ARTICLE

Cross-Allergy Among the ß-lactam Antibiotic Agents: A Review of the Risks

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ABSTRACT

Background: Allergies to ß-lactam antibiotics are often encountered in pharmacists' daily practice. The frequency and risks of cross-allergy between agents may lead to uncertainty in the prescribing of ß-lactam antibiotics.

Objective: To review and summarize the current literature pertaining to the incidence and risks of immunoglobulin-E (IgE)-mediated allergy and of cross-allergy between the ß-lactam antibiotics, and to formulate a concise approach to allergy assessment and prescribing in these situations.

Methods: The search terms "penicillins", "cephalosporins", and "carbapenems" (along with the specific drug names "imipenem", "meropenem", and "ertapenem"), as well as "allergy" and "drug hypersensitivity", were used to search the MEDLINE and Reactions databases for pertinent English-language articles. The bibliographies of the review articles identified in this way were also perused for pertinent references.

Results: Of all the ß-lactam antibiotics, true (IgE-mediated) allergy occurs most frequently with penicillins. The risks of cross-allergy with penicillins and cephalosporins are well delineated; however, cross-reactivity between other classes and among agents within an individual class is not as clear.

Conclusions: Recommendations for the approach to allergy assessment and prescribing of the ß-lactam agents in patients with various ß-lactam allergies are presented. In some situations, specific skin testing will indicate whether a drug can safely be prescribed. In most cases, some monitoring or supervision is appropriate when the drug is administered.

Key words: penicillins, cephalosporins, carbapenems, allergy, drug hypersensitivity

Can J Hosp Pharm 2005;58:90-6

RÉSUMÉ

Historique : Les allergies aux bêtalactamines sont chose courante dans la pratique quotidienne du pharmacien. La fréquence et les risques d'allergie croisée entre les divers médicaments de cette classe peuvent expliquer une certaine hésitation à prescrire les bêtalactamines.

Objectif : Passer en revue et présenter un résumé de la littérature actuelle pour ce qui est de l'incidence et des risques d'allergie à médiation par l'immunoglobuline E (IgE) et d'allergie croisée entre les bêtalactamines, ainsi que formuler un démarche concise pour l'évaluation de l'allergie et la prescription dans de telles circonstances.

Méthodes : Les mots clés «penicillins», «cephalosporins», «carbapenems» (accompagnés des noms de médicaments spécifiques : «imipenem», «meropenem» et «ertapenem»), «allergy» et «drug hypersensitivity» ont servis à la recherche, dans les bases de données MEDLINE et Reactions, d'articles pertinents en anglais. Les bibliographies des articles de synthèse ainsi identifiés ont été attentivement examinées à la recherche de références pertinentes.

Résultats : De toutes les bêtalactamines, la vraie allergie (à médiation par l'IgE) survient le plus souvent avec les pénicillines. Les risques d'allergie croisée avec les pénicillines et les céphalosporines sont bien définis, ce qui, en revanche, n'est pas aussi clair pour la réactivité croisée avec les carbapénems et entre les médicaments d'une même classe.

Conclusions : Des recommandations relativement à la démarche en matière d'évaluation de l'allergie et de prescription des bêtalactamines chez les patients présentant différentes allergies aux bêtalactamines sont présentées. Dans certains cas, un test cutané spécifique permettra de dire si tel ou tel médicament est sûr. Dans la plupart des cas, il est indiqué d'effectuer une certaine surveillance ou supervision durant l'administration du médicament.

Mots clés : pénicillines, céphalosporines, carbapénems, allergie, hypersensibilité aux médicaments

INTRODUCTION

ß-Lactam antibiotics, which comprise the penicillin, cephalosporin, and carbapenem families, are so called because they all have a ß-lactam ring (Figure 1). ß-Lactam agents are frequently prescribed because they are bactericidal, relatively inexpensive, effective against a wide range of pathogens, and well tolerated. The most frequent side effect reported with ß-lactam antibiotics, particularly penicillin, is allergy.[1,2]

Pharmacists often encounter patients with allergies to medications, particularly antibiotics. For a patient who is allergic to a ß-lactam agent, the implications are greater than simply the risk of reaction to the specific drug. There is also the potential for an allergic reaction to agents both within and among the ß-lactam families. Lack of knowledge of the patient's particular type of allergic reaction, as well as the risks of cross-reaction, can be a source of confusion and could lead to the avoidance of a generally safe, effective group of antibiotics. The objective of this review is to present the current data regarding the incidence and risks of allergy mediated by immunoglobulin E (IgE) and of cross-allergy between the ß-lactam antibiotics, and to formulate a concise approach to prescribing and monitoring in these situations.

METHODS

Two databases — MEDLINE (from 1994 to 2004 for penicillins and cephalosporins and from 1985 to 2004 for carbapenems) and Reactions (from 1983 to 2003) — were searched for pertinent English-language articles (limited to human studies). The MeSH terms "drug hypersensitivity", "penicillins", "cephalosporins", and "carbapenems" and the key words "allergy", "imipenem", "meropenem", and "ertapenem" were used. The bibliographies of articles identified in this way were also reviewed and pertinent references retrieved. Because true "allergic" reactions are IgE-mediated, this mechanism was the focus of the review.

For each ß-lactam class, information regarding the risks of cross-allergy is presented, followed by a concise summary or "take-home message" of the information (in italic text). Although aztreonam, a monobactam, also falls within the ß-lactam family, it is not discussed here, as it is not available in Canada and, except for rare case reports, it is not considered cross-reactive in patients allergic to penicillins or cephalosporins.[1,2]

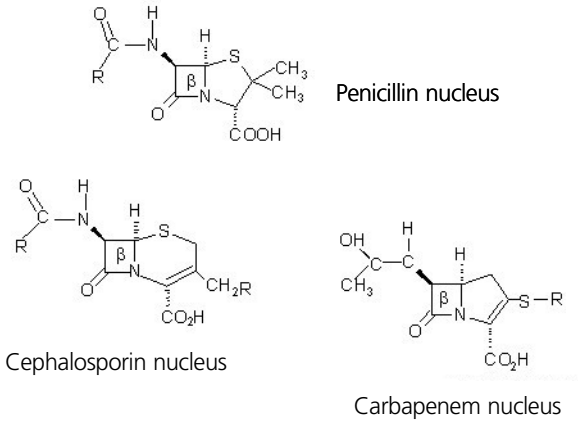

Figure 1. Basic structure of various ß-lactam antibiotics. β = ß-lactam ring, R = side chain (variable).

RESULTS

Classification of Allergic Reactions

Allergic reactions to ß-lactams have been categorized by clinical syndrome, immune mechanism, or time to onset (Table 1).[1–4] Type 1 reactions are mediated by IgE antibodies directed at specific combinations of metabolites and serum proteins. When the metabolite–protein complex is recognized and cross-links with specific preformed IgE antibodies bound to tissue mast cells, inflammatory mediators such as histamine and leukotrienes are released, which results in the signs and symptoms of an allergic reaction.[3] IgE-mediated reactions can be classified as immediate or accelerated. Immediate reactions are manifested by anaphylaxis with or without hypotension and usually occur within minutes to 1 h of administration of the allergen. Accelerated reactions may present within 48 to 72 h and are characterized by laryngeal edema, angioedema, and/or urticaria.[1,3,4] Patients may report a feeling of shortness of breath, chest tightness, throat tightening, pruritis, dizziness, or feelings of warmth or impending doom; rarely, they may experience severe nausea, vomiting, abdominal pain, or diarrhea.

Type II, III, and IV immunologic reactions are considered late reactions, occurring at least 72 h after drug administration. These reactions are not IgE-mediated, and, in contrast to IgE-mediated reactions, skin testing is not used to assess the risk of cross-allergy.[1,3,4]

Of all types of allergic reactions, IgE anaphylactic reactions are the most feared; these are implicated in cross-reactivity between the ß-lactam agents. This review therefore focuses on IgE-mediated allergic reactions. It should be emphasized, however, that for patients with a history of severe non-IgE-mediated

Table 1. Classification of Allergic Reactions[1-6]

Reaction Type	Immunologic Mechanism	Time to Onset	Clinical Syndrome	Detected by Skin Testing
I	IgE antibody mediated	< 1 h	Immediate: anaphylaxis, hypotension, urticaria (hives), laryngeal edema, angioedema, bronchoconstriction, hyperperistalsis	Yes
		1–72 h	Accelerated: urticaria, laryngeal edema, angioedema, wheezing	
II	Cytotoxic reactions (IgG, IgM)	> 72 h	Hemolytic anemia, thrombocytopenia, neutropenia	No
III	Immune complex reactions (IgG, IgM)	Usually > 7 days; may occur after drug is discontinued	Serum sickness (fever, rash, lymphadenopathy, arthralgias, myalgias), nephritis	No
IV (subclasses a–d)	T cell mediated	> 72 h	Contact dermatitis, exfoliative dermatitis, maculopapular or morbilliform rashes, Stevens-Johnson syndrome	No*

Note: IgE = immunoglobulin E, IgG = immunoglobulin G, IgM = immunoglobulin M.
*Patch testing with the specific agent may be used to confirm these delayed (non-IgE) reactions. See text for more details.

immunotoxic reactions (e.g., Stevens-Johnson syndrome, exfoliative dermatitis, vasculitic syndromes) the inciting agent or any drug in the same class should not be readministered.[1,3,4] Because it is not known if the risk of a recurrent reaction extends to all ß-lactam agents, the clinician should avoid all ß-lactam agents in these patients, if possible.

Penicillin Allergy

The true incidence of penicillin allergy is unknown, although 5% to 20% of the population report this type of allergy, often with a vague or unconfirmed history.[1,3,4] The penicilloyl derivative is the most frequently implicated metabolite in IgE-mediated reactions to penicillin.[3] Anaphylaxis, the most severe of the type I reactions, occurs in 0.01% to 0.05% of penicillin courses and is fatal in 10% of such cases.[1,3,7] It occurs most commonly in people 20 to 49 years old and in patients who have undergone parenteral administration of the drug.[1,3,7] Fear of anaphylaxis may prevent the clinician from prescribing penicillin and other ß-lactam agents to patients with a history of penicillin allergy,[3] which in turn may result in the use of less effective, more toxic, more expensive or broader-spectrum alternatives.

The most common reactions to penicillin are type IV delayed hypersensitivity reactions.[1,3,4,6] These present most frequently as a maculopapular or morbilliform rash and occur in 1% to 4% of patients taking penicillin.[3] The incidence of rashes due to the aminopenicillins (ampicillin or amoxicillin) is generally higher (5.2% to 9.5%) and is significantly higher (69% to 100%) among patients with viral illness, the most common example being infectious mononucleosis caused by Epstein-Barr virus.[1,3,5] Until recently, delayed reactions were considered idiopathic, with an unknown immunological mechanism, but it is now thought that they are caused by T cell stimulation; these reactions are subclassified on the basis of the specific T cells activated.[4,6]

Patch testing can be used to identify or confirm delayed-type allergy to specific agents.[8] The procedure involves patch, prick, and/or intradermal testing with the suspect drug, with results read shortly after application and again after 1 to 4 days.[8,9] This form of testing is not to be confused with the skin testing used to detect immediate IgE-mediated reactions, which is read after 15 to 30 min, as discussed below.

Allergic reactions must be differentiated from side effects or drug intolerance, so a detailed history and assessment of the reaction must be obtained (Table 2). For patients reporting a "rash", it is especially important to differentiate between hives, which are IgE-mediated reactions, and more benign maculopapular reactions. This will help to determine if the patient is indeed allergic, the type of allergic reaction, and the associated risks of cross-reactivity with other ß-lactam agents.

Penicillin-specific IgE decreases over time; therefore, the risk of allergy decreases with time. After 10 years, 70% of adults with a documented penicillin allergy have undetectable levels of IgE.[1,10] An individual's risk of penicillin allergy is not increased by having a family member with a penicillin allergy.[1,5]

Penicillin-Allergic Patients

Risks of Prescribing Penicillins

In general, administration of any penicillin agent to a patient with a history of penicillin allergy should be

Table 2. Information Required for an Allergy History[1-3]

Detailed description of the reaction, including symptoms, severity, duration
Route of drug administration and duration of therapy
Interval between initiation of therapy and reaction (timing of onset)
Whether the reaction required treatment
How long ago the reaction occurred (patient's age at time of reaction)
History of other antibiotics taken since the reaction and outcome (refer to old charts)
Presence of a medical alert bracelet
Whether skin testing has ever been performed (and if so, the results)
Consideration of possible causes of the reaction (antibiotic, other drugs, disease)

avoided, although an exception may be made for patients who experienced a late-onset, non-urticarial rash following the administration of an aminopenicillin.[1,3] If an accurate history cannot be obtained, or there is uncertainty as to whether the rash was strictly maculopapular or morbilliform, the clinician should err on the side of caution and assume that the rash was urticarial.[4,5]

Skin testing performed by an experienced clinician is the most accurate way of assessing true IgE-mediated allergy to penicillin.[1] Such testing is indicated for patients with a history of penicillin allergy for whom penicillin therapy is warranted. The procedure (epicutaneous scratch or prick followed by intradermal administration of the agent) is not without risk, as systemic reactions to skin testing have been described.[7,11] Such reactions occur in less than 1% of patients overall but more frequently (greater than 2%) among patients with a positive test result.[7,11]

Penicillin skin testing is performed with determinants of both the major metabolite (benzylpenicilloyl [Pre-Pen, not available in Canada at the time of writing]) and the minor metabolites (not commercially available; aqueous penicillin G is used).[1] It has also been recommended that the aminopenicillins (amoxicillin and ampicillin) be included as reagents for skin testing.[8,12] In vitro tests for IgE antibodies (e.g., by radioallergosorbent testing and enzyme-linked immunosorbent assay) are not sensitive and are not recommended.[1,4]

Among people who have been labelled as allergic to penicillin, only 10% to 20% will have a positive result when IgE skin testing is performed.[3,5,13] Patients with positive skin test results have a 50% or greater chance of an immediate allergic reaction if penicillin is readministered.[1] Therefore, prescribing penicillin for a patient with a positive skin test result should be avoided, unless desensitization is performed.[1,3] Desensitization involves the administration of incremental doses of the agent to be prescribed, at intervals of 15 to 30 min, orally or by the IV route (or both). This procedure must be performed by an experienced clinician in a monitored setting and only after informed consent has been obtained.[5,14] Desensitization does not ensure that future administration of the same antibiotic will be safe. If a subsequent course of therapy is required, the patient must again undergo evaluation and possibly desensitization.[14]

Patients with a negative skin test result may be carefully challenged with incremental doses of a penicillin (orally, followed by intravenously, if required) in a supervised setting; only up to 3% of these patients will experience an IgE-mediated reaction, the majority of which are urticaria or mild cutaneous reactions.[1-3,7] In one recent study,[15] patients with a history of IgE-mediated penicillin allergy and a negative skin test result were not resensitized to penicillin during repeat courses of oral penicillin, which suggests that repeat skin testing may not be required for patients with an initial negative result.

Recommendation: Skin testing is necessary for patients with a history of type I allergy to penicillin if a penicillin is required. If the result of skin testing is negative, the patient may receive penicillin under supervision. If the result is positive, avoid penicillin or attempt desensitization.

Risks of Prescribing Cephalosporins

Skin reactions to cephalosporins (e.g., urticaria, rash, pruritis) occur at a frequency of 1% to 3%. Anaphylaxis is rare (0.0001% to 0.1%).[13] Because cephalosporins also contain the ß-lactam ring (Figure 1), there is potential for cross-reactivity in penicillin-allergic patients. Complicating the issue is the fact that hypersensitivity reactions with cephalosporins may be due to the various side chains as well as the ß-lactam nucleus.[12,13,16,17] In addition, the original cephalosporins (cephalothin and cephaloridine) were contaminated with minute quantities of penicillin, which might have resulted in overestimates of cross-allergy.[3,17]

Previous studies have indicated that the risk of allergy to cephalosporins is 4 to 8 times greater among patients with a reported penicillin allergy than among patients without a history of allergy.[7,13] In an analysis of previous reports (the majority using older cephalosporins), 5.6% of patients with a positive result on penicillin skin testing had allergic reactions (including some cases of anaphylaxis) within 24 h of receiving a

cephalosporin, whereas the frequency was only 1.7% among those with a negative skin test result (similar to the incidence in the general population).[5] A similar summary incorporating 2 newer cross-allergy studies found a reaction rate of 4.4%.[13] This is lower than the 10.9% (14/128) cross-reactivity rate observed in a recent investigation in which patients with a history of immediate reactions to a penicillin and a positive skin test result were challenged with skin tests to a variety of cephalosporins.[18] Nine (64%) of the 14 patients had positive results to cefamandole and/or cephalothin, which have side chains similar to those of the penicillin agents used for skin testing (benzylpenicillin, ampicillin). If these patients are excluded, the incidence of cross-reactivity to cefuroxime, ceftazidime, ceftriaxone or cefotaxime was 3.9% (5/128).[18] Thus, higher-generation cephalosporins appear to have a lower propensity (less than 4%) than first-generation cephalosporins (specifically, cefazolin and cephalexin) to cross-react in penicillin-allergic patients.[7,17-19] These figures must also be interpreted in light of the fact that some patients may be predisposed to allergic reactions and may have reacted on this basis, rather than experiencing a true cross-reaction.[20,21]

Patients with negative results to penicillin skin tests are not at greater risk for allergy to cephalosporins and may receive these drugs.[1,13] One study showed no cross-reactivity among 41 patients with documented allergy (mostly IgE-mediated) to penicillin G, amoxicillin or cloxacillin who were given cefazolin, cefuroxime, and ceftriaxone.[12] None of these cephalosporins has a side chain similar to the penicillin that provoked the allergic reaction.[12] The risk is higher for penicillin-allergic patients who received cephalosporins with a similar side chain (e.g., ampicillin and cephalexin, penicillin G and cephalothin) and has ranged from 12% to 38%.[12,17]

In a chart review of patients undergoing orthopedic surgery,[22] 73% of those reporting penicillin allergy received cefazolin preoperatively. Only 1 of the 300 patients may have had an allergic reaction associated with cefazolin administration. Although the authors noted that those who had had severe or anaphylactic reactions were probably among those given an alternative antibiotic, this study did support the safety of cefazolin, a first-generation cephalosporin, for surgical prophylaxis in most patients with a claim of penicillin allergy.[22]

It is generally recommended that clinicians avoid cephalosporins and use an alternative class of antibiotic for patients with a history of immediate IgE-mediated reaction to penicillin, unless penicillin skin testing has been performed and the result is negative.[1,3] This restrictive approach has been recently challenged, however, on the basis that the risk of cross-allergy with third-generation cephalosporins is thought to be insignificant and the potential of cross-allergy with first- or second-generation cephalosporins exists only if the cephalosporin has a similar side chain to the culprit penicillin.[17,19] Unfortunately, the specific penicillin to which the patient previously reacted is not always known. Romano and others[18] proposed skin testing with cefuroxime or ceftriaxone at a concentration of 2 mg/mL, followed by administration of the agent if the result of the test is negative.[18]

Recommendation: Obtain a thorough history of the penicillin allergy. Patients with a history of non-IgE-mediated reactions to penicillin may receive cephalosporins. If the patient has a history of IgE-mediated allergy to penicillin, cephalosporins should be avoided whenever possible. If a cephalosporin is required, it should be administered under close supervision. Skin testing to cephalosporins has been proposed. Alternatively, in nonurgent situations, penicillin skin testing may be performed, and the cephalosporin administered if the result is negative.

Cephalosporin-Allergic Patients

Risks of Prescribing Cephalosporins

Patients experiencing an allergic reaction to a particular cephalosporin should not receive that cephalosporin again.[13] The risk of cross-reaction when a different cephalosporin is given is not known precisely, but it may be influenced by the various side chains possibly involved in the immune response.[1,13,16] One study showed that almost half (42.3%) of patients with an immediate allergic reaction to cephalosporins were cross-allergic when skin tested to other cephalosporins (most having the same or a similar side chain), whereas the remainder (57.7%) reacted only to the culprit cephalosporin.[16]

There appears to be less cross-allergy risk between cephalosporins than between members of the penicillin family, but the risk of cross-allergy between different cephalosporins is higher than between cephalosporins and penicillins.[13,16] Skin testing with the desired cephalosporin has been suggested, although the negative predictive value is unknown.[1,16]

Recommendation: Because of the unpredictable risk, a cephalosporin should not be prescribed to any patient who is allergic to another cephalosporin without skin testing to the desired cephalosporin; the desired

cephalosporin should be administered in a supervised, controlled setting.

Risks of Prescribing Penicillins

In a study of 30 patients with immediate allergy to second- and third-generation cephalosporins, 13.3% had positive results on skin testing to penicillin determinants.[16] The incidence of cross-allergy may be higher among those with allergy to first-generation cephalosporins.[16] Patients with a history of an immediate IgE-mediated allergy to a cephalosporin who require therapy with penicillin should undergo penicillin skin testing, as previously described.[1,13] Patients who test positive should not receive penicillin without undergoing desensitization, but patients with a negative result may receive penicillin.[1,13] If skin testing is not available, penicillins should be avoided in patients with an IgE-mediated reaction to cephalosporins.

Recommendation: If the patient has a history of an immediate reaction to cephalosporin, perform penicillin skin testing before prescribing a penicillin. If the result is negative, penicillin may be administered under supervision. If the result is positive, perform desensitization before prescribing penicillin.

Patients Allergic to Penicillin or Cephalosporins: Risks of Prescribing Carbapenems

Little is known about the true cross-reactivity between the ß-lactam-containing carbapenems (meropenem, imipenem, and ertapenem) and the penicillins and cephalosporins. However, the limited evidence available indicates that the risk of cross-allergy is higher between penicillins and carbapenems than between penicillins and cephalosporins. In one study, dermal testing was used to evaluate the potential for cross-reactivity to imipenem in patients with a history of penicillin allergy.[23] Almost half of the 20 patients for whom the result of penicillin skin testing was positive also reacted to skin testing with imipenem and its metabolite. None of those with negative results on penicillin skin testing reacted to imipenem.[23] The authors concluded that carbapenems should not be prescribed for patients with a history of immediate allergic reaction to penicillins.

To mimic the clinical setting, the frequency of allergy to imipenem was assessed in a group of bone marrow transplant patients with a reported history of allergy to penicillin.[24] The overall incidence of cross-allergy in these patients was 9.5%. However, in 90% of the patients the penicillin allergy was self-reported, none of the patients had a history of anaphylaxis to penicillin, and some patients were not given the drug after it was prescribed, which created a selection bias.[24]

Prescott and others[25] retrospectively compared the incidence of allergic reactions among patients with and without a documented or reported history of allergy to penicillin (excluding amoxicillin or ampicillin) who subsequently received at least one dose of meropenem or imipenem. The incidence of allergic reactions was 11% (11/100) among patients with a history of penicillin allergy but only 2.7% (3/111) among those without a penicillin allergy (p = 0.024). The incidence of cross-allergy was the same for imipenem and meropenem. The majority of penicillin-allergic patients reacted within 3 days of starting the carbapenem; cutaneous reactions (rash or hives) were most commonly reported. Anaphylaxis occurred in one patient, who had a history of rash in reaction to penicillin and received meropenem. Although a history of cephalosporin allergy was not significant in predicting carbapenem allergy, only 9 patients who were allergic to cephalosporin but not to penicillin were included in the study.[25] Because this was a retrospective study, specific details of the penicillin allergy were not always available and allergies could therefore not be confirmed. The analysis does, however, indicate an increased risk of allergy to carbapenems in patients with a history of penicillin allergy.

No studies examining the potential for cross-allergy with ertapenem were located. Patients with a serious allergy to ß-lactam agents were excluded from clinical studies with ertapenem, although those with a history of mild rash have been enrolled.* Until further information is available, the higher likelihood of cross-allergy in penicillin-allergic patients observed in the aforementioned studies should be considered to hold true for all carbapenems.

Because of the common ß-lactam ring, cross-allergy between cephalosporins and carbapenems is possible, but its frequency is assumed to be low, since most reactions to cephalosporins are believed to involve the side chains rather than the ß-lactam ring.[1,4] Nevertheless, as with penicillins, it would be prudent to avoid use of carbapenems in patients with an immediate allergic reaction to cephalosporin, if possible.

Recommendation: In general, avoid using carbapenems in patients with a history of immediate IgE-mediated allergy to penicillins and, perhaps, cephalosporins.

*E. Prégent, MD, Director, Medical Services, Merck Frosst Canada Ltd, personal communication, October 3, 2002.

CONCLUSIONS

Among patients with a history of penicillin allergy, 80% to 90% have negative results on IgE penicillin skin tests, and therefore have no higher risk than the general population when receiving a cephalosporin. Patients with a positive skin test result have a 5% to 10% chance of cross-reaction when given a cephalosporin (less if it is a third-generation cephalosporin), and this reaction is often not life-threatening. The importance of obtaining a good allergy history to identify those with true IgE-mediated allergies cannot be overemphasized. This will aid the clinician in making the most informed decision and should curtail unnecessary avoidance of a useful family of antibiotics.

References

1. 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. A*nn Allergy Asthma Immunol* 1999;83:665-700.
2. Boguniewicz M. Adverse reactions to antibiotics. Is the patient really allergic? *Drug Saf* 1995;13:273-80.
3. Salkind AR, Cuddy PG, Foxworth JW. Is this patient allergic to penicillin? *JAMA* 2001;285:2498-505.
4. 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.
5. Shepherd GM. Allergy to ß-lactam antibiotics. *Immunol Allergy Clin North Am* 1991;11:611-33.
6. Pichler WJ. Delayed drug hypersensitivity reactions. *Ann Intern Med* 2003;139:683-93.
7. Lin RY. A perspective on penicillin allergy. *Arch Intern Med* 1992;152:930-7.
8. Romano A, Quaratino D, Di Fonso M, Papa G, Venuti A, Gasbarrini G. A diagnostic protocol for evaluating nonimmediate reactions to aminopenicillins. *J Allergy Clin Immunol* 1999;103:1186-90.
9. Barbaud A, Gonçalo M, Bruynzeel D, Bircher A; European Society of Contact Dermatitis. Guidelines for performing skin tests with drugs in the investigation of cutaneous adverse drug reactions. *Contact Dermatitis* 2001;45:321-8.
10. Finke SR, Grieco MH, Connell JT, Smith EC, Sherman WB. Results of comparative skin tests with penicilloyl-polylysine and penicillin in patients with penicillin allergy. *Am J Med* 1965;38:71-82.
11. Valyasevi MA, Van Dellen RG. Frequency of systematic reactions to penicillin skin tests. *Ann Allergy Asthma Immunol* 2000;85:363-5.
12. Novalbos A, Sastre J, Cuesta J, de las Heras M, Lluch-Bernal M, Bombín C, et al. Lack of allergic cross-reactivity to cephalosporins among patients allergic to penicillins. *Clin Exp Allergy* 2001;31:438-43.
13. Kelkar PS, Li JTC. Cephalosporin allergy. *N Engl J Med* 2001;345:804-9.
14. Knowles S. Drug allergies. *Pharm Pract* 1993;9(2). Continuing education program insert. 7 p.
15. Solensky R, Earl HS, Gruchalla RS. Lack of penicillin resensitization in patients with a history of penicillin allergy after receiving repeated penicillin courses. *Arch Intern Med* 2002;162:822-6.
16. Romano A, Mayorga C, Torres MJ, Artesani MC, Suau R, Sánchez F, et al. Immediate allergic reactions to cephalosporins: cross-reactivity and selective responses. *J Allergy Clin Immunol* 2000;106:1177-83.
17. Kim S, Warrington RJ. Clinical cross-reactivity between penicillins and cephalosporins. *Can J Allergy Clin Immunol* 1998;3:12-5.
18. Romano A, Guéant-Rodriguez R, Viola M, Pettinato R, Guéant JL. Cross-reactivity and tolerability of cephalosporins in patients with immediate hypersensitivity to penicillins. *Ann Intern Med* 2004;141:16-22.
19. Anne S, Reisman RE. Risk of administering cephalosporin antibioitics to patients with histories of penicillin allergy. *Ann Allergy Asthma Immunol* 1995;74:167-70.
20. Smith JW, Johnson 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.
21. Strom BL, Schinnar R, Apter AJ, Margolis DJ, Lautenbach E, Hennessy S, et al. Absence of cross-reactivity between sulfonamide antibiotics and sulfonamide nonantibiotics. *N Engl J Med* 2003;349:1628-35.
22. Goodman EJ, Morgan MJ, Johnson PA, Nichols BA, Denk N, Gold BB. Cephalosporins can be given to penicillin-allergic patients who do not exhibit an anaphylactic response. *J Clin Anesth* 2001;13:561-4.
23. Saxon A, Adelman DC, Patel A, Hajdu R, Calandra GB. Imipenem cross-reactivity with penicillin in humans. *J Allergy Clin Immunol* 1988;82:213-7.
24. McConnell SA, Penzak SR, Warmack TS, Anaissie EJ, Gubbins PO. Incidence of imipenem hypersensitivity reactions in febrile neutropenic bone marrow transplant patients with a history of penicillin allergy. *Clin Infect Dis* 2000;31:1512-4.
25. Prescott WA, DePestel DD, Ellis JJ, Regal RE. Incidence of carbapenem-associated allergic-type reactions among patients with versus patients without a reported penicillin allergy. *Clin Infect Dis* 2004;38:1102-7.

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Disclosure
There were no conflicts of interest in the writing of the manuscript, and no financial support was received.

Acknowledgements
The author would like to acknowledge and thank Anne Massicotte, BPharm, MSc, and Dr F. Auclair, MD, FRCPC, for their valuable input in reviewing an earlier version of this article.