin, as a cross-reaction between different cephalosporins or as a cross-reaction to other β-lactam antibiotics, namely, penicillin. Historically, frequent reports of anaphylaxis following administration of first- and second-generation cephalosporins to patients with a history of penicillin allergy led to the belief of a high degree of allergic cross-reactivity. More recent evidence reveals a significantly lower risk of cross-reactivity between penicillins and the newer-generation cephalosporins. The current thought is that a shared side chain, rather than the β-lactam ring structure, is the determining factor in immunologic cross-reactivity. Understanding the chemical structure of these agents has allowed us to identify the allergenic determinants for penicillin; however, the exact allergenic determinants of cephalosporins are less well understood. For this reason, standardized diagnostic skin testing is not available for cephalosporins as it is for penicillin. Nevertheless, skin testing to the cephalosporin in question, using a nonirritating concentration, provides additional information, which can further guide the work-up of a patient suspected of having an allergy to that drug. Together, the history and the skin test results can assist the allergist in the decision to recommend continued drug avoidance or to perform a graded challenge versus an induction of tolerance procedure.

Keywords Cephalosporins · Immediate hypersensitivity · IgE mediated · Diagnosis · Management

Introduction

Owing to their broad spectrum of activity and low toxicity profile, cephalosporins have emerged as one of the most commonly prescribed classes of antibiotics for the treatment of various sinopulmonary, skin, and soft tissue infections. In the past, allergic reactions to cephalosporins were considered primarily in conjunction with penicillin allergy; however, as cephalosporin use has increased, the prevalence of immediate hypersensitivity reactions to specific cephalosporins also appears to be on the rise [1]. Unlike penicillin, in which the chemical structure of the allergenic determinants is known, the exact allergenic determinants of cephalosporins have not yet been elucidated. Consequently, standardized diagnostic skin testing for cephalosporin allergy is not available, often creating a diagnostic dilemma for the consulting allergist.

In this article, we review the diagnosis and management of immediate, IgE-mediated hypersensitivity reactions to cephalosporins, with special focus on the use of nonirritating skin testing, graded challenges, and induction of drug tolerance procedures. An OVID and PubMed search using keywords “immediate hypersensitivity” and “cephalosporin” yielded over 100 related articles, which were reviewed, and the most relevant references were selected for inclusion in this article.

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Background

Chemical Structure and Classification of Cephalosporins

The antibiotic class of cephalosporins consists of five generations of cephalosporins and the closely related cephamycins (cefoxitin and cefotetan). Cephalosporins are semisynthetic derivatives of cephalosporin C, an antibacterial compound first isolated from the cultures of the fungus *Cephalosporium acremonium*, whereas the cephamycins, generally regarded as second-generation cephalosporins, are derived from various *Streptomyces* species.

As members of the β-lactam class of antibiotics, cephalosporins consist of a six-membered dihydrothiazine ring fused to a core, four-membered cyclic amide β-lactam ring with two side chains, R_1 and R_2 (Fig. 1). Variation in the spectrum of activity and duration of action of individual cephalosporins depends on the different side chains bound to the "R" sites. The grouping of cephalosporins into generations is based on their clinical spectrum of activity (Table 1).

Determining Antigenic Elements

The immunologic behavior of different β-lactam antibiotics is determined by their degree of chemical instability. In penicillins, the condensed fusion of the β-lactam ring structure with a thiazolide ring (Fig. 1) causes increased tension within the β-lactam ring, resulting in spontaneous opening of the ring. This allows the highly reactive carbonyl group to bind easily to the amino groups of plasma and cell-surface proteins, forming the highly stable conjugate protein, benzyl penicilloyl [3]. Benzyl penicilloyl, the major antigenic determinant of benzylpenicillin, comprises approximately 95 % of cell-bound penicillin [4]. The remaining portion of penicillin can degrade further into various minor antigenic determinants, primarily penicilloate and penilloate. The predictable degradation of penicillin into stable major and minor antigenic determinants enables penicillin skin testing to be standardized, thus creating a reliable tool in the diagnosis of IgE-mediated penicillin allergy.

In contrast, the core cephalosporin structure is less reactive, leading to slower protein conjugation. Eventual opening of the β-lactam ring produces a highly unstable protein conjugate, termed the cephalosporyl determinant, which undergoes further degradation as the dihydrothiazine ring ruptures, creating multiple antigenic fragments [5]. The creation of several unstable degradation products makes the isolation and identification of cephalosporin antigenic determinants variable and complex. As a result, standardization of cephalosporin skin testing has not yet been achieved.

Despite the difficulty in identifying the specific antigenic elements responsible for immediate hypersensitivity reactions to cephalosporins, several studies have demonstrated that cephalosporins generate unique structures capable of provoking an IgE-mediated immunologic response. Different studies cite serological and clinical evidence that IgE antibodies reacting with various cephalosporins recognize portions of a side chain, such as the methylene group [6, 7], full-side chains [6, 8–14], a combination of a side chain and part of the β-lactam ring [1, 3, 15, 16], and even the entire cephalosporin molecule [17–21]. Therefore, immediate hypersensitivity reactions can be to a specific cephalosporin, to multiple cephalosporins that have identical or similar side chains, or as a cross-reaction to other β-lactam antibiotics.

Cross-Reactivity Among Cephalosporins

Cross-reactivity among cephalosporins appears to be due to the similarity of the side chains, R_1 and R_2. During cephalosporin degradation, the dihydrothiazine ring ruptures, leading to the subsequent expulsion of the R_2 group. The R_1 group remains intact and appears to contribute more to the allergenicity and cross-reactivity of cephalosporins, compared to the lost R_2 group [3]. However, evidence from in vitro studies demonstrates that cross-reactivity occurs between cephalosporins with identical or similar R_1-side chains and between those cephalosporins with similar R_2-side chains [16, 19, 22] (Tables 2 and 3). Findings from multiple case reports reinforce these conclusions. Romano et al. [23] described a patient with a history of a severe, immediate hypersensitivity reaction to ceftriaxone, who demonstrated cross-reactivity with cefotaxime, which has an identical R_1-side chain. Similarly, Saenz de San Pedro et al. [24] reported a patient who displayed cross-reactivity between cefuroxime and cefotaxime, which possess very similar R_1-side chains. Furthermore, Orhan et al [9] showed evidence of cross-reactivity between cefepime, cefotaxime, ceftriaxone, and ceftazidime, likely due to their identical or similar R_1-side chains.

With regards to cross-reactivity due to similar R_2-side chains, Romano et al. [12] described a patient with an

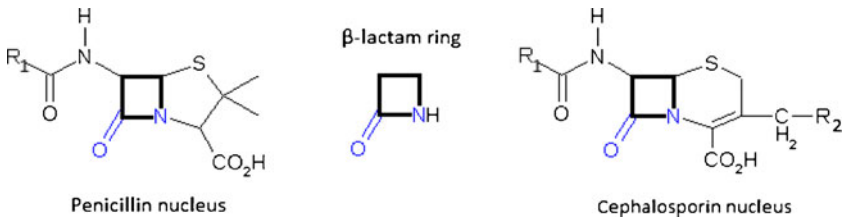

Fig. 1 The basic chemical structures of penicillins and cephalosporins

Table 1 Classification of Cephalosporins and Spectrum of Activity [2]

First generation	Second generation	Third generation	Fourth generation	Fifth generation
Cefadroxil	Cefaclor	Cefdinir	Cefepime	Ceftaroline
Cefatrizine	Cefamandole	Cefditoren		
Cefazolin	Cefmetazole	Cefetamet		
Cephalexin	Cefminox	Cefixime		
Cephaloglycin	Cefonicid	Cefmenoxime		
Cephaloridine	Cefotetan	Cefodizime		
Cephalothin	Cefotiam	Cefoperazone		
Cephapirin	Cefoxitin	Cefotaxime		
Cephradine	Cefprozil	Cefpiramide		
	Cefuroxime	Cefpodoxime		
	Loracarbef	Cefsulodin		
		Ceftazidime		
		Ceftibuten		
		Ceftizoxime		
		Ceftriaxone		
		Moxolactam		
Spectrum of activity	Gram-positive cocci coverage	Gram-negative cocci coverage		
First generation	Good	Poor		
Second generation	Poor	Good		
Third generation	Poor	Excellent		
Fourth generation	Good	Excellent		
Fifth generation	Good	Excellent		

anaphylactic reaction to cefoperazone who displayed positive skin test results to both cefoperazone and cefamandole, which share an identical R_2-side chain.

Selective immediate hypersensitivity reactions to individual cephalosporins have also been reported [12, 19, 20, 25–29]. In these cases, the patients showed lack of cross-reactivity with all other cephalosporins evaluated, demonstrating the possibility that the entire cephalosporin molecule may be involved in hypersensitivity.

Classification of Hypersensitivity Reactions

Historically, immunologic reactions to drugs were divided into four categories, based on the Gell and Coombs [30]

Table 2 β-Lactam antibiotics sharing identical or similar R_1-side chains [4, 9, 24, 43]

Identical R_1-side chain groups						
1	2	3	4	5	6	7
Amoxicillin	Ampicillin	Ceftriaxone[c]	Cefoxitin[b]	Cefamandole[b]	Ceftazidime[c]	Cefepime[d] [9]
Cefadroxil[a]	Cefaclor[b]	Cefotaxime[c]	Cephaloridine[a]	Cefonicid[b]	Aztreonam	Cefotaxime[c]
Cefprozil[b]	Cephalexin[a]	Cefpodoxime[c]	Cephalothin[a]			Ceftriaxone[c]
Cefatrizine[a]	Cephradine[a]	Cefditoren[c]				
	Cephaloglycin[a]	Ceftizoxime[c]				
	Loracarbef[b]	Cefmenoxime[c]				
Similar R_1-side chain groups						
1	2	3	4	5	6	
Cefaclor[b]	Cefuroxime[b] [24]	Ceftazidime[c] [9]	Ceftazidime[c] [9]	Ceftazidime[c] [9]	Benzylpenicillin [43]	
Cefadroxil[a]	Cefotaxime[c]	Ceftriaxone[c]	Cefotaxime[c]	Cefepime[d]	Cephalothin[a]	

[a] First generation cephalosporin

[b] Second generation cephalosporin

[c] Third generation cephalosporin

[d] Fourth generation cephalosporin

Table 3 Cephalosporins sharing identical R_2-side chains [4]

Identical R_1-side chain groups					
1	2	3	4	5	6
Cephalexin[a]	Cefotaxime[c]	Cefuroxime[b]	Cefotetan[b]	Cefaclor[b]	Ceftibuten[c]
Cefadroxil[a]	Cephalothin[a]	Cefoxitin[b]	Cefamandole[b]	Loracarbef[b]	Ceftizoxime[c]
Cephradine[a]	Cephaloglycin[a]		Cefmetazole[b]		
	Cephapirin[a]		Cefpiramide[c]		

[a]First generation cephalosporin
[b]Second generation cephalosporin
[c]Third generation cephalosporin

hypersensitivity reactions, types I to IV. More recently, the World Allergy Organization recommended dividing immunologic drug reactions into immediate reactions (onset within 1 h of exposure) and delayed reactions (onset after 1 h of exposure), based upon the timing of the appearance of symptoms [31].

For the clinician, a practical approach would be to identify a reaction as IgE-mediated or non-IgE-mediated as it could aid in the diagnosis and management of the drug reaction (Table 4). Immediate reactions and some delayed reactions [31] are regarded as IgE mediated. Symptoms associated with IgE-mediated drug reactions include pruritis, urticaria, angioedema, laryngeal edema, wheezing, and/or cardiorespiratory collapse [4].

Non-IgE-mediated reactions comprise a wide group of delayed reactions, including type II (cytotoxic), type III (immune complex), and type IV (cell mediated) hypersensitivity reactions [30], as well as other reactions caused by mechanisms not identified by the categories above [32]. Symptoms of non-IgE-mediated reactions can include maculopapular eruptions, delayed-appearing urticaria and/or angioedema, hemolytic anemia and other blood dyscrasias, serum sickness, Stevens–Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN).

IgE-Mediated Reactions to Cephalosporins

The majority of allergic reactions to cephalosporins consist of cutaneous rashes, occurring in 1–2.8 % of patients [33]. In most cases, the reactions occur within 24 h of drug exposure, and their mechanism is unknown [34]. Studies indicate the incidence of anaphylactic reactions to cephalosporins is rare, with a relative risk ranging from 1:1,000 to 1:1,000,000 [34–40]. However, cases of anaphylaxis leading to death are reported [41–43], and as the prevalence of cephalosporin use increases, so do the cases of anaphylaxis [1].

Cross-Reactivity with Penicillin

Retrospective studies during the 1960s and 1970s reported that patients who had a history of penicillin allergy and were not previously skin tested to penicillin, reacted with administration

Table 4 Classification of drug hypersensitivity reactions [30, 31]

Immunologic type	Gell–Coombs classification	Time of onset	Clinical signs	Skin testing indicated
IgE-mediated	Type I	Immediate (<1 h)	Urticaria	Yes
		Delayed (>1 h)[a]	Angioedema	
			Laryngeal edema	
			Wheezing	
			Hypotension	
Non IgE-mediated	Type II	Delayed (>1 h)	Hemolytic anemia	No
			Thrombocytopenia	
			Neutropenia	
	Type III	Delayed (>1 h)	Serum sickness	No
			Drug fever	
			Vasculitis	
			Tissue injury	
	Type IV	Delayed (>1 h)	Contact dermatitis	No
			Maculopapular rash	
			Stevens–Johnson Syndrome	
			Toxic epidermal necrolysis	
			Interstitial nephritis	

Ig immunoglobulin
[a]Some IgE-mediated reactions appear after 1 h, particularly with oral administration of a drug. However, the majority of IgE-mediated reactions, which may lead to severe anaphylactic reactions, occur within the first hour after drug administration [31].

of a cephalosporin approximately 10 % of the time. This cited rate was based on the widely referenced reviews of Dash [44] and Petz [45, 46], which reported allergic reactions in 7.7 % [44] and 8.2 % [45, 46], respectively, of "penicillin allergic" patients (diagnosed on patient history alone) who received either first-generation or second-generation cephalosporins. The high cross-reactivity described by Dash and Petz is likely due to the fact that before the 1980s, some of the early first-generation cephalosporins were contaminated with trace amounts of penicillin [47]. Moreover, all penicillin allergic patients who reacted to a cephalosporin before 1980 had been treated with the first-generation cephalosporins, cephalothin, and cephaloridine, which share similar side chains with benzylpenicillin. Additionally, the authors' more liberal use of the term "allergy" might not have taken into account the fact that penicillin-allergic patients have a 3-fold increased risk of adverse reaction to any medication [48].

This is in contrast to a more recently reported risk of cephalosporin allergy of <1 % in those patients with a personal history of penicillin allergy, who did not undergo previous penicillin skin testing [4], and approaching 2 % in patients with a history of penicillin allergy with a positive penicillin skin test [49–52].

The similarity in the chemical structures of penicillins and cephalosporins has led to the perception that a high rate of cross-reactivity exists between the two. However, findings from lab studies comparing the differences in degradation pathways of penicillins and cephalosporins indicate that the β-lactam ring structure alone is less likely the cause of cross-reactivity reactions. Upon degradation, penicillin forms a stable penicilloate ring, with preservation of the thiazolidine ring, while cephalosporin degradation leads to destruction of both the β-lactam and dihydrothiazine rings, producing various unstable antigenic fragments [5, 53–56]. These findings are supported by two studies using monoclonal antibody analysis.

Experiments with monoclonal antibodies in mice by Nagakura et al. [57] demonstrated that nearly all antibodies recognize unique cephalosporin epitopes, with little or no recognition of penicillins. A second study by Mayorga et al. [58] evaluated the antigenic contribution of different regions of the penicillin molecule, by introducing monoclonal antibodies raised against amoxicillin-protein conjugates. None of the antibodies recognized the thiazolide ring or the conjugated nuclear region of the penicillins. However, 11 of 12 monoclonal antibodies recognized an epitope in which the side chain was the major constituent.

A number of studies indicate that the R_1-side chain shared by some penicillins and cephalosporins, rather than the β-lactam ring structure, is the determining factor in immunologic cross-reactivity [1, 59–65]. The aminopenicillins, amoxicillin, and ampicillin share the same R_1-side chain with several first- and second-generation cephalosporins, (Table 2) and consequently, the rate of cross-reactivity between these antibiotics has been shown to be as high as 38 %. Miranda et al [66] and Sastre et al. [67] identified 8 of 21 (38 %) and 2 of 16 (12.5 %) patients, respectively, with confirmed amoxicillin allergy, who developed immediate reactions after administration of cefadroxil, a first-generation cephalosporin with an identical R_1-side chain. Furthermore, Audicana et al. [62] reported that 31 % of patients allergic to ampicillin reacted to cephalexin, which possess identical R_1-side chains. A recent meta-analysis confirmed a positive trend toward increased cephalosporin cross-reactivity in patients with positive skin tests to penicillin or amoxicillin when administered a first-generation cephalosporin [68]. Therefore, amoxicillin-allergic patients should avoid or receive via induction of drug tolerance cefadroxil, cefprozil, and cefatrizine. Likewise, patients allergic to ampicillin should avoid or receive via induction of drug tolerance cephalexin, cefaclor, cephradine, cephalogylcin, and loracarbef.

Cross-reactivity has been reported to occur infrequently between penicillins and first-, second-, third-, and fourth-generation cephalosporins with different side chains. Blanca et al. [63] reported that 17 of 19 (89.4 %) patients with a known penicillin allergy tolerated challenges to a therapeutic dose of a first-generation (cephaloridine) and a second-generation (cefamandole) cephalosporin with dissimilar side chains to penicillin. In a study by Novalbos et al. [69], all 41 patients with confirmed penicillin allergies, who were skin test negative to three cephalosporins with dissimilar side chains to penicillin [i.e., cefazolin (first-generation), cefuroxime (second-generation), and ceftriaxone (third-generation)], tolerated an incremental 2-day challenge with the respective cephalosporin. Similarly, Romano et al. [49] skin tested 128 penicillin-allergic patients to first-generation (cephalothin), second-generation (cefamandole and cefuroxime), and third-generation (ceftazidime, cefotaxime, and ceftriaxone) cephalosporins with different side chains compared to penicillin. Fourteen (10.9 %) were skin test positive to one or more of the cephalosporins. Of the 128 patients, 101 (7 skin test positive patients and 94 skin test negative patients) tolerated a graded challenge using second-generation (cefuroxime) and third-generation (ceftriaxone, ceftazidime) cephalosporins.

Diagnosis and Management of Immediate Hypersensitivity to Cephalosporins

Patient History

In the evaluation of a patient presenting with a suspected cephalosporin allergy, a detailed history must be obtained in order to determine the proper management strategy. Important components of the history should include the identification of the exact cephalosporin used, what R-group side

chain the cephalosporin possesses, through what route the antibiotic was administered (i.e. oral, intravenous, or intramuscular) and whether or not the patient has had any previous reactions to penicillins or other cephalosporins. The evaluating physician should obtain a detailed description of the presenting symptoms, which organ systems were involved, and the severity of the reaction. Key to the evaluation is the timing of the reaction in relation to administration of the cephalosporin, as it will help in categorizing the reaction as immediate (IgE mediated) or delayed (non-IgE mediated).

Finally, information should also be obtained regarding the type of illness for which the antibiotic was prescribed, any possible reactions to foods, and what other medications the patient was taking.

Skin Testing

The exact allergenic determinants of cephalosporins have not yet been identified, preventing standardization of diagnostic cephalosporin skin testing. However, Empedrad et al. [70] proposed that eliciting a positive skin test result using a concentration of a free, whole drug that is known to be nonirritating to the skin suggests that drug-specific IgE antibodies may be present. In their study, 0.02 ml intradermal injections of serial 10-fold dilutions of commercially prepared intravenous (IV) antibiotic solutions were performed on subjects with no history of drug allergy. The highest concentration of drug that would not elicit an irritant skin reaction in all individuals tested was identified and established for each antibiotic tested. A concentration of 10 mg/m for ceftriaxone, cefuroxime, ceftazidime, and cefotaxime and a concentration of 33 mg/ml for cefazolin was found to be nonirritating (Table 5). In another study, Romano et al. [23] demonstrated that using a concentration of 2 mg/ml of injectable cephalosporins, mixed in normal saline, was nonirritating to the skin. Forty healthy subjects were skin prick-tested using 2 mg/ml concentration as the reagent. If the prick test responses were negative, 0.01 ml of the reagent solution was injected intradermally on the volar forearm skin. In a follow-up study, Romano et al. [13] further proved that skin testing at such a concentration is a sensitive tool for evaluating subjects with immediate reactions to cephalosporins. Cephalosporin allergy was confirmed in 29 of 30 subjects with a history of immediate hypersensitivity to cephalosporins who were skin tested with six different injectable cephalosporins using the 2 mg/ml concentration mixed in 0.9 % NaCl.

Table 5 Nonirritating concentrations of intravenous-administered cephalosporins for skin testing [70]

Cephalosporin	Full-strength concentration (mg/ml)	Dilution	Nonirritating concentration (mg/ml)
Cefazolin	330	1:10	33
Cefotaxime	100	1:10	10
Ceftazidime	100	1:10	10
Ceftriaxone	100	1:10	10

In other studies, various concentrations of cephalosporins, ranging from 0.5 to 250 mg/ml in normal saline, have been used to diagnose immediate hypersensitivity to injectable cephalosporins by intradermal testing [20, 26, 27, 52, 71, 72]. Oral preparations of cephalosporins have also been used for skin prick and intradermal testing. The use of the pure drug in a powder form [17, 73, 74] or at 200 mg/ml in normal saline [28] has been described.

Although skin testing to cephalosporins can be a valuable diagnostic tool in confirming immediate hypersensitivity to cephalosporins, its limitations must be considered. Studies attempting to determine the sensitivity of cephalosporin skin testing yielded variable results. Atanaskovic et al. [75]. observed that, of the 241 children diagnosed with a history of hypersensitivity reactions to cephalosporins, the rate of positive skin tests to the cephalosporins tested (cefaclor, cephalexin, and cefotaxime) ranged from 0.3 % (cefotaxime) to 29.2 % (cefaclor). In two other recent studies, skin test sensitivity varied from 30.7 % (39 out of 127 persons) [1] to 69.7 % (53 of 76 subjects) [17]. Additionally, in a study of 128 patients skin tested to cephalosporins, the negative predictive value approximated 82 % [49]. Therefore, further studies are needed to fully establish cephalosporin skin testing sensitivity.

Despite the lack of standardization in cephalosporin skin testing, performing skin prick/puncture testing followed by intradermal testing using the native drug, diluted in normal saline, at a concentration of 2 mg/ml (a further 10-fold dilution or lower may be needed if initial reaction was severe or life threatening) can aid in the diagnosis (Table 6). When using such a nonirritating concentration, a positive cephalosporin skin test result (wheal diameter >3 mm for prick and >5 mm for intradermal testing) suggests the presence of drug-specific IgE antibodies, consistent with a cephalosporin allergy. However, because the negative predictive value of cephalosporin skin testing is not yet known, a negative result does not rule out the presence of drug specific IgE antibodies. One approach would be to follow a negative skin test with a cautious graded challenge.

In assessing patients with immediate reactions to cephalosporins, skin testing with the penicillin derivatives, when available, should be included. Ideally, both major and minor determinant reagents are used. Penicilloyl polylysine (PREPEN), the major determinant, is available in a premixed solution. The only minor determinant that is commercially available is penicillin G and should be used at a concentration of 10,000 U/ml. The other minor determinants, penicilloate and penilloate, are not available commercially in the USA, but locally formulated versions are used in

Table 6 Example of how to prepare a cephalosporin antibiotic for skin testing

Oral cephalosporin (*Cefuroxime 250 mg/5 ml suspension*)
Steps to mixing a 2-mg/ml concentration for skin prick or intradermal testing:
1. Reconstitute cefuroxime 250 mg/5 ml suspension (GlaxoSmithKline LLC, Philadelphia, PA, USA) per manufacturer's instructions using 0.9 % normal saline in place of water
2. Remove 6 ml from a 30-ml vial of sterile albumin saline with phenol (0.4 %) diluent (Jubilant Hollister-Stier, Spokane, WA, USA) to obtain a vial containing 24 ml of diluent solution
3. Add 1 ml of constituted cefuroxime 250 mg/5 ml suspension to the 24 ml diluent solution vial
Recommended dose for intradermal testing: *0.02 ml*
Intravenous cephalosporin (*Ceftriaxone 1,000 mg/50 ml*)
Steps to mixing a 2-mg/ml concentration for skin prick or intradermal testing:
1. Reconstitute ceftriaxone 1,000 mg/50 ml solution (Roche Laboratories Inc, Nutley, NJ, USA) per manufacturer's instructions using 0.9 % normal saline
2. Add 1 ml of constituted ceftriaxone 1,000 mg/5 ml solution to a 9-ml vial of sterile albumin saline with phenol (0.4 %) diluent (Hollister-Stier, Spokane, WA, USA)
Recommended dose for intradermal testing: *0.02 ml*

various research settings. Skin testing with only the commercially available determinants (PRE-PEN and penicillin G) appears to have adequate negative predictive value [4]. About 90 % of patients with a history of penicillin allergy have negative penicillin skin testing [39, 40] and can safely receive cephalosporins. Patients who are skin test positive to penicillin have an approximate 2 % risk of reacting to cephalosporins [4], and therefore, the cephalosporin should be administered via a graded challenge or an induction of tolerance procedure. When patients with a history of penicillin allergy do not undergo penicillin skin testing, but are given cephalosporins directly, the chance of reacting to the cephalosporin is likely <1 % [4]. However, since cases of fatal anaphylaxis have been reported following cephalosporin administration [41–43], giving a cephalosporin by means of a graded challenge should be strongly considered.

In Vitro Tests

Serum-specific IgE Assays

Radioimmunoassay and fluoroenzymeimmunoassay (FEIA) techniques have been used to detect specific IgE to a limited number of cephalosporins [7, 13, 14, 17, 19, 63, 76, 77]. While these techniques have been employed in research settings for the recognition of the antigenic determinants of different cephalosporins, they are not commonly used in the clinical setting due to their poor sensitivity compared to skin testing and lack of availability. The only commercially available cephalosporin FEIA IgE immunoassay is for cefaclor (ImmunoCAP, Phadia, Uppsala, Sweden) [77].

Basophil Activation Test

In the context of drug hypersensitivity reactions, the basophil activation test is a quantitative measurement of the surface protein, CD63, expressed on basophils after stimulation with the culprit drug [78]. The sensitivity of the basophil activation test (BAT) has been reported to be 50–60 % with a specificity higher than 90 % [78–80]. However, data are limited in using this method in the evaluation of cephalosporin allergy [78, 79]. Further studies using commercially available tests are needed before it can be employed as a diagnostic tool.

Drug Provocation Testing

When there is a definite medical indication for the cephalosporin in question, either induction of drug tolerance or graded challenge procedures may be considered. The choice of whether to administer the cephalosporin via an induction of drug tolerance or a graded challenge depends on the likelihood that the patient is allergic at the time of the procedure. Patients who, based on their history and/or diagnostic test results, are highly likely to be allergic to the cephalosporin in question should undergo an induction of drug tolerance procedure. Patients with a questionable history and negative or inconclusive diagnostic test results would be candidates for a graded challenge.

Importantly, neither procedure should ever be performed on patients suspected of having had a severe non-IgE-mediated reaction, such as SJS, TEN, exfoliative dermatitis, interstitial nephritis, hepatitis, or hemolytic anemia [4]. Additionally, drug provocation testing should not be performed on patients with severe comorbid illnesses (i.e., cardiac, hepatic, renal, or other diseases) [81].

Induction of Drug Tolerance (Desensitization)

Drug tolerance is a temporary state in which a patient with a known drug allergy will tolerate the culprit drug without an adverse reaction. An induction of drug tolerance procedure temporarily modifies a patient's response to a drug, allowing safe treatment with it. Tolerance is maintained only as long as the patient continues to take the specific drug. The term *induction of drug tolerance* encompasses both IgE-mediated desensitization as well as non-IgE-mediated mechanisms and has replaced the term *drug desensitization* [4].

Induction of drug tolerance involves the administration of incremental doses of the drug, starting at a dose small enough to ensure that if a reaction occurs, it will be less severe and easier to treat, and gradually increasing the dose

Table 7 Example protocol for oral cephalosporin induction of drug tolerance [83]

Step	Time interval (min/h)	Concentration (mg/ml)[a]	Amount (ml)	Dose given (mg)	Cumulative dose (mg)
1	0:00	0.5	0.1	0.05	0.05
2	0:15	0.5	0.2	0.1	0.15
3	0:30	0.5	0.4	0.2	0.35
4	0:45	0.5	0.8	0.4	0.75
5	1:00	0.5	1.6	0.8	1.55
6	1:15	0.5	3.2	1.6	3.15
7	1:30	0.5	6.4	3.2	6.35
8	1:45	5	1.2	6	12.35
9	2:00	5	2.4	12	24.35
10	2:15	5	5	25	49.35
11	2:30	50	1	50	100
12	2:45	50	2	100	200
13	3:00	50	4	200	400
14	3:15	50	8	400	800
Observe patient for 30 min, then give full therapeutic dose					

[a]Dilutions prepared from antibiotic suspension, 250 mg/5 ml

until the final therapeutic dose is achieved. A typical starting dose is often 1/10,000th of the final dose or twice the dose used in the skin prick or intradermal skin testing [32], followed by doubling of the previous dose at 15- to 30-min intervals until the therapeutic dose is reached (Tables 7 and 8). The length of the procedure can vary, depending on the drug and route of administration, but, in most cases, can be accomplished within 4–12 h. Induction of drug tolerance should be performed in a closely monitored setting, with a staff trained in the treatment of anaphylaxis, under the direct supervision of a physician familiar with the procedure. There are no comparative studies comparing the safety of different routes of administration (oral vs. intravenous), but it has been suggested that the oral route has a lower risk of anaphylaxis [82]. Once the drug is discontinued, the procedure must be repeated if another course of the drug is indicated.

Induction of drug tolerance with a cephalosporin should be considered in a patient with a history of an allergy to penicillin requiring a cephalosporin who had a positive reaction to penicillin skin testing or who reacted positively to cephalosporin skin testing. It may also be considered in any patient with a history of a severe or life-threatening anaphylactic reaction to a cephalosporin. Additionally, an induction of drug tolerance may be considered in a cephalosporin-allergic patient requiring penicillin, who reacted positively to penicillin skin testing (Fig. 2).

Table 8 Example protocol for intravenous cephalosporin induction of drug tolerance (desensitization) [4]

Step	Time interval (h/min)	Concentration (mg/ml)[a]	Rate (ml/h)	Dose given (mg)	Cumulative dose (mg)
1	0:00	0.04	2	0.02	0.02
2	0:15	0.04	5	0.05	0.07
3	0:30	0.04	10	0.1	0.17
4	0:45	0.04	20	0.2	0.37
5	1:00	0.4	5	0.5	0.87
6	1:15	0.4	10	1	1.87
7	1:30	0.4	20	2	3.87
8	1:45	0.4	40	4	7.87
9	2:00	4	10	10	17.87
10	2:15	4	20	20	37.87
11	2:30	4	40	40	77.87
12	2:45	4	75	922.13	1000
End	5:49.4				

[a]Preparation of different antibiotic concentrations: (1) 0.04 mg/ml concentration, inject 10 mg of antibiotic suspension into 250 ml of 0.9 % sodium chloride solution; (2) 0.4 mg/ml concentration, inject 100 mg of antibiotic suspension into 250 ml of 0.9 % sodium chloride solution; (3) 4 mg/ml concentration, inject 1,000 mg of antibiotic suspension into 250 ml of 0.9 % sodium chloride solution

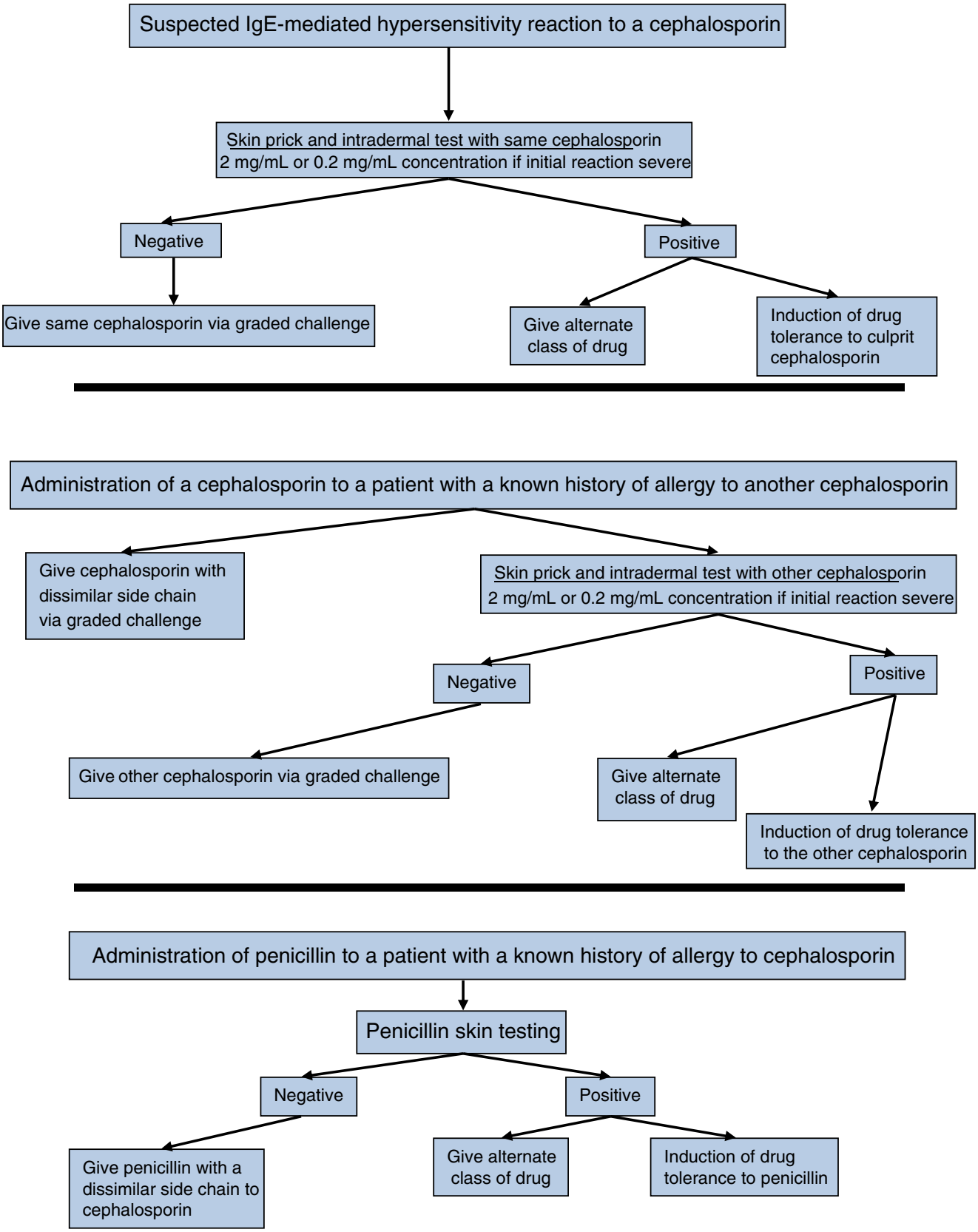

Fig. 2 Cephalosporin algorithms [4]

Table 9 Example of a graded challenge using oral cefuroxime [4]

Step	Time interval (h/min)	Dilution	Dose given (mg)[a]	Volume of oral solution (ml)
1	0:00	1:100	2.5	0.05
2	0:30	1:10	25	0.5
3	1:00	1:1	250	5

[a]Dilutions prepared from antibiotic suspension, 250 mg/5 ml

Graded Challenge

A graded challenge, also known as test dosing, involves the administration of progressively increasing doses of a drug until a therapeutic dose is reached, to a patient who is unlikely to be allergic to it [4]. The graded challenge should not be performed unless the benefit of treatment with the drug outweighs the risk associated with the challenge.

A conventional approach to a graded challenge is to start with a dose 1/100th of the final therapeutic dose, increasing by 10-fold every 30–60 min until the full treatment dose has been achieved (Table 9) [4]. The number of steps included in the procedure may be as little as 2 or it may consist of multiple steps. However, graded challenges comprising more than four or five steps may modify the immune response to the drug, thus inducing drug tolerance in the patient. Therefore, future courses of the drug should be approached with caution [4].

In the case of cephalosporins, a graded challenge might be helpful in disproving a diagnosis of cephalosporin allergy in a patient with a doubtful history, who did not react to cephalosporin skin testing. A graded challenge may also be useful in the penicillin-allergic patient requiring a cephalosporin who underwent a negative cephalosporin skin test. Additionally, graded challenges can be beneficial in the management of patients with a history of cephalosporin allergy who require treatment with another cephalosporin possessing a dissimilar R-group side chain (Fig. 2).

Conclusions

Although the exact allergenic determinants of cephalosporins are not yet completely known, skin testing to penicillin and to the cephalosporin in question, using a nonirritating concentration, provides additional information, which can further guide in the decision to either recommend continued drug avoidance or to perform a graded challenge versus induction of tolerance procedure.

A positive skin test to the cephalosporin in question suggests the possible presence of drug-specific IgE antibodies, and thus, avoidance of the cephalosporin or an induction of drug tolerance would be recommended if no alternative therapies are available. Since its negative predictive value is unknown, a negative cephalosporin skin test must be interpreted with caution and performing a graded challenge to the cephalosporin in question or to an alternate cephalosporin with a dissimilar side chain should be considered.

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