

Review Articles

Current Concepts

CEPHALOSPORIN ALLERGY

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CEPHALOSPORIN antibiotics are widely prescribed for common infections such as bronchitis, otitis media, pneumonia, and cellulitis. They are also administered as first-line prophylaxis for many types of surgical procedures. A relative contraindication to these agents is a history of allergy to penicillin. In this situation, many clinicians select a different class of antibiotic, such as vancomycin. However, the emergence of antimicrobial-resistant organisms demands that the selection of antibiotics be made only after careful evaluation. In this article, we review allergy to cephalosporins, with special attention to the risks of administering them to patients with a history of penicillin allergy.

REACTIONS TO CEPHALOSPORINS

Common reactions to cephalosporins include a maculopapular or morbilliform skin eruption, drug fever, and a positive antiglobulin, or Coombs', test (Table 1). Less common reactions include urticaria, eosinophilia, serum-sickness-like reactions, and anaphylaxis. Acute interstitial nephritis and drug-induced cytopenias are rare.

Skin Reactions

The frequency of cephalosporin-induced skin reactions such as urticaria, rash, exanthem, and pruritus is between 1 and 3 percent.¹ Severe skin reactions to cephalosporins are rare and seem to be less common than with penicillins. Exfoliative dermatitis as a result of cefoxitin therapy and the Stevens-Johnson syndrome as a result of cephalixin therapy have been reported.^{8,9}

Serum-Sickness-like Reaction

A serum-sickness-like reaction consisting of rash and arthritis has been described in children given cefaclor.¹⁰ To date, there are no reports of such reactions in adults.

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TABLE 1. ADVERSE REACTIONS TO CEPHALOSPORINS.

TYPE OF REACTION	FREQUENCY	REFERENCES
	%	
Dermatologic	1.0–2.8	Norrby, ¹ Sanders et al., ² Arndt and Jick, ³ Platt ⁴
Positive direct antiglobulin test	1.0–2.0	Sanders et al., ² Platt, ⁴ Meyers ⁵
Anaphylaxis	0.0001–0.1	Gadde et al., ⁶ Sogn et al. ⁷
Fever	0.5–0.9	Sanders et al., ² Meyers ⁵
Eosinophilia	2.7–8.2	Sanders et al., ² Platt ⁴

Fever

Cephalosporins can cause febrile reactions.¹¹ In a study of 101 patients who received cephalosporin (cefazidime, cefsulodin, or cefoperazone), 2 had a febrile reaction.¹²

Anaphylaxis

Studies suggest that anaphylactic reactions to cephalosporin are rare (frequency, 0.0001 to 0.1 percent) (Table 2)^{5,28}; however, deaths have been reported.^{13–15} The risk of anaphylaxis from cephalosporin may be increased in patients with a history of allergy to penicillin (Table 3). One study evaluated 9388 patients with no history of penicillin allergy who were treated with cephaloridine, cephalothin, or cephalixin, and only 2 cases of anaphylaxis (0.02 percent) were observed.²⁷ A review article²⁸ reported data from a survey of pharmaceutical manufacturers on the risk of anaphylaxis: 17 cases of anaphylaxis from ceftriaxone were reported from 1985 to 1990, and 11 cases of anaphylaxis from cefoxitin were reported from 1986 to 1990.

Immunohematologic Reaction

Some patients who receive cephalosporins have positive antiglobulin tests. As is the case with penicillin, the cephalosporin may combine with the red-cell membrane, and then specific antibodies against the cephalosporin may react with the drug. A positive direct antiglobulin test caused by a cephalosporin is clinically important, because these results can lead to an apparent incompatibility in the minor cross-match test and thus confuse the evaluation of a hemolytic disorder that is not due to cephalosporin therapy. However, cephalosporin-induced immune hemolytic anemia is uncommon.

CROSS-REACTIVITY WITH PENICILLIN

Because penicillin-related compounds are produced by the cephalosporium mold, early cephalosporin an-

TABLE 2. REPORTED CASES OF ANAPHYLAXIS FROM CEPHALOSPORINS.

REFERENCE	NO. OF PATIENTS	TYPE OF CEPHALOSPORIN	ROUTE OF ADMINISTRATION	HISTORY OF PENICILLIN ALLERGY	OUTCOME
Hoffman et al. ¹³	1	Cephalexin	Oral	Yes	Fatal
Pumphrey and Davis ¹⁴	1	Unknown	Unknown	Yes	Fatal
	5	Unknown	Unknown	No	Fatal
Spruill et al. ¹⁵	1	Cephalothin	Intravenous	Yes	Fatal
	1	Cephalothin	Intravenous	No	Fatal
Nordt et al. ¹⁶	1	Cephalexin	Topical dermal	Yes	Nonfatal
Grouhi et al. ¹⁷	1	Cefaclor	Oral	Yes	Nonfatal
Rothschild and Doty ¹⁸	1	Cephalothin	Intravenous	Yes	Nonfatal
Barnett and Hirshman ¹⁹	1	Cephapirin	Intravenous	No	Nonfatal
Konno and Nagase ²⁰	1	Cefazolin	Intravenous	No	Nonfatal
Mizutani et al. ²¹	1	Cefotiam	Oral	No	Nonfatal
Romano et al. ²²	1	Ceftriaxone	Intramuscular	No	Nonfatal
Kaplan and Weinstein ²³	1	Cephaloridine	Intravenous	No	Nonfatal
Saleh and Tischler ²⁴	1	Cephaloridine	Intravenous	No	Nonfatal
Zeok and Tsueda ²⁵	1	Cephalothin	Intravenous	Yes	Nonfatal
Bloomberg ²⁶	3	Cefotetan	Intravenous	No	Nonfatal
Petz ²⁷	2	Cephalothin	Unknown	No	Unknown
	2	Cephalothin	Unknown	Yes	Unknown
Lin ²⁸	11	Cefoxitin	Unknown	Unknown	Unknown
	17	Ceftriaxone	Unknown	Unknown	Unknown

tibiotics contained trace amounts of penicillin. Thus, penicillin contamination may have led early studies of allergy to cephalosporins and penicillin to overestimate the degree of cross-reactivity.³²

The cross-reactivity among cephalosporins and between cephalosporins and penicillins has been examined in laboratory and clinical settings; nevertheless, this complex issue remains unresolved.^{28,32} The specific haptens involved in hypersensitivity to cephalosporin have not been identified. The number of potential haptens is large, because both side-chain and nuclear components of the cephalosporins may participate in the hypersensitivity reaction.³² Laboratory tests suggest that cephalosporin derivatives have less cross-reactivity among themselves than do penicillin derivatives, but the degree of cross-reactivity between cephalosporins is greater than that between cephalosporins and penicillin.³² These assessments are severely limited by the fact that the cephalosporin haptenic determinants are unknown.

According to a review of the literature on allergy to penicillin,²⁸ of 15,987 patients who were treated with cephaloridine, cephalexin, cephalothin, cefazolin, or cefamandole, 8.1 percent of those with a history of penicillin allergy had reactions, as compared with 1.9 percent of those without such a history. Thus, the risk of reactions was increased by a factor of approximately four among patients who were allergic to penicillin.

There have been numerous studies of patients with a history of allergy to penicillin who subsequently re-

TABLE 3. REPORTED REACTIONS TO CEPHALOSPORINS IN PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY.

REFERENCE (YEAR)	SKIN TEST FOR PENICILLIN ALLERGY	NO. OF SUBJECTS CHALLENGED	NO. OF REACTIONS (%)
Assem and Vickers ²⁹ (1974)	Positive	3	3 (100)
Warrington et al. ³⁰ (1978)	Positive	3	0
Solley et al. ³¹ (1982)	Positive	27	0
Saxon et al. ³² (1987)	Positive	62	1 (1.6)
Blanca et al. ³³ (1989)	Positive	19	2 (10.5)
Shepherd and Burton ³⁴ (1993)	Positive	9	0
Audicana et al. ³⁵ (1994)	Positive	12	0
Total		135	6 (4.4)
Sullivan et al. ³⁶ (1981)	Negative	23	0
Solley et al. ³¹ (1982)	Negative	151	2 (1.3)
Shepherd and Burton ³⁴ (1993)	Negative	159	0*
Audicana et al. ³⁵ (1994)	Negative	18	0
Total		351	2 (0.6)
Thoburn et al. ³⁷ (1966)	Not done	11	2 (18.2)
Girard ³⁸ (1968)	Not done	23	2 (8.7)
Total		34	4 (11.8)

*Four patients had a suspected allergic reaction after at least 24 hours.

ceived cephalosporin antibiotics (Tables 2 and 3). Early reports from the 1960s suggested that the rate of reaction among these patients was as high as 18 percent,^{37,38} but a 1975 review suggested that it may be closer to 7 percent (as compared with the overall rate of reactions to cephalosporins of about 1 percent) (Table 4).³⁹

In several studies, patients with a history of allergy to penicillin had skin tests for penicillin allergy (Table 3).³⁹ In one study, only 2 of 151 patients with a history of allergy to penicillin and negative skin tests who received cephalosporins had a reaction (1.3 percent).³¹ In a similar study, none of the 159 patients had an immediate reaction, but 4 (2.5 percent) had possible reactions one or more days after receiving the cephalosporin.³⁴ A smaller number of patients with a history of penicillin allergy and positive skin tests have been challenged with cephalosporins, and the results suggest that these patients may be at increased risk for a reaction to cephalosporins (4.4 percent) (Table 3). However, these prospective studies are too small to evaluate accurately the value of skin testing in patients with a history of allergy to penicillin.

A retrospective study of 350,000 reports of adverse drug reactions identified 12 fatal anaphylactic reactions to antibiotics over a five-year period.¹⁴ Six of these fatal reactions were attributed to cephalosporins, and three of the six reactions were in patients with a history of allergy to penicillin (or amoxicillin).

Whether patients with a history of anaphylaxis from penicillin are more likely to have a serious reaction to cephalosporin than patients with other types of reactions has not been studied directly. However, studies of penicillin allergy show that patients with a history of anaphylaxis from penicillin have a significantly higher rate of positive skin tests for penicillin.^{6,7}

Together, these studies suggest that the risk of an allergic reaction to cephalosporins in patients with a history of allergy to penicillin may be up to eight times as high as the risk in those with no history of allergy to penicillin. The studies also suggest that patients with

a history of allergy to penicillin but negative skin tests are not at increased risk for allergy to cephalosporin. Thus, testing for a penicillin allergy may be useful in patients with a history of allergy to penicillin who require cephalosporin therapy.

The product label for all cephalosporin antibiotics states,

Before therapy with [the cephalosporin] is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to [the cephalosporin], other cephalosporins, penicillins, or other drugs. If [this product] is to be administered to penicillin-sensitive patients, caution should be exercised because cross-hypersensitivity among beta-lactam antibiotics has been clearly documented and may occur in up to 10% of patients with a history of penicillin allergy.

RISK FACTORS

The most important risk factor for allergy to cephalosporins is a history of allergy to penicillin or cephalosporins. Patients with a history of allergy to penicillin seem to have a greater risk (by a factor of about three) of a subsequent reaction to any drug.⁴⁰ As reviewed above, patients with a history of allergy to penicillin and a positive skin test may be at higher risk for a reaction to cephalosporin than those who have only a history of allergy to penicillin. A prior reaction to cephalosporin may be a risk factor for future reactions to cephalosporin. A history of atopy (allergic rhinitis, asthma, or atopic dermatitis) does not seem to be an independent risk factor for the development of an allergy to beta-lactam antibiotics, although atopic persons, especially those with asthma, may be predisposed to severe and fatal reactions should anaphylaxis occur.⁴¹

Medical History

The medical history of patients with reactions to antibiotics should include a detailed description of the symptoms (e.g., urticaria, pruritus, angioedema, or respiratory difficulties) and severity (e.g., mild or life-threatening). Studying the time course of the reaction can help determine whether the event was a drug reaction; for example, anaphylaxis typically develops within minutes after the administration of the drug. Evaluating a 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 or to another drug (e.g., aspirin).

It is important to elicit a history of all antibiotic reactions. A history of reaction to multiple antibiotics may narrow the therapeutic options. Similarly, it is useful 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 even cast doubt on a current diagnosis of allergy to an antibiotic. Careful review of medical records can provide additional information about the use of and allergies to antibiotics.

TABLE 4. FREQUENCY OF REACTIONS TO CEPHALOSPORINS IN PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY.*

DRUG	TOTAL NO. OF PATIENTS	ALLERGIC REACTIONS TO CEPHALOSPORINS	HISTORY OF PENICILLIN ALLERGY	
			TOTAL NO.	REACTION TO CEPHALOSPORINS
			number (percent)	
Cephalexin	6,573	73 (1.1)	69	5 (7.2)
Cephaloridine	10,967	92 (0.8)	255	20 (7.8)
Cephalothin	1,983	21 (1.1)	138	8 (5.8)

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Tests for Cephalosporin Allergy

Attempts to develop a skin test for allergy to cephalosporins have been unsuccessful, and skin testing with the native drug alone has little predictive value. No anti-cephalosporin IgE antibody assays are available clinically.

Skin Tests for Penicillin Allergy

Skin tests for allergy to penicillin can be useful in evaluating patients with a history of allergy to penicillin who have a clinical indication for cephalosporin treatment. The preferred test for identifying an allergy to penicillin is the direct skin test with both major and minor determinants.⁴² About 80 to 95 percent of patients who have a history of allergy to penicillin will have negative skin-test results.⁴²

RECOMMENDATIONS

Patients with Penicillin Allergy

One common therapeutic approach to patients with an allergy to penicillin is to select an antibiotic that does not contain a beta-lactam ring. This strategy avoids the risks of cross-sensitivity. Macrolides, quinolones, sulfonamides, and vancomycin are among the antibiotics that do not show cross-sensitivity to cephalosporins or penicillin. Decreased antimicrobial effectiveness, increased cost, and increased antimicrobial resistance (particularly to vancomycin) are potential drawbacks to this strategy. This approach may be attractive if there are many appropriate antibiotics for the clinical indication or if the patient has a history of a serious (or unidentified) reaction to penicillin.

Another common strategy is to administer the cephalosporin to a patient with a history of allergy to penicillin. In this strategy, the risk of anaphylaxis from or a reaction to cephalosporin is not considered high enough to warrant either the selection of a non-beta-lactam antibiotic or further evaluation. Many clinicians who follow this strategy select patients whose previous reaction to penicillin was not life-threatening or anaphylactic. The appeal of this approach is that serious reactions to cephalosporins are rare. The main drawback is the potential increased risk of a drug reaction or anaphylaxis. A published guideline on the diagnosis and management of drug hypersensitivity discourages this practice.⁴³ Nevertheless, this approach may be attractive if the allergy to penicillin is mild, the indication for the use of cephalosporin antibiotics is strong, skin testing for penicillin allergy is impractical, or treatment for drug reactions is readily available.

A third strategy is to evaluate the patient with a history of allergy to penicillin with tests for allergy to penicillin.⁴⁴ With this strategy, a cephalosporin is given to patients with negative tests and withheld from patients with positive tests. Most patients (80 to 90 percent) have negative skin tests and will be able to receive cephalosporins. The main drawbacks are the accessi-

bility of such tests and the costs of testing. This strategy may be attractive for patients who have a strong indication for cephalosporin therapy but who have a history of a serious reaction to penicillin.

Patients with Cephalosporin Allergy

Skin testing for penicillin allergy can be helpful for patients with a history of allergy to a cephalosporin who require penicillin. If the test is negative, they can receive penicillin; if it is positive, they should either receive an alternative medication or undergo desensitization to penicillin.

A patient who has had an allergic reaction to a cephalosporin should not receive that cephalosporin again. The risk of a drug reaction when a different cephalosporin is administered to a patient with a history of allergy to one cephalosporin is unknown. Some have suggested that the degree of cross-reactivity among cephalosporins is low.^{32,45} In fact, rabbit antibodies against cephalosporins with different side chains do not cross-react.⁴⁶ Thus, side-chain-specific antibodies may predominate in the immune response to cephalosporins.

Cross-reactivity (or the absence of it) between a cephalosporin and other beta-lactam antibiotics can be explained in part by the structure of the side chains. The side chains of cefamandole, cefaloram, cephalothin, and cephaloridine are similar to that of penicillin G.⁴⁷ 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. Whether these structural similarities result in heightened cross-sensitivity is not known.

Serum-sickness-like reactions to cefaclor are caused by a hereditary defect in metabolism.⁴⁸ Patients who have a history of such reactions to cefaclor can take other cephalosporins without difficulty, including loracarbef, which is structurally similar to cefaclor.⁴⁸

Desensitization

Desensitization to cephalosporins has been described but has not been standardized, and experience is limited. Desensitization to cephalosporins can be considered for patients with a previous life-threatening reaction to penicillin or cephalosporin who require antimicrobial therapy with a cephalosporin and for patients with a history of allergy to penicillin and positive skin tests for penicillin allergy.

Although successful desensitization to cefotaxime and ceftazidime has been reported,^{49,50} desensitization can result in drug reactions such as bronchospasm or rash⁵⁰ and should be conducted by trained personnel in a hospital setting (Table 5).

Test Dosing

Test dosing consists of the administration of a small dose of the drug, less than the dose that potentially would cause a serious reaction, followed by relatively

TABLE 5. REPORTED PROTOCOLS FOR INTRAVENOUS DESENSITIZATION TO CEPHALOSPORINS.

PROTOCOL	DOSE mg
14-Day protocol for desensitization to cefotaxime*	
Day 1	1
Day 2	2
Day 3	4
Day 4	8
Day 5	16
Day 6	32
Day 7	60
Day 8	120
Day 9	200
Day 10	400
Day 11	800
Day 12	1600
Day 13	3200
Day 14	4000
2-Day protocol for desensitization to ceftazidime†	
Day 1	
Dose 1	0.025
Dose 2	0.05
Dose 3	0.1
Dose 4	0.2
Dose 5	0.4
Dose 6	0.83
Dose 7	1.66
Dose 8	2.5
Dose 9	6
Dose 10	12
Dose 11	25
Dose 12	50
Dose 13	100
Dose 14	307
Day 2	
Dose 1	0.5
Dose 2	1
Dose 3	2
Dose 4	4
Dose 5	8
Dose 6	16.5
Dose 7	32.3
Dose 8	50
Dose 9	100
Dose 10	200
Dose 11	586

*Data are from Papakonstantinou et al.⁴⁹

†Data are from Ghosal and Taylor.⁵⁰ Ceftazidime was infused in a stepwise manner every 15 minutes.

large incremental increases in the dose until the full therapeutic dose is given. The administration of a cephalosporin to a patient who is potentially allergic to that drug is hazardous and is not recommended. In one patient, an intravenous test dose of 140 mg of cephalothin did not produce anaphylaxis, but a subsequent bolus of 1 g did result in anaphylaxis.²⁵

CONCLUSIONS

A detailed history of medications and allergies, supplemented by a careful review of medical records,

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 such an allergy who have a clinical indication for cephalosporins. The majority of these patients have negative tests and should not be at increased risk for a reaction to cephalosporins. Desensitization to cephalosporins can be considered for high-risk patients.

REFERENCES

- Norrby SR. Side effects of cephalosporins. *Drugs* 1987;34:Suppl 2:105-20.
- Sanders CV, Greenberg RN, Marier RL. Cefamandole and cefoxitin. *Ann Intern Med* 1985;103:70-8.
- Arndt KA, Jick H. Rates of cutaneous reactions to drugs: a report from the Boston Collaborative Drug Surveillance Program. *JAMA* 1976;235:918-23.
- Platt R. Adverse effects of third-generation cephalosporins. *J Antimicrob Chemother* 1982;10:Suppl C:135-40.
- Meyers BR. Comparative toxicities of third-generation cephalosporins. *Am J Med* 1985;79:96-103.
- Gadde J, Spence M, Wheeler B, Adkinson NF Jr. Clinical experience with penicillin skin testing in a large inner-city STD clinic. *JAMA* 1993;270:2456-63.
- Sogn DD, Evans R III, Shepherd GM, et al. Results of the National Institute of Allergy and Infectious Diseases Collaborative Clinical Trial to test the predictive value of skin testing with major and minor penicillin derivatives in hospitalized adults. *Arch Intern Med* 1992;152:1025-32.
- Kannangara DW, Smith B, Cohen K. Exfoliative dermatitis during cefoxitin therapy. *Arch Intern Med* 1982;142:1031-2.
- McArthur JE, Dymont PG. Stevens-Johnson syndrome with hepatitis following therapy with ampicillin and cephalixin. *N Z Med J* 1975;81:390-2.
- Murray DL, Singer DA, Singer AB, Veldman JP. Cefaclor — a cluster of adverse reactions. *N Engl J Med* 1980;303:1003.
- 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.
- 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.
- Hoffman DR, Hudson P, Carlyle SJ, Massello W III. Three cases of fatal anaphylaxis to antibiotics in patients with prior histories of allergy to the drug. *Ann Allergy* 1989;62:91-3.
- Pumphrey RS, Davis S. Under-reporting of antibiotic anaphylaxis may put patients at risk. *Lancet* 1999;353:1157-8.
- Spruill FG, Minette LJ, Sturmer WQ. Two surgical deaths associated with cephalothin. *JAMA* 1974;229:440-1.
- Nordt SP, Cantrell FL, Rodriguez GJ. Anaphylactic reaction to dermal exposure to cephalixin. *Am J Emerg Med* 1999;17:492-3.
- Grouhi M, Hummel D, Roifman CM. Anaphylactic reaction to oral cefaclor in a child. *Pediatrics* 1999;103:809. abstract.
- Rothschild PD, Doty DB. Cephalothin reaction after penicillin sensitization. *JAMA* 1966;196:372-3.
- Barnett AS, Hirshman CA. Anaphylactic reaction to cephalixin during spinal anesthesia. *Anesth Analg* 1979;58:337-8.
- Konno R, Nagase S. Anaphylactic reaction to cefazolin in pregnancy. *J Obstet Gynecol* 1995;21:577-9.
- Mizutani H, Ohyanagi S, Shimizu M. Anaphylaxis from cefotiam hexetil hydrochloride (CTM-HE) in an atopic nurse. *Clin Exp Dermatol* 1996;21:246.
- Romano A, Quarantino D, Venemalm L, Torres MJ, Venuti A, Blanca M. A case of IgE-mediated hypersensitivity to ceftriaxone. *J Allergy Clin Immunol* 1999;104:1113-4.
- Kaplan K, Weinstein L. Anaphylaxis to cephaloridine in a nurse who prepared solutions of the drug. *JAMA* 1967;200:75-7.
- Saleh Y, Tischler E. Severe anaphylactic reaction to intravenous cephaloridine in a pregnant patient. *Med J Aust* 1974;2:490-1.
- Zeok SS, Tsueda K. Failure of a cephalothin test dose to produce anaphylaxis. *Anesth Analg* 1980;59:393-4.
- Bloomberg RJ. Cefotetan-induced anaphylaxis. *Am J Obstet Gynecol* 1988;159:125-6.

27. Petz LD. Immunologic reactions of humans to cephalosporins. *Postgrad Med J* 1971;47:Suppl:64-9.
28. Lin RY. A perspective on penicillin allergy. *Arch Intern Med* 1992;152:930-7.
29. Assem ES, Vickers MR. Tests for penicillin allergy in man. II. The immunological cross-reaction between penicillins and cephalosporins. *Immunology* 1974;27:255-69.
30. Warrington RJ, Simons FE, Ho HW, Gorski BA. Diagnosis of penicillin allergy by skin testing: the Manitoba experience. *Can Med Assoc J* 1978;118:787-91.
31. Solley GO, Gleich GJ, Van Dellen RG. Penicillin allergy: clinical experience with a battery of skin-test reagents. *J Allergy Clin Immunol* 1982;69:238-44.
32. Saxon A, Beall GN, Rohr AS, Adelman DC. Immediate hypersensitivity reactions to beta-lactam antibiotics. *Ann Intern Med* 1987;107:204-15.
33. Blanca M, Fernandez J, Miranda A, et al. Cross-reactivity between penicillins and cephalosporins: clinical and immunologic studies. *J Allergy Clin Immunol* 1989;83:381-5.
34. Shepherd GM, Burton DA. Administration of cephalosporin antibiotics to patients with a history of penicillin allergy. *J Allergy Clin Immunol* 1993;91:262. abstract.
35. Audicana M, Bernaola G, Urrutia I, 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.
36. Sullivan TJ, Wedner HJ, Shatz GS, Yecies LD, Parker CW. Skin testing to detect penicillin allergy. *J Allergy Clin Immunol* 1981;68:171-80.
37. Thoburn R, Johnson JE III, Cluff LE. Studies on the epidemiology of adverse drug reactions. IV. The relationship of cephalothin and penicillin allergy. *JAMA* 1966;198:345-8.
38. Girard JP. Common antigenic determinants of penicillin G, ampicillin and the cephalosporins demonstrated in men. *Int Arch Allergy Appl Immunol* 1968;33:428-38.
39. Dash CH. Penicillin allergy and the cephalosporins. *J Antimicrob Chemother* 1975;1:Suppl:107-18.
40. Smith JW, Johnson JE III, Cluff LE. Studies on the epidemiology of adverse drug reactions. II. An evaluation of penicillin allergy. *N Engl J Med* 1966;274:998-1002.
41. DeSwarte RD, Patterson R. Drug allergy. In: Patterson R, Grammer LC, Greenberger PA, eds. *Allergic diseases: diagnosis and management*. 5th ed. Philadelphia: Lippincott-Raven, 1997:317-412.
42. Levine BB, Zolov DM. Prediction of penicillin allergy by immunological tests. *J Allergy* 1969;43:231-44.
43. 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.
44. Li JT, Markus PJ, Osmon DR, Estes L, Gosselin VA, Hanssen AD. Reduction of vancomycin use in orthopedic patients with a history of antibiotic allergy. *Mayo Clin Proc* 2000;75:902-6.
45. Levine BB. Antigenicity and cross-reactivity of penicillins and cephalosporins. *J Infect Dis* 1973;128:Suppl:S364-S366.
46. Hamilton-Miller JM, Abraham EP. Specificities of haemagglutinating antibodies evoked by members of the cephalosporin C family and benzylpenicillin. *Biochem J* 1971;123:183-90.
47. Batchelor FR, Dewdney JM, Weston RD, Wheeler AW. The immunogenicity of cephalosporin derivatives and their cross-reaction with penicillin. *Immunology* 1966;10:21-33.
48. Mendelson LM. Adverse reactions to β -lactam antibiotics. *Immunol Allergy Clin North Am* 1998;18:745-57.
49. Papakonstantinou G, Bogner JR, Hofmeister F, Hehlmann R. Cefotaxime desensitization. *Clin Invest* 1993;71:165-7.
50. Ghosal S, Taylor CJ. Intravenous desensitization to ceftazidime in cystic fibrosis patients. *J Antimicrob Chemother* 1997;39:556-7.

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