

Cephalosporin allergy

Arvind Madaan, MD, James T.-C. Li, MD, PhD*

Division of Allergic Diseases, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA

Beta-lactam drugs are the most commonly prescribed class of antibiotics. They are also the most important cause of adverse drug reactions mediated by an immunologic mechanism [1–3]. Among β -lactam allergic patients, penicillins are the most frequently implicated agents and the best studied so far [2,4], possibly because of the higher consumption of these drugs [3] and the stability of the conjugates formed by their derivatives [5,6]. Cephalosporins have some structural similarities to penicillins (Fig. 1) [7]; however, unlike determinants derived from benzylpenicillin, cephalosporin allergenic determinants have not been clearly identified, even though a wide variety of these agents is increasingly prescribed.

Mechanisms of cephalosporin hypersensitivity

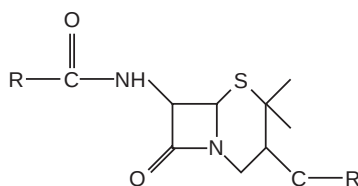
Antigenic determinants: stability, immunogenicity, and cross-reactivity

The major antigenic determinant of benzylpenicillin is benzylpenicilloyl, which is formed by the nucleophilic attack on the penicillin molecule by the amino group of proteins found in plasma or cell membranes [5,6,8]. Although the equivalent determinant, cephalosporoyl, also may be formed with cephalosporins [9], less is known about the immunologic response to this structure [8].

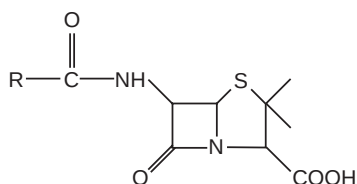
The whole bicyclic structure remains after benzylpenicilloyl formation, whereas important changes occur in the degradation of cephalosporins that produce a wide variety of different metabolites [8,9]. These changes are probably responsible for the differences in the stability and immunogenicity of the haptenic structures formed. Hybridoma studies have demonstrated that, in addition to common determinants, cephalosporins can generate unique structures capable of inducing a specific immunologic response. These unique determinants do not

* Corresponding author.

E-mail address: li.james@mayo.edu (J.T.-C Li).



Cephalosporin nucleus



Penicillin nucleus

Fig. 1. Structural similarities of cephalosporin and penicillin molecules. (From Goodman EJ, Morgan MJ, Johnson PA, et al. Cephalosporins can be given to penicillin-allergic patients who do not exhibit an anaphylactic response. *J Clin Anesth* 2001;13(8):561–4; with permission.)

cross-react with the classic structures [10]. Allergic reactions to cephalosporins may occur because of sensitization to determinants shared with penicillins or to unique cephalosporin haptens [4,11,12].

Anticephalosporin IgE antibody assays are available for clinical use in Australasia [11,13]. Baldo et al have identified some of the specific haptenic determinants involved in hypersensitivity to cephalosporins [11,13]. The cross-reactivity between cephalosporins and penicillin G results partly from the presence of IgE directed against a small methylene substituent group linking the side chain to the rest of the penicillin molecule [13]. Cephalosporins exhibit greater heterogeneity of allergenic determinants than penicillins because of their extra side chain on the dihydrothiazine ring. Differences in fine structural recognition sites in patients who are allergic to cefaclor have been demonstrated [3,11]. A spectrum of allergenic determinants ranging in specificity from side-chain groups to compound determinants embracing one or both ring structures have been described [3,11,13,14].

Reactions to cephalosporins

Maculopapular or morbilliform skin eruptions, drug fever, and a positive antiglobulin or Coombs' test are some of the more common reactions to cephalosporins (Table 1) [15]. Urticaria, eosinophilia, serum sickness–like

Table 1
Adverse reactions to cephalosporins

Type of reaction	Frequency (%)
Dermatologic	1.0–2.8
Positive direct antiglobulin test	1.0–2.0
Anaphylaxis	0.0001–0.1
Fever	0.5–0.9
Eosinophilia	2.7–8.2

From Kelkar PS, Li JT. Cephalosporin allergy. *N Engl J Med* 2001;345(11):804–9; with permission.

reactions, and anaphylaxis are less common. Acute interstitial nephritis and drug-induced cytopenias are rare.

Skin reactions

Cephalosporin-induced skin reactions such as urticaria, rash, exanthem, and pruritus occur in approximately 1% to 3% of patients [16]. The overall incidence of severe skin reactions to cephalosporins is lower than with penicillins; however, exfoliative dermatitis owing to cefoxitin therapy and Stevens-Johnson syndrome owing to cephalixin therapy have been reported [17,18].

Serum sickness–like reaction

A serum sickness–like reaction consisting of rash and arthritis has been described in children given cefaclor [19].

Fever

Cephalosporins may result in febrile reactions [20]. Mastella and colleagues [21] reported the development of febrile reactions in 2 of 101 patients who were administered ceftazidime, cefsulodin, or cefoperazone for the treatment of pseudomonas infections in cystic fibrosis.

Anaphylaxis

In a recent review, Kelkar and Li comprehensively summarized the studies suggesting that anaphylactic reactions to cephalosporin are rare (frequency, 0.0001% to 0.1%) [22,23]. Nevertheless, deaths following cephalosporin administration have been reported [24–26]. The risk of anaphylaxis from cephalosporin may be increased in patients with a history of allergy to penicillin. Petz [27] evaluated 9388 patients with no history of penicillin allergy who were treated with cephaloridine, cephalothin, or cephalixin, and noted only 2 cases of anaphylaxis (0.02%). Lin [23] reported data from a survey of pharmaceutical manufacturers on the risk of anaphylaxis. Seventeen cases of anaphylaxis from ceftriaxone were reported from 1985 to 1990 and 11 cases of anaphylaxis from cefoxitin from 1986 to 1990. Cross-reactivity between cephalosporins and penicillins is discussed later in this article.

Immunohematologic reactions

Some patients may have a positive antiglobulin test following cephalosporin administration. In these situations, the cephalosporin molecule may combine with the red cell membrane, and the specific antibody against the cephalosporin may react with the drug. A positive direct antiglobulin test caused by a cephalosporin can lead to an apparent incompatibility in the minor cross-match test and may confuse the evaluation of a hemolytic disorder that is unrelated to cephalosporin therapy. Fortunately, cephalosporin-induced immune hemolytic anemia is uncommon.

Cross-reactivity of cephalosporins with penicillin

In vitro studies have shown moderate allergic cross-reactivity between cephalosporins and penicillins because they share a common β -lactam ring [9,28–31]. Most of the cross-reactions between penicillins and cephalosporins have involved first- and second-generation cephalosporins [32,33]. Patients who experience adverse reactions to only third-generation cephalosporins may have lesser cross-reactivity with penicillin when compared with first-generation cephalosporins, because the latter have more structural similarities with penicillin [13]. In fact, the cross-reactivity between penicillins and second- or third-generation cephalosporins (excluding cefamandole) is probably no higher than the cross-reactivity between penicillins and other classes of antibiotics [34].

Approximately 1% to 8% of patients with penicillin-specific IgE antibodies are thought to develop an immediate-type hypersensitivity to cephalosporins (Table 2) [35,36]. There have been numerous instances of documented anaphylactic reactions, including fatalities, in historically penicillin-allergic patients who have received cephalosporins [25,26,37–39]. Because drug-allergic patients may have an increased risk for allergic reactions to unrelated, non-cross-reacting compounds [40,41], such reactions to cephalosporins in penicillin-allergic individuals may sometimes be due to de novo development of specific IgE antibodies rather than true cross-reactivity.

Although IgE antibodies to the β -lactam ring of penicillin are of major importance, some reactions to cephalosporins may not be directed to the β -lactam ring and may be side chain specific [33,42]. The side chains of

Table 2
Frequency of reactions to cephalosporins in patients with a history of penicillin allergy

Drug	Total number of patients	Allergic reactions to cephalosporins (%)	History of penicillin allergy	
			Total number	Reaction to cephalosporins (%)
Cephalexin	6573	73 (1.1)	69	5 (7.2)
Cephaloridine	10967	92 (0.8)	255	20 (7.8)
Cephalothin	1983	21 (1.1)	138	8 (5.8)

Data from Dash CH. Penicillin allergy and the cephalosporins. J Antimicrob Chemother 1975; 1(Suppl):107–18.

cefamandole, cefaloram, cephalothin, and cephaloridine are similar to that of penicillin G [43]. Cephalexin has a side chain identical to that of ampicillin, cefadroxil has the same side chain as amoxicillin, and ceftazidime has the same side chain as aztreonam. It is not clear whether these structural similarities result in heightened clinical cross-sensitivity.

Cross-reactivity among cephalosporins might be explained by the presence of same (eg, ceftriaxone and cefotaxime) or similar (eg, ceftriaxone and cefuroxime) side chain structures. Selective responses to specific cephalosporins may be explained by patient reactivities to the entire molecule, as previously demonstrated with cefaclor [11].

Most studies of cross-reactivity between penicillins and cephalosporins have involved subjects who were sensitized to penicillins [8,28,33,44–46]. Few studies have evaluated cross-reactivity with penicillin or other β -lactams in subjects with primary hypersensitivity to cephalosporins [47,48]. The findings [10,48] indicate that there are antibodies that recognize structures unique to cephalosporins, with little or no recognition of penicillins.

The lack of experimental findings on the spectrum of cephalosporin allergenic determinants has hindered the diagnosis of adverse reactions to these drugs and retarded the understanding of allergenic cross-reactions between cephalosporins and between cephalosporins and penicillins [11]. Cephalosporin allergenic determinants have not been identified fully, and cephalosporin conjugates are reported to be unstable [49]. There is no reliable test to predict cross-reactivity to another cephalosporin molecule in a patient with known hypersensitivity to a cephalosporin. The timing of the diagnostic evaluation can also influence the results. Negative responses on assays performed several months after reactive episodes might result from the IgE titer falling below the cutoff values with the passage of time following an allergic reaction. In vitro IgE antibody testing appears to be less sensitive than skin tests, particularly in subjects with allergic reactions to ceftazidime and cefotaxime.

Cross-reactivity of cephalosporins with carbapenems and monobactams

Carbapenems (eg, imipenem) should be considered potentially cross-reactive with cephalosporins because of similarities of the β -lactam ring [50]. Ceftazidime has some cross-reactivity with aztreonam because both drugs have some identical side chains [51,52].

Clinical approach to cephalosporin allergy

Risk factors

A history of a prior allergy to a penicillin or cephalosporin is probably the most important risk factor for an allergic reaction to a cephalosporin. In general, patients with a history of allergy to penicillin have a threefold greater risk of a

subsequent reaction to any medication [53]. A history of allergy to penicillin coupled with the presence of a positive penicillin skin test identifies a patient at a higher risk for a reaction to cephalosporin when compared with a patient with a similar history who has negative skin testing. A patient with a prior reaction to cephalosporin is at risk for future reactions with the same or a related cephalosporin. Atopic individuals, especially those with asthma, may be predisposed to more severe and even fatal reactions in the event of anaphylaxis; however, a history of atopy (allergic rhinitis, asthma, or atopic dermatitis) by itself does not seem to be an independent risk factor for the development of an allergy to β -lactam antibiotics [54].

Patient history

A detailed history is the first step in making the diagnosis and managing a patient with suspected cephalosporin allergy. The following points in the medical history need specific attention in a patient with a history of reactions to any antibiotic, including penicillins and cephalosporins:

- A detailed description of the symptoms (eg, urticaria, pruritus, angioedema, or respiratory difficulties) and their severity (eg, mild or life threatening) should be obtained.
- The time course of the reaction should be noted. This may help in determining whether the event was actually a drug reaction. For example, anaphylaxis typically develops within minutes after drug administration.
- A complete list of all the medications the patient was taking at the time of the event can help determine whether the symptoms were caused by a reaction to the antibiotic in question or to another drug (eg, aspirin).
- A detailed history of all previous reactions to antimicrobial agents, particularly β -lactam antibiotics, should be obtained. A history of reaction to multiple antibiotics may narrow the therapeutic options. It is clinically helpful to know which antibiotics a patient has used, including those that were well tolerated. Identifying antibiotics that have been tolerated in the past may widen the therapeutic options or may cast doubt on a current diagnosis of allergy to an antibiotic.
- In addition to the patient history, a careful review of the medical records can provide additional information about the use of and allergic reactions to any antibiotic.

Management of cephalosporin allergy

Administration of cephalosporin to patients with a history of allergy to penicillin

Before 1980, penicillin history–positive, skin test–positive patients who were given cephalosporin had a reaction rate of approximately 10% to 20%. Since

1980, the reaction rate in these patients when given a cephalosporin has been as low as 2% [55]. This change has been attributed to use of the first-generation cephalosporins cephalothin or cephaloridine before 1980 and their cross-reactivity with benzylpenicillin. Contamination of these early first-generation cephalosporins with trace amounts of penicillin was also reported before 1980.

The following clinical approaches are usually followed in the administration of cephalosporins to patients with a history of penicillin allergy:

Use of a non- β -lactam antibiotic is the simplest approach and avoids the risk of cross-reactivity between penicillins and cephalosporins. Antibiotics that do not show cross-sensitivity to cephalosporins or penicillin include macrolides, quinolones, tetracyclines, sulfonamides, and vancomycin. Decreased antimicrobial effectiveness and the increased cost and development of antimicrobial resistance (particularly to vancomycin) are considered the potential drawbacks to this approach. This strategy is reasonable if the patient has a history of a serious (or unidentified) reaction to penicillin, or if there is more than one suitable antibiotic for the specific clinical indication.

Administration of a cephalosporin may be chosen when the risk of anaphylaxis from or a reaction to a cephalosporin is not considered high enough to warrant the selection of a non- β -lactam antibiotic or further evaluation. Clinicians who follow this approach usually select patients whose previous reaction to penicillin was not life threatening; however, this practice is discouraged by one of the published guidelines on the diagnosis and management of drug hypersensitivity [49]. This approach may be attractive if the previous allergy to penicillin was mild, if the indication for the use of cephalosporin antibiotics is strong, if skin testing for penicillin allergy is impractical, and if the treatment for drug reactions is readily available.

Fatal anaphylaxis to cephalosporins in patients with a history of penicillin allergy has been reported. For this reason, the guidelines from the Joint Taskforce on Practice Parameters [56] recommend that patients with a history of penicillin allergy undergo penicillin allergy skin testing before the administration of a cephalosporin (Fig. 2C).

Patients with negative penicillin skin tests are at no greater risk for having an allergic reaction to β -lactam antibiotics and can receive cephalosporins with low risk. Because this group includes the vast majority of patients labeled penicillin allergic, elective skin testing effectively makes penicillins and cephalosporins available to these patients. On the other hand, administration of cephalosporins to patients who have positive penicillin skin tests should be avoided or approached more cautiously. The main drawbacks are the accessibility of such tests and the costs of testing. This strategy may be attractive for patients who have a strong indication for cephalosporin therapy with a history of a serious reaction to penicillin, providing penicillin allergy skin tests are available.

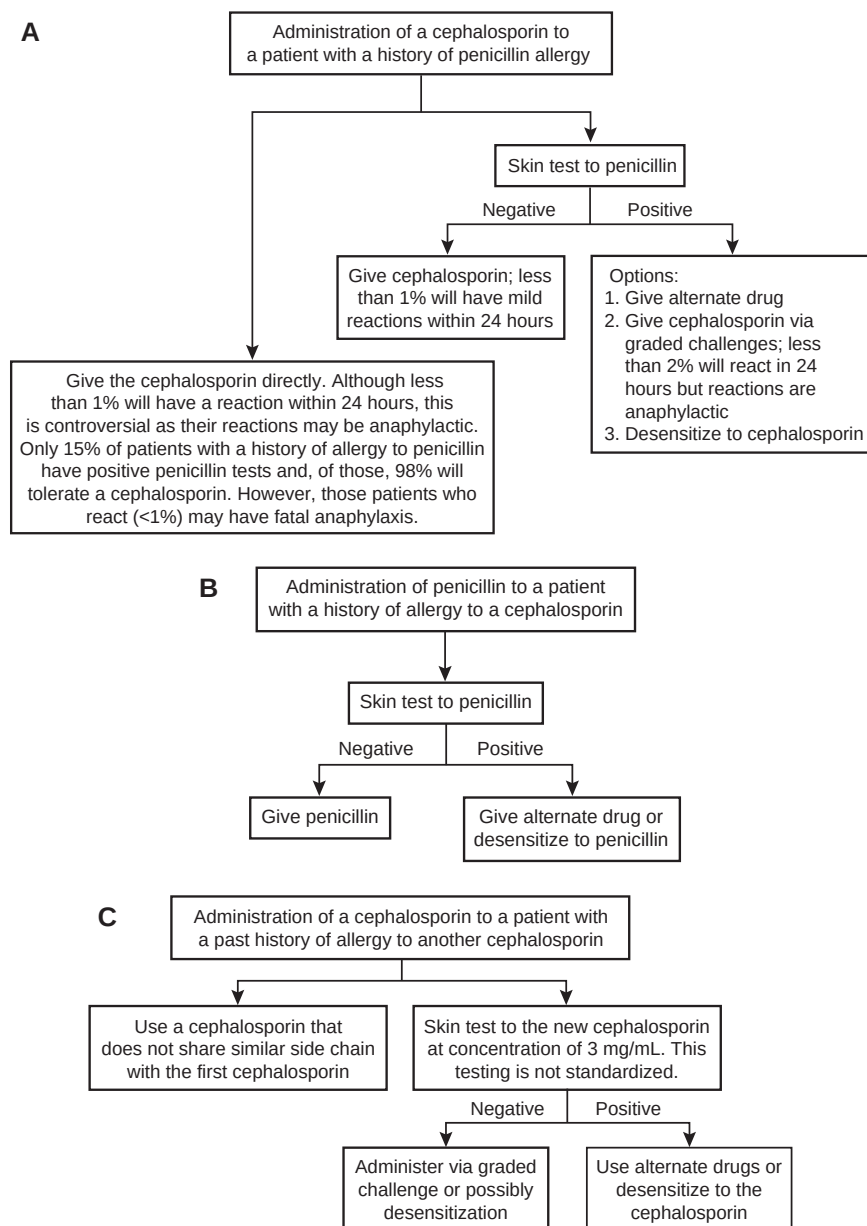


Fig. 2. Clinical scenarios of cephalosporin allergy. (A) Administration of a cephalosporin to a patient with a history of penicillin allergy. (B) Administration of penicillin to a patient with a history of cephalosporin allergy. (C) Administration of a cephalosporin to a patient with a history of allergy to another cephalosporin. (Adapted from Joint Council of Allergy, Asthma and Immunology. Annals of allergy, asthma, & immunology, part 2: evidence-based commentary. Available at: www.jcaai.org/Param/Drugs/Commentary.htm; with permission. Accessed May 28, 2004.)

Primary cephalosporin allergy

A patient who has had an allergic reaction to a cephalosporin is at increased risk for a drug reaction if he or she is exposed to the same cephalosporin agent. The risk of a reaction to a different cephalosporin in such a patient is unknown. Previous studies suggest that the degree of cross-reactivity among cephalosporins may be low [29,57]. Serum sickness–like reactions to cefaclor have been proposed to be caused by a hereditary defect in its metabolism [58]. Patients who have a history of such reactions to cefaclor can take other cephalosporins without difficulty. This recommendation also applies to loracarbef, which is structurally similar to cefaclor [58].

In patients with a history of allergy to a cephalosporin who require penicillin, skin testing for penicillin allergy may help in choosing the right antibiotic. If the test is negative, the patient can receive penicillin; if it is positive, the patient should receive an alternative medication or undergo desensitization to penicillin.

In the absence of standardized skin tests for cephalosporins, the physician's ability to identify patients at risk for immediate-type allergic reactions during future treatment courses with cephalosporins is limited [59]. Dilutions of native cephalosporins have been used in an attempt to detect the presence of IgE antibodies to these agents [1,44,57,60]. The positive and negative predictive values of skin testing performed with the free drug are unknown. A negative skin test does not exclude an immediate-type allergy. A positive skin test response using a nonirritating concentration of the native antibiotic can suggest the presence of drug-specific IgE antibodies [56,61]. Solensky and Mendelson have suggested that it might be reasonable to use such skin testing in selected patients who have histories of immediate reactions to nonpenicillin antibiotics [59].

To determine whether a given concentration of a cephalosporin is nonirritating, one can refer to previous reports in the literature, or skin test several nonallergic volunteers. The nonirritating skin test concentrations of some of the common cephalosporins are listed in Table 3 [62]. The only way to prove or disprove unequivocally whether a patient has an allergy to a specific cephalosporin is to challenge the patient with the suspect medication. Because provocative challenges can be life threatening, they should be undertaken only if no acceptable alternative agents can be substituted.

Clinically, if a patient with a past history of allergy to one cephalosporin agent requires another cephalosporin, the following can be considered: (1) use a non β -lactam antibiotic; (2) perform a graded challenge with a different cephalosporin (preferably one that does not share side chain determinants with the original one); or (3) perform cephalosporin skin testing, although such skin testing is not standardized, and the negative predictive value is unknown.

Cephalosporin skin testing

Concentrations of 3 mg/mL of a parenteral cephalosporin preparation are usually nonirritating, but each cephalosporin requires concurrent evaluation for

Table 3

Nonirritating skin test concentrations of selected cephalosporins

Antibiotic	Full-strength concentration (mg/mL)	Nonirritating concentration (dilution from full strength)
Cefotaxime	95	10-fold
Cefuroxime	90	10-fold
Cefazolin	330	10-fold
Ceftazidime	250	10-fold
Ceftriaxone	250	10-fold

Adapted from Empedrad RB, Earl HS, Gruchalla RS. Determination of nonirritating concentrations of commonly used antimicrobial drugs [abstract]. *J Allergy Clin Immunol* 2000;105(Suppl):S272; with permission.

its irritation potential in nonallergic subjects (Table 3). Skin testing can be done with a prick/puncture test at 3 mg/mL concentration followed by an intracutaneous test (if the prick test reaction is negative at 15 minutes). If the previous clinical reaction was life threatening, testing should start at ≤ 0.3 mg/mL. A positive cephalosporin skin test implies the presence of drug-specific IgE antibodies, and the patient should receive an alternate drug or undergo desensitization. A negative skin test at an intracutaneous concentration of 3 mg/mL is of limited clinical value [59].

Because the negative predictive value of cephalosporin skin testing is unknown, a cautious graded challenge should be performed. A graded challenge is not an immunologic desensitization. Its goal is to administer a medication to a patient cautiously (who is unlikely to be truly allergic to it) in a way that reduces the risk of a serious reaction. Graded challenges usually begin with 1/100 or less of the full therapeutic dose. Several-fold increasing incremental doses are given at 15- to 30-minute intervals until the therapeutic dose is reached. Patients should be monitored for any adverse reactions before administration of each dose. Factors that might modify the pace at which stepwise challenges are performed include the likelihood that a particular medication caused the previous reaction, the length of time elapsed since the reaction, and the physician's experience and comfort level with such procedures [32,59].

Desensitization

Desensitization to cephalosporins has been described but has not been standardized, and experience is limited. It may be considered for patients with a previous life-threatening reaction to penicillin or cephalosporin who require antimicrobial therapy with a cephalosporin, or for patients with a history of allergy to penicillin and positive skin tests for penicillin allergy. Most desensitization protocols start with approximately 1/10,000 of the full dose. Doses are doubled every 15 minutes over the course of 4 to 6 hours until the recommended dose is reached. Successful desensitization to cefotaxime and ceftazidime has been reported [63,64]. Desensitization can result in drug reactions such as bronchospasm or rash [64] and should be conducted by trained personnel in a

Table 4

Examples of published intravenous protocols for desensitization to cephalosporin allergy

14-Day protocol (cefotaxime desensitization) [63]		2-Day protocol (ceftazidime desensitization; infusion doses given every 15 minutes) [64]			
Protocol	Dose (mg)	Day 1	Dose (mg)	Day 2	Dose (mg)
Day 1	1	Dose 1	0.025	Dose 1	0.5
Day 2	2	Dose 2	0.05	Dose 2	1.0
Day 3	4	Dose 3	0.1	Dose 3	2.0
Day 4	8	Dose 4	0.2	Dose 4	4.0
Day 5	16	Dose 5	0.4	Dose 5	8.0
Day 6	32	Dose 6	0.83	Dose 6	16.5
Day 7	60	Dose 7	1.66	Dose 7	32.3
Day 8	120	Dose 8	2.5	Dose 8	50.0
Day 9	200	Dose 9	6.0	Dose 9	100.0
Day 10	400	Dose 10	12.0	Dose 10	200.0
Day 11	800	Dose 11	25.0	Dose 11	586.0
Day 12	1600	Dose 12	50.0	—	—
Day 13	3200	Dose 13	100.0	—	—
Day 14	4000	Dose 14	307.0	—	—

hospital setting, with intravenous access, and with a physician present at all times (Table 4) [59].

Summary

Allergic reactions to cephalosporins may occur because of sensitization to cephalosporin determinants shared with penicillin or to unique cephalosporin haptens. The exact nature of the haptenic determinants resulting from the degradation of currently available cephalosporins is incompletely understood. Cephalosporin skin testing or specific IgE immunoassays have limited clinical utility. The diagnosis of cephalosporin allergy should be made by a detailed case history with attention to the temporal relation following administration as well as the type and intensity of reactions to the specific agent. This history should be supplemented by a careful review of the medical records, which can be useful in guiding therapeutic decisions. Patients with a history of allergy to cephalosporins or penicillin may be at increased risk for a reaction to cephalosporins. Skin testing for an allergy to penicillin may be helpful in patients with a history of penicillin allergy who have a clinical indication for cephalosporin use. Most of these patients have negative tests and should not be at increased risk for a reaction to cephalosporins.

References

- [1] Romano A, Mayorga C, Torres MJ, et al. Immediate allergic reactions to cephalosporins: cross-reactivity and selective responses. *J Allergy Clin Immunol* 2000;106:1177–83.

- [2] Weiss M, Adkinson NF. Immediate hypersensitivity reactions to penicillin and related antibiotics. *Clin Allergy* 1988;18:515–40.
- [3] Baldo BA. Diagnosis of allergy to penicillins and cephalosporins: structural and immunochemical considerations. *Allergy Clin Immunol Int* 2000;12:206–12.
- [4] Blanca M, Vega JM, Garcia J, Miranda A, Carmona MJ, Juarez C, et al. New aspects of allergic reactions to beta-lactams: cross-reactions and unique specificities. *Clin Exp Allergy* 1994;24:407–15.
- [5] Batchelor FR, Dewdney JM, Gazzard D. Penicillin allergy: the formation of the penicilloyl determinant. *Nature* 1965;206:362–4.
- [6] Levine BB, Ovary Z. Studies on the mechanism of the formation of the penicillin antigen III: the N-(D-(-benzylpenicilloyl) group as an antigenic determinant responsible for hypersensitivity to penicillin G. *J Exp Med* 1961;114:875–904.
- [7] Goodman EJ, Morgan MJ, Johnson PA, et al. Cephalosporins can be given to penicillin-allergic patients who do not exhibit an anaphylactic response. *J Clin Anesth* 2001;13(8):561–4.
- [8] Dewdney JM. Immunology of the antibiotics. In: Sela M, editor. *Antigens* 5. New York: Academic Press; 1977. p. 73–245.
- [9] Batchelor FR, Dewdney M, Weston RD, Wheeler AW. The immunogenicity of cephalosporin derivatives and their cross-reaction with penicillin. *Immunology* 1966;10:21–33.
- [10] Nagakura N, Shimizu T, Masuzawa T, Yanagihara Y. Anti-cephalexin monoclonal antibodies and their cross-reactivities to cepheps and penams. *Int Arch Allergy Appl Immunol* 1990;93:126–32.
- [11] Pham NH, Baldo BA. Beta-lactam drug allergens: fine structural recognition patterns of cephalosporin-reactive IgE antibodies. *J Mol Recognit* 1996;9:287–96.
- [12] Baldo BA. Penicillins and cephalosporins as allergens—structural aspects of recognition and cross-reactions. *Clin Exp Allergy* 1999;29:744–9.
- [13] Harle DG, Baldo BA. Drugs as allergens: an immunoassay for detecting IgE antibodies to cephalosporins. *Int Arch Allergy Appl Immunol* 1990;92:439–44.
- [14] Baldo BA, Pham NH, Zhao A. Chemistry of drug allergenicity. *Curr Opin Allergy Clin Immunol* 2001;1:327–35.
- [15] Kelkar PS, Li JT. Cephalosporin allergy. *N Engl J Med* 2001;345(11):804–9.
- [16] Norby SR. Side effects of cephalosporins. *Drugs* 1987;34(Suppl 2):105–20.
- [17] Kannangara DW, Smith B, Cohen K. Exfoliative dermatitis during cefoxitin therapy. *Arch Intern Med* 1982;142:1031–2.
- [18] McArthur JE, Dymont PG. Stevens-Johnson syndrome with hepatitis following therapy with ampicillin and cephalixin. *N Z Med J* 1975;81:390–2.
- [19] Murray DL, Singer DA, Singer AB, Veldman JP. Cefaclor—a cluster of adverse reactions. *N Engl J Med* 1980;303:1003.
- [20] Young EJ, Fainstein V, Musher DM. Drug-induced fever: cases seen in the evaluation of unexplained fever in a general hospital population. *Rev Infect Dis* 1982;4:69–77.
- [21] Mastella G, Agostini M, Barlocco G, et al. Alternative antibiotics for the treatment of *Pseudomonas* infections in cystic fibrosis. *J Antimicrob Chemother* 1983;12(Suppl A):297–311.
- [22] Meyers BR. Comparative toxicities of third-generation cephalosporins. *Am J Med* 1985;79:96–103.
- [23] Lin RY. A perspective on penicillin allergy. *Arch Intern Med* 1992;152:930–7.
- [24] Hoffman DR, Hudson P, Carlyle SJ, Massello III W. Three cases of fatal anaphylaxis to antibiotics in patients with prior histories of allergy to the drug. *Ann Allergy* 1989;62:91–3.
- [25] Pumphrey RS, Davis S. Under-reporting of antibiotic anaphylaxis may put patients at risk. *Lancet* 1999;353:1157–8.
- [26] Spruill FG, Minette LJ, Sturner WQ. Two surgical deaths associated with cephalothin. *JAMA* 1974;229:440–1.
- [27] Petz LD. Immunologic reactions of humans to cephalosporins. *Postgrad Med J* 1971;47(Suppl):64–9.
- [28] Assem ESK, Vickers MR. Tests for penicillin allergy in man. II. The immunological cross-reactivity between penicillin and cephalosporins. *Immunology* 1974;27:255–69.

- [29] Levine BB. Antigenicity and cross-reactivity of penicillins and cephalosporins. *J Infect Dis* 1973;128(Suppl):S364–6.
- [30] Petz LD. Immunologic cross-reactivity between penicillins and cephalosporins: a review. *J Infect Dis* 1978;137(Suppl):S74–9.
- [31] Shibata K, Atsumi T, Horiuchi Y, et al. Immunological cross-reactivity of cephalothin and its related compounds with benzylpenicillin (penicillin G). *Nature* 1966;212:419.
- [32] Anne S, Reisman RE. Risk of administering cephalosporin antibiotics to patients with histories of penicillin allergy. *Ann Allergy Asthma Immunol* 1995;74:167–70.
- [33] Blanca M, Fernandez J, Miranda A, Terrados S, Torres MJ, Vega JM, et al. Cross-reactivity between penicillins and cephalosporins: clinical and immunological studies. *J Allergy Clin Immunol* 1989;83:381–5.
- [34] Robinson JL, Hameed T, Carr S. Practical aspects of choosing an antibiotic for patients with a reported allergy to an antibiotic. *Clin Infect Dis* 2002;35:26–31.
- [35] Bernstein IL, Gruchalla RS, Lee RE, et al. Disease management of drug hypersensitivity: a practice parameter. *Ann Allergy Asthma Immunol* 1999;83:665.
- [36] Dash CH. Penicillin allergy and the cephalosporins. *J Antimicrob Chemother* 1975;1(Suppl): 107–18.
- [37] Kabins SA, Eisenstein B, Cohen S. Anaphylactoid reaction to an initial dose of sodium cephalothin. *JAMA* 1965;193:165.
- [38] Rothschild PD, Doty DB. Cephalothin reactions after penicillin sensitization. *JAMA* 1966; 196:372.
- [39] Scholand JF, Tennenbaum JJ, Cerilli GJ. Anaphylaxis to cephalothin in a patient allergic to penicillin. *JAMA* 1968;206:130.
- [40] Moseley EK, Sullivan TJ. Allergic reactions to antimicrobial drugs in patients with a history of prior drug allergy [abstract]. *J Allergy Clin Immunol* 1991;87:226.
- [41] Sullivan TJ, Ong RC, Gilliam LK. Studies of the multiple drug allergy syndrome [abstract]. *J Allergy Clin Immunol* 1989;83:270.
- [42] Silva-Dan F, McPhillips S, Warrington RJ. The frequency of skin test reactions to side chain penicillin determinants. *J Allergy Clin Immunol* 1993;91:694–702.
- [43] Batchelor FR, Dewdney JM, Weston RD, Wheeler AW. The immunogenicity of cephalosporin derivatives and their cross-reaction with penicillin. *Immunology* 1966;10:21–33.
- [44] Audicana M, Bernalda G, Urrutia I, Echechipia S, Gastaminza G, Muñoz D, et al. Allergic reactions to beta-lactams: studies in a group of patients allergic to penicillin and evaluation of cross-reactivity with cephalosporin. *Allergy* 1994;49:108–13.
- [45] Sastre J, Quijano LD, Novalbos A, Hernandez G, Cuesta J, de las Heras M, et al. Clinical cross-reactivity between amoxicillin and cephadroxil in patients allergic to amoxicillin and with good tolerance of penicillin. *Allergy* 1996;51:383–6.
- [46] Miranda A, Blanca M, Vega JM, Moreno F, Carmona MJ, Garcia J, et al. Cross-reactivity between a penicillin and a cephalosporin with the same side chain. *J Allergy Clin Immunol* 1996;98:671–7.
- [47] Igea JM, Fraj J, Davila I, Cuevas M, Cuesta J, Hinojosa M. Allergy to cefazolin: study of in vivo cross-reactivity with other beta-lactams. *Ann Allergy* 1992;68:515–9.
- [48] Romano A, Quarantino D, Aimone-Gastin I, Mayorga C, Papa G, Venuti A, et al. Cephalosporin allergy: characterization of unique and cross-reacting cephalosporin antigens. *Int J Immunopathol Pharmacol* 1997;10:187–91.
- [49] Hamilton-Miller JMT, Newton GGF, Abraham EP. Products of aminolysis and enzymic hydrolysis of the cephalosporins. *Biochem J* 1970;116:371–84.
- [50] Saxon A, Adelman DC, Patel A, et al. Imipenem cross-reactivity with penicillin in humans. *J Allergy Clin Immunol* 1988;82:213–7.
- [51] Adkinson Jr NF. Immunogenicity and cross-allergenicity of aztreonam. *Am J Med* 1990;88: 12S–5S, 38S–42S.
- [52] Alvarez JS, Sacristan Del Castillo JA, Sampedro Garcia I, Alsar Ortiz MJ. Immediate hypersensitivity to aztreonam. *Lancet* 1990;335:1094.

- [53] Smith JW, Johnson III JE, Cluff LE. Studies on the epidemiology of adverse drug reactions. II. An evaluation of penicillin allergy. *N Engl J Med* 1966;274:998–1002.
- [54] DeSwarte RD, Patterson R. Drug allergy. In: Patterson R, Grammer LC, Greenberger PA, editors. *Allergic diseases: diagnosis and management*. 5th edition. Philadelphia: Lippincott–Raven; 1997. p. 317–412.
- [55] Shepherd GM. Allergy to β -lactam antibiotics. *Immunol Allergy Clin North Am* 1991;11: 611–33.
- [56] Bernstein IL, Gruchalla RS, Lee RE, et al, Joint Task Force on Practice Parameters, American Academy of Allergy, Asthma and Immunology, Joint Council of Allergy, Asthma and Immunology. Executive summary of disease management of drug hypersensitivity: a practice parameter. *Ann Allergy Asthma Immunol* 1999;83:665–700.
- [57] Saxon A, Beall GN, Rohr AS, Adelman DC. Immediate hypersensitivity reactions to beta-lactam antibiotics. *Ann Intern Med* 1987;107:204–15.
- [58] Mendelson LM. Adverse reactions to β -lactam antibiotics. *Immunol Allergy Clin North Am* 1998;18:745–57.
- [59] Solensky R, Mendelson LM. Systemic reactions to antibiotics. *Immunol Allergy Clin North Am* 2001;21(4):679–97.
- [60] Ponvert C, LeClainche L, deBlick J, et al. Allergy to β -lactam antibiotics in children. *Pediatrics* 1999;104:e45.
- [61] Adkinson Jr NF. Risk factors for drug allergy. *J Allergy Clin Immunol* 1984;74:567–72.
- [62] Empedrad RB, Earl HS, Gruchalla RS. Determination of nonirritating concentrations of commonly used antimicrobial drugs [abstract]. *J Allergy Clin Immunol* 2000;105(Suppl):S272.
- [63] Papakonstantinou G, Bogner JR, Hofmeister F, Hehlmann R. Cefotaxime desensitization. *Clin Invest* 1993;71:165–7.
- [64] Ghosal S, Taylor CJ. Intravenous desensitization to ceftazidime in cystic fibrosis patients. *J Antimicrob Chemother* 1997;39:556–7.