Analysis of Therapeutic Options in Patients Reporting a Penicillin or Cephalosporin Allergy

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ABSTRACT

The majority of patients with a purported β-lactam allergy tolerate β-lactam therapy without incident. The objective of this study was to determine the potential for direct drug cost-avoidance by comparing therapies predicted by a decision analysis model (DAM) using routine allergy consults versus actual therapies received. Based on history, 100 patients were categorized as either probably allergic (Group A; 29%), possibly allergic and requiring an allergy consult (Group B; 53%), or unlikely to be allergic (Group C; 18%). These probabilities were incorporated into a DAM to predict the potential for β-lactam allergy. Patients in Group C and 84% of Group B were considered likely able to tolerate β-lactam therapy based on history and/or probability of a negative skin test as reported in the literature. Direct drug cost-avoidance was calculated as the difference between actual therapy received and therapy indicated by the model. The actual cost of therapy was $156/patient while the potential cost according to the model was $165/patient. A direct drug cost-avoidance of -$25/course (i.e., increased cost) for prophylactic therapy and $31/course for active treatment was calculated. This study suggested no direct drug cost-avoidance when routine allergy consults were used as part of the DAM, although cost-avoidance may be achieved in select subsets of patients.

Key Words: allergy, β-lactam, cost-avoidance, decision analysis model, hypersensitivity, penicillin

RÉSUMÉ

La majorité des patients qui ont une présumée allergie aux bêta-lactames tolèrent les traitements aux bêta-lactames sans incidents. L'objectif de cette étude était de déterminer la possibilité d'éviter les coûts directs en médicaments en comparant les traitements théoriques déterminés par un modèle d'analyse de décision (MAD) qui utilise une méthode de consultation, habituelles pour les allergies versus les traitements actuellement reçus. Selon les antécédents, 100 patients ont été catégorisés soit comme étant probablement allergiques, Groupe A (29 %), soit possiblement allergiques et nécessitant une consultation pour leur allergie, Groupe B (53 %), soit encore peu probablement allergiques, Groupe C (18 %). Ces probabilités ont été incorporées au MAD pour prédire la probabilité d'allergie au bêta-lactame. Les chercheurs ont estimé que les patients du Groupe C et 84 % de ceux du Groupe B étaient vraisemblablement capables de

tolérer un traitement aux bêta-lactames, en se fondant sur les antécédents et (ou) la probabilité d'un résultat négatif à l'épreuve cutanée, comme on le rapporte dans la documentation. L'évitement des coûts directs en médicaments a été calculé comme la différence entre le traitement actuellement reçu et le traitement indiqué selon le modèle d'analyse de décision. Le coût actuel du traitement était de 156 $ par patient, alors que le coût potentiel du traitement selon le MAD était de 165 $ par patient. Les coûts directs évités qui ont été calculés étaient de -25 $ par traitement (c.-à-d. un coût supérieur) pour le traitement prophylactique et de 31 $ par traitement pour le traitement actif. Cette étude porte à croire qu'il n'y a eu aucun évitement des coûts directs en médicaments avec la méthode de consultation habituelle pour les allergies utilisée avec le MAD, bien qu'il soit possible d'éviter des coûts chez certains sous-groupes de patients choisis.

Mots clés : allergie, bêta-lactame, évitement des coûts, hypersensibilité, modèle d'analyse de décision, pénicilline.

INTRODUCTION

The majority of patients with a purported history of β-lactam allergy tolerate β-lactam therapy without incident.[1-4] This is usually due to either an incorrect initial diagnosis of allergy[5] or the patient classifying an adverse drug reaction as an allergy.[6] As well, hypersensitivity to β-lactam antibiotics may be transient in nature[7,8] and, hence, may not recur upon rechallenge.

Clinicians frequently prescribe alternate antibiotic therapy (for patients with a purported penicillin allergy history) despite β-lactam antibiotics being indicated as the drug class of choice. A 1 to 5% incidence of allergic

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cross-reaction (between penicillins and first generation cephalosporins) has been suggested[9,10] but authors of recent reviews of this subject have stated that it is safe to administer cephalosporins to penicillin allergic patients and that the actual incidence of cross-reactivity cannot be determined at this time.[11-13] Nevertheless, many clinicians remain reluctant to prescribe a cephalosporin for a patient with a purported penicillin allergy history.

The use of an alternate therapy in this situation is of concern for several reasons. First, in the absence of a history of hypersensitivity, penicillins and other β-lactams are well-tolerated and are frequently considered to be the therapy of choice.[14] Alternative agents include vancomycin, erythromycin, clindamycin, and ciprofloxacin; all have serious adverse effects associated with their use.[15-18] Alternate therapy may negatively alter the patient outcome and the hospital cost by contributing to (i) greater drug costs, (ii) longer duration of therapy required due to suboptimal treatment, (iii) increased length of hospital stay as a result of adverse reactions or complications, or (iv) development of antibiotic resistance to second-line agents.

Skin tests using both major and minor determinants identify those patients who are at risk of IgE-mediated allergic reactions to penicillin with a sensitivity of greater than 95%.[3,19] Even when patients with a history indicative of a true allergy are skin-tested, the majority will have negative results. Studies which selected for history-positive patients[5,20,21] or which included patients with unknown histories[2,3,6,22,23] observed positive skin test results in 10 to 19% of their populations. Lin et al[9,24] reported positive skin test results in 28.8% of study populations with positive β-lactam allergy histories and 16.4% of study populations with unselected histories.

The Allergy and Immunology Department, London Health Sciences Centre assesses the validity of allergy histories and performs skin testing as required to determine the patient's actual allergy status. Physicians from the department usually receive consults on patients with a documented penicillin allergy who will benefit from a long duration or life-saving course of β-lactam therapy. The Pharmacy and the Allergy and Immunology Departments developed this study to determine if it was cost-effective to have pharmacists provide the initial assessment of patients reporting β-lactam allergies and then have the allergist consulted for all equivocal histories.

METHODOLOGY

Patients were eligible if they had a purported β-lactam allergy identified through the drug distribution computer system using the attributes of penicillin and cephalosporin allergy and were receiving antibiotic therapy for one of the following indications: osteomyelitis, meningitis, cellulitis, syphilis, endocarditis, septic arthritis, pneumonia, peritonitis, bites (human or animal), toxic shock syndrome, tetanus, urinary tract infections, or where a β-lactam was indicated for surgical prophylaxis. For the purposes of this study, therapy was considered to be prophylactic if a dose was given prior to surgery and/or post-operatively for a period of up to 7 days. All other courses of antibiotics were considered to be active treatment. Information regarding indication, cultures, and allergy were obtained directly from the health record.

A previously compiled list of signs and symptoms was utilized by the investigator to record the patient's allergy history and to assess the probability of an allergic reaction. The history, to complete this list, was obtained directly from the patient. Other parameters noted during the interview were route of administration, time to reaction onset, time lapsed since the reaction without further rechallenge, and result of rechallenge. Patients were eligible for the interview if they were mentally competent, able to communicate effectively with the interviewer, and were agreeable to be interviewed for the purpose of obtaining a complete allergy history.

A decision analysis model (DAM) has been used to formalize the decision making process of prescribing antibiotic therapy and to analyze each of the component decisions in a stepwise fashion. Decision analysis provides a means for weighing the expected benefits of different actions that can result in different outcomes.[25] A DAM was developed (Figure 1) and information obtained from
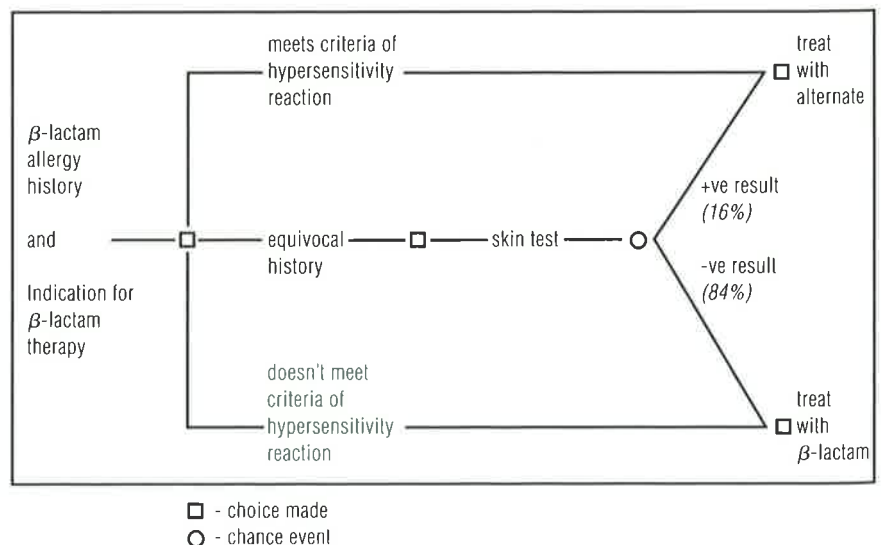

Figure I. Decision Analysis Model: Prediction of Treatment Options in Penicillin Allergic Patients

the interviews was used to determine the probabilities of each option. For the model to identify populations that would benefit from penicillin skin testing, the concept of treatment thresholds as defined by Redelmeier et al[26] was utilized. The criteria utilized to establish these thresholds were validated by an allergist and are presented in Table I. At the initial choice mode, the investigator determined the appropriate option: 1) meets criteria of hypersensitivity reaction; 2) equivocal history; or 3) does not meet criteria of hypersensitivity reaction. The categorization based on history alone was reviewed by the allergist. For the purposes of this study, a hypersensitivity reaction was defined as either a Type I (IgE mediated) or a Type II (IgG or IgM mediated) reaction. Histories of a delayed cutaneous reaction were attributed to IgG or IgM mediated reactions.

Patients with an equivocal history would require a skin test to further define their probability of a reaction and, hence, predict appropriate therapy. For the purpose of this study, predicted probability of a positive skin test in our population was considered to be 16%. This value was extracted from literature based on the inclusion of patients with unknown histories, exclusion of strongly positive and very weak penicillin allergy histories, and the skin test determinants used.[2,3,5,6,9,20-24]

Cost analysis was performed for each group then collectively analyzed. For patients categorized as Group A (those who had a strong history of an allergic reaction), no change in therapy and, hence, no alteration in cost occurred. For Group B patients (those with an equivocal history), all patients would require skin testing. Sixteen percent of these would be expected to have positive results and thus would require alternate antimicrobial therapy. The cost analysis of this group was performed by calculating the difference between the cost of therapy predicted by the model (16% of the cost of therapy received plus 84% of the cost of β-lactam therapy based on predicted skin test results) and the cost of the therapy actually received. The cost of a consult by a physician in the Allergy and Immunology Department and a skin test ($110.00) for all patients in Group B was included in the cost of therapy predicted by the model. Costs for Group C patients (those unlikely to have had an allergic reaction) were estimated based on β-lactam therapy without an allergy consult.

The β-lactam therapy chosen was based on culture and sensitivity results when available and, when not available, by utilizing references to determine the drug of choice in the absence of a β-lactam allergy.[14] The references for the use of antimicrobial prophylaxis in surgery were based on the guidelines published by The Medical Letter[27] and recommendations of Conte and Barriere.[28] The cost of predicted β-lactam therapies was calculated using the drug acquistion cost for an appropriate dose and duration for an equivalent duration of therapy as that received by the patient.

The average direct drug cost avoidance per course was calculated. Prophylactic and active treatment courses were analyzed separately. Data are presented as the mean ± standard deviation. Student's paired t-test was used to compare the cost of therapy received to the cost of therapy predicted by the model.

Approval of this study was obtained from the Ethics Review Board of the University of Western Ontario.

Table I.   Categorization of Allergy

Allergy Probable (Group A)	Allergy Possible (Group B)	Allergy not Probable (Group C)

i) anaphylaxis
    - respiratory effects
    - swelling of the face
	i) skin effects only *without other symptoms*	i) gastrointestinal effects *without other symptoms*

ii) Serum sickness
    - swollen joints, fever
      haematuria, rash
    - delayed onset of 1-2 weeks
    - resolves in 3 days-6 weeks
	ii) ALLERGY PROBABLE
	    but occurred ≥ 25 years ago
	
	iii) unknown
	    presentation
		ii) only positive family history
		
		iii) Toxicity
		    - seizures
		    - hepatitis
		    - nephritis
		    - haemolytic anemia
		    - injection site reaction

iii) IgG/IgM
    - skin effects with onset
      > 3 days
    - kidney dysfunction
		iv) idiosyncratic presentation

vi) positive rechallenge		v) negative rechallenge

RESULTS

From February 16 to May 13, 1993, 6,850 patients were admitted to London Health Sciences Centre. Of these, 208 (3%) had an indication for β-lactam therapy and had a documented penicillin or cephalosporin allergy. One hundred patients were able to be interviewed for the purpose of this study. Twenty-two patients were unable to be interviewed due to intubation, deafness, language barriers, or decreased cognitive status. One patient refused to give consent to be interviewed. One patient was receiving a desensitization protocol. The remaining 84 patients were unavailable

at interview times or were discharged prior to being interviewed.

Forty-five patients had reacted to a parenteral form of penicillin, 35 to an oral dosage form, 5 to both parenteral and oral, 1 to a topical form, 13 could not recall the route and one patient had never received penicillin. Nine patients reported a delayed onset of the reaction of 4 or more days. Forty-two patients experienced their reaction to penicillin more than 25 years prior to the interview. Fourteen patients had had a positive reaction when rechallenged while 3 patients had had no reaction when rechallenged.

Thirty-two courses of therapy were for treatment of established or suspected infections while 83 were for prophylaxis. Of the 100 patients interviewed, 15 received both prophylaxis and active treatment therapies. The mean duration of a prophylactic course of therapy was 2.2 ± 2.2 days. The mean duration of a course of active therapy was 11.8 ± 7.0 days.

Using the predefined criteria in Table I, 29 patients had a high probability of allergy (Group A); 53 had an equivocal history which required skin testing for further differentiation (Group B), and 18 were deemed not to be allergic (Group C). This probability information was incorporated into the DAM.

Study patients were receiving the following alternate antimicrobial agents: vancomycin (33 patients), erythromycin (28 patients), clindamycin (26 patients), and ciprofloxacin (6 patients). The therapy received was not always limited by the patient's allergy status. As seen in Table II, 30 patients received β-lactam therapy even when the patient had a documented allergy to penicillin. No adverse effects were noted as a result of β-lactam therapy in any of the patients with purported penicillin allergies.

The actual cost of therapy for the 100 patients (115 courses) was $15,592.66 ($155.93/patient; $135.59/course). The potential cost according to the DAM was $16,500.65 ($165.01/patient; $143.48/course). The actual cost of 32 courses of active treatment was $9,234.02 ($288.56/course) while the predicted cost for active treatment was $8,252.27 ($257.88/course). The difference between the actual and predicted active treatment cost could result in a positive though insignificant direct drug cost-avoidance of $30.68/course

(p=0.70). The actual cost of 83 prophylactic regimens was $6,070.63 ($73.14/course) while the predicted cost for prophylaxis was $8,169.45 ($98.43/course). The difference between the actual and the predicted prophylactic treatment costs could result in a significant, negative direct drug cost-avoidance (i.e., increased cost) of $25.29/course (p=0.03)(Table III).

DISCUSSION

In order to consider the validity of a history of β-lactam hypersensitivity and to assess if a skin-test is indicated, a detailed description of the nature of the reaction and its time course should be obtained. First it is necessary to determine whether or not the signs and symptoms can be directly linked to the β-lactam therapy. The types of hypersensitivity reactions must be well defined and differentiated from reactions not originating from an immune response. A hypersensitivity reaction can be immediate, accelerated, or delayed.[29] Allergic reactions occur more frequently following parenteral administration than following other routes. An immediate reaction may be strictly cutaneous such as urticaria, or may be systemic such as anaphylaxis. These reactions are IgE-mediated and usually occur within 30 minutes of drug administration. An accelerated hypersensitivity reaction usually presents between 30 minutes and 72 hours after

Table II. β-Lactam Use in Patients with a Purported Penicillin Allergy

β-lactam received	Allergy probable n=29	Allergy possible n=53	Allergy not probable n=18
Penicillin	-	4	1
Cephalosporin	4	15	5
Imipenem	-	1	-

Table III. Cost Analysis

	Cost / Course		
	Actual	**Predicted (based on DAM)**	**Direct Drug Cost Avoidance**
Overall n=115	$135.59 ± 207.86	$143.48 ± 181.31	- $ 7.89 p=0.71
Treatment courses n=32	$288.56 ± 327.99	$257.88 ± 303.68	$ 30.68 p=0.70
Prophylactic courses n=83	$ 73.14 ± 82.71	$ 98.43 ± 62.38	- $ 25.29 p=0.03

DAM = Decision analysis model

drug administration as a cutaneous reaction predominately on the trunk. Delayed hypersensitivity reactions are often IgG or IgM-mediated and occur after 3 days. These reactions are less clinically significant due to their decreased mortality relative to IgE-mediated hypersensitivity reactions. Serum sickness and exanthematous rashes are common presentations of delayed hypersensitivity. The IgG and IgM-mediated reactions cannot be detected by a skin test. In the DAM, these reactions would have to be identified by history alone and be assigned to the "meets hypersensitivity criteria" arm, as a skin test is not indicated. Nonhypersensitivity reactions to β-lactam antibiotics include those due to toxicity and adverse effects. They can be serious reactions such as nephrotoxicity, neurologic toxicity, or blood dyscrasias but are considered atypical immune reactions and cannot be detected by a skin test. Gastrointestinal adverse effects are most common and include glossitis, stomatitis, epigastric distress, nausea, vomiting, diarrhea, and possibly pseudomembranous colitis as a severe complication.[29]

Very liberal criteria were used to develop the DAM and categorization criteria. By including unknown histories, distant past histories, and histories meeting only minimal requirements for an allergy identified a large proportion of patients (53%) were identified as having an equivocal allergy history and, hence, requiring an allergy consult. Direct comparison with other studies was not feasible as none evaluated patients for skin testing as a percentage of the general penicillin allergic population. A history of a reaction at least 25 years prior was included in the group although Sullivan et al[7] demonstrated a strong positive correlation between the time lapsed since the initial reaction presentation and the proportion of patients not reacting to a skin test. These patients could be expected to have a similar probability of having a positive skin test (less than 22% as seen at 10 years[7]) as the general history positive group (16%) if they had not been exposed to penicillin in the interim and resensitized.

Routine screening using a form was useful in identifying both patients who were probably and who were unlikely to be allergic. In the latter case, 18 patients were deemed to not have a penicillin allergy based on their reaction history and, hence, would tolerate other β-lactams. Just by identifying this group alone, the predicted cost of therapies was lower than actual costs by $774.25. A screening form such as the one used in this study could result in an estimated potential annual cost avoidance of $6,000.00 ($40.00/patient identified as probably not allergic). By determining if an inappropriate allergy label is in place, restrictions may be removed from antibiotic therapy. Using the form to standardize history-taking and the table of criteria for categorization

required a maximum of 15 minutes of the pharmacist's time to complete. It could be implemented as a means to standardize and facilitate practice to produce positive outcomes in therapy and cost-savings.

Other studies have shown the importance of allergy history-taking. Tripp et al[30] found that the penicillin allergy label could be removed from 13% of patients' charts based solely on information obtained from the history. They further supported the removal of the allergy labels by following those patients who went on to receive a penicillin or a cephalosporin without a skin test result. Two percent of the patients were rechallenged and did not react.

Many of our patients received a β-lactam despite the fact that several of them had a relatively high probability of hypersensitivity. This prescribing practice could have occurred if the physician was unaware of the allergy and neither pharmacy nor nursing intervened. As well, the physician may have been aware but had reason to believe that the history was negative or was vague enough to warrant the possible risk of cross-sensitivity in using a cephalosporin. In one case, physicians of the Allergy and Immunology Department advised use of a β-lactam. This further skews the cost analysis data since these patients still incurred the cost of an allergy consult if indicated by the model even though the therapy received and predicted by the model were both β-lactams. Furthermore, 4 patients who were classified as Group A (Table II) received a cephalosporin without adverse sequelae. This represents at least a 4% false positive allergy history using the categorization criteria.

For completeness, false negatives as a result of the skin test used in the model should be considered and the cost of potential allergic reactions could be incorporated into the model. The incidence of a probable IgE-mediated allergic reaction in history positive, skin test negative patients is less than 1% when a skin test using a major and minor determinant is used.[9] Our model predicts that 45 of the 53 patients requiring a skin test would have a negative result. Thus, the predicted incidence of a false negative test is 0.45% of the study patients or 0.85% of the skin-tested patients. Since this situation is predicted to occur rarely, its cost is insignificant and was not included in our model.

Not all patients identified were able to be interviewed. The main reasons were inability to communicate (22 of 108) or unavailability at interview times (84 of 108). Incorporating these patients into the DAM would further increase the total cost of predicted therapy. All patients unable to communicate a history for screening purposes would require the added cost of an allergy consult and skin test to validate their allergy. Those patients who had a length of stay shorter than the period

between their identification and the interview likely received such brief courses of therapy that even switching to a β-lactam therapy would not offset costs incurred by the allergy consult and skin test.

The DAM was used to estimate the direct drug cost avoidance accrued through the initiation of a penicillin allergy screening program. All patients for whom an antibiotic was ordered and who were reported to be penicillin allergic were included in this study regardless of the duration of their therapy. The majority of courses studied (83%) were actually for prophylaxis and were for a relatively short duration (2.2 ± 2.2 days). It is unlikely that the cost of the allergy consult could be offset by direct drug cost-avoidance given this short duration of therapy. In fact, the calculated break points at which the cost of β-lactam therapy plus allergy consult would equal the alternate drug cost was approximately 3 days of vancomycin therapy, 4 days of clindamycin therapy, and 9 days of erythromycin therapy. In contrast to the prophylactic regimens, the treatment courses with a longer duration of 11.8 ± 7.0 days resulted in a small cost-avoidance ($30.68/course).

While this study and the developed DAM did not support the widespread application of allergy consults to the total penicillin-allergic population requiring antimicrobial therapy, our conclusions have several limitations. First, the model was specific to our hospital patient population, their duration of therapy, and antibiotics and dosages used. Deviations in any of these factors would affect the cost analysis. Secondly, the relatively high use of β-lactam therapy despite a history of penicillin allergy biased our findings. Thirdly, the criteria established for this study were sufficient to categorize the patients, but without performing actual skin tests, we were unable to determine the validity of the DAM. Fourthly, each patient was considered to have received a finite therapy of 1, or at most, 2 antibiotic courses (one prophylactic and one active). In reality some patients may require subsequent courses and go on to receive yet another non-β-lactam antibiotic if the allergy label is not removed which could further increase their lifetime cost of therapy. Our DAM considers an allergy consult for each course of therapy but the recommendation should be to only skin test (cost $10.00) for each subsequent course of therapy.[13]

Based on allergy history analyses, a considerable number of patients with a purported penicillin allergy were identified as being likely able to tolerate β-lactam therapy. This study observed no direct drug cost-avoidance when routine allergy consults were used without regard to the duration of therapy. Subgroup analysis of particular alternate therapies and further definition of duration of therapy may reveal subsets of patients in whom cost-avoidance may be accrued. ▣

REFERENCES

1. Green GR, Peters GA, Gerace JE. Treatment of bacterial endocarditis in patients with penicillin hypersensitivity. *Ann Intern Med* 1967;67:235-49.
2. Levine BB, Zolov DM. Prediction of penicillin allergy by immunological tests. *J Allergy* 1969;43:231-44.
3. Green Gr, Rosenblum AH, Sweet LC. Evaluation of penicillin hypersensitivity: value of clinical history and skin testing with penicilloyl-polylysine and penicillin G. *J Allergy Clin Immunol* 1977;60:339-45.
4. Holgate ST. Penicillin allergy: how to diagnose and when to treat. *Br Med J* 1988;296:1213.
5. Solley GO, Gleich GJ, VanDellen RG. Penicillin allergy: clinical experience with a battery of skin-test reagents. *J Allergy Clin Immunol* 1982;69:238-44.
6. Saxon A, Beall GN, Rohr AS, Adelman DC. Immediate hypersensitivity reactions to beta-lactam antibiotics. *Ann Intern Med* 1987;107:204-15.
7. Sullivan TJ, Wedner HJ, Shatz GS, Yecies LD, Parker CW. Skin testing to detect penicillin allergy. *J Allergy Clin Immunol* 1981;68:171-80.
8. Sher TH. Penicillin hypersensitivity- A review. *Ped Clin N A* 1983;30:161-76.
9. Lin RY. Managing the penicillin-allergic patient. *Drug Ther* 1992;35-46.
10. MacNab KA. Cross allergenicity of penicillins and cephalosporins. *Can J Hosp Pharm* 1989;42:81-4.
11. Blanca M, Vega JM, Garcia J, Miranda A, Carmona MJ, Juarez C, et al. New aspects of allergic reactions to betalactams: crossreactions and unique specificities. *Clin Exp Allergy* 1994;24:407-15.
12. Anne S, Reisman RE. Risk of administering cephalosporin antibiotics to patients with histories of penicillin allergy. *Ann Allergy Asthma Immunol* 1995;74:167-70.
13. Kishiyama JL, Adelman DC. The cross-reactivity and immunology of β-lactam antibiotics. *Drug Saf* 1994;10:318-27.
14. Sanford JP. Guide to Antimicrobial Therapy 1992. Baltimore: Antimicrobial Therapy Inc;1992.
15. Hermans PE, Wilhelm MP. Vancomycin. *Mayo Clin Proc* 1987;62:901-5.
16. Wilson WR, Cockerill III FR. Tetracyclines, chloramphenicol, erythromycin, and clindamycin. *Mayo Clin Proc* 1987;62:906-15.
17. Sande MA, Mandell GL. Antimicrobial agents: tetracyclines, chloramphenicol, erythromycin, and miscellaneous antibacterial agents. In: Gilman AG, Goodman LS, Rall TW, Murad F, eds. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 8th ed. New York: Mac Millan Publishing Company; 1990:1170-98.
18. Ciprofloxacin. *Med Lett Drugs Ther* 1988;30:11-4.
19. Van Arsdel Jr. PP, Larson EB. Diagnostic tests for patients with suspected allergic disease. *Ann Intern Med* 1989;110:304-12.
20. Warrington RJ. Diagnosis of penicillin allergy by skin testing: the Manitoba experience. *Can Med Assoc J* 1978;118:787-91.
21. Kerr JR. Penicillin allergy: A study of incidence as reported by patients. *Br J Clin Pharmacol* 1994;48:5-7.
22. Gadde J, Spence M, Wheeler B, Adkinson NF. Clinical experience with penicillin skin testing in a large inner-city STD clinic. *JAMA* 1993;270:2456-63.
23. Sogn DD, Evans III R, Shepherd GM, Casale TB, Condemi J, Greenberger PA, 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;153:1025-32.

24. Lin RY. A perspective on penicillin allergy. *Arch Intern Med* 1992;152:930-7.

25. Goel V. Decision analysis: applications and limitations. *Can Med Assoc J* 1992;147:413-7.

26. Redelmeier DA, Sox Jr HC. The role of skin testing for penicillin allergy. *Arch Intern Med* 1990;150:1939-45.

27. Antimicrobial prophylaxis in surgery. *Med Lett Drugs Ther* 1992;34:5-8.

28. Conte JE, Barriere SL. Manual of Antibiotics and Infectious Diseases 6th ed. Philadelphia: Lea and Febiger; 1988.

29. Alanis A, Weinstein AJ. Adverse reactions associated with the use of oral penicillins and cephalosporins. *Med Clin NA* 1983;67:113-29.

30. Tripp DM, Brown GR. Pharmacist assessment of drug allergies. *Am J Hosp Pharm* 1993;50:95-8.