Prospective Assessment of Nephrotoxicity with Concomitant Aminoglycoside and Vancomycin Therapy

Suzette E. Salama and Coleman Rotstein

ABSTRACT

There is conflicting evidence about the nephrotoxic potential of vancomycin in combination with aminoglycosides. In a prospective fashion, we have attempted to address the issue of nephrotoxicity associated with aminoglycosides and vancomycin, while studying the risk of pharmacokinetic factors potentially associated with nephrotoxicity.

At a university-affiliated 600-bed teaching hospital, 492 consecutive patients receiving aminoglycosides and/or vancomycin were monitored. The patients were divided into three groups: A) patients receiving an aminoglycoside, B) patients receiving vancomycin, and C) patients receiving aminoglycoside concurrently with vancomycin. In Groups A, B and C, nephrotoxicity, defined as a 50% reduction in creatinine clearance, developed in 4.5%, 0% and 25% of patients, respectively. Using univariate analysis, it was found that the variables predisposing patients in Groups A and C to toxicity included: underlying diseases (malignant vs. non-malignant disease); prolonged duration of therapy; elevated trough serum aminoglycoside concentration and the use of concomitant nephrotoxic medications. Multivariate analysis revealed that the most significant predisposing factor was the number of potentially nephrotoxic concomitant drugs administered with the aminoglycoside and vancomycin. The results of this study suggest that there is increased nephrotoxicity associated with concurrent administration of aminoglycosides and vancomycin particularly when two or more other potential nephrotoxic medications are given.

Key Words: *aminoglycoside, nephrotoxicity, vancomycin*

Can J Hosp Pharm 1993;46:53-59

RÉSUMÉ

Les preuves concernant la néphrotoxicité de la vancomycine en combinaison avec les aminoglycosides sont contradictoires. Dans le cadre d'une étude prospective, nous avons essayé de résoudre ce problème tout en étudiant le risque des facteurs pharmacocinétiques qui peuvent être associés à la néphrotoxicité.

Dans un hôpital de 600 lits affiliés à une université, on a surveillé 492 patients consécutifs qui ont reçu des aminoglycosides et (ou) de la vancomycine. Les patients ont été répartis en trois groupes: A) patients recevant un aminoglycoside; B patients recevant la vancomycine et C) patients recevant les deux substances. On a ensuite déterminé la néphrotoxicité pour les groupes A, B et C, ce terme étant défini par une réduction de 50% de la clairance de la créatinine. Les résultats étaient respectivement de 4,5%, 0% et 25%. Au moyen d'une analyse à une seule variable, on a constaté que les variables qui prédisposaient les patients des groupes A et C à la néphrotoxicité comprennent les maladies sous-jacentes (affection maligne ou non), un traitement prolongé, une concentration sérique élevée d'aminoglycosides associée au creux et l'administration d'autres médicaments néphrotoxiques. L'analyse multivariée révèle que le facteur prédisposant le plus significatif est le nombre de médicaments potentiellement néphrotoxiques administrés avec les aminoglycosides et la vancomycine. Les résultats de l'étude suggèrent qu'on assiste à une hausse de la néphrotoxicité en raison de l'administration concurrente d'aminoglycosides et de vancomycine, surtout lorsqu'on administre déjà deux ou plusieurs autres médicaments éventuellement néphrotoxiques.

Mots clés: *aminoglycosides, néphrotoxicité, vancomycine*

Suzette E. Salama, B.Pharm., Ph.D., Department of Pharmacy, Henderson General Division, Hamilton Civic Hospitals, Hamilton, Ontario.
Coleman Rotstein, M.D., Division of Infectious Diseases, McMaster University, Hamilton, Ontario and the Department of Pharmacy, Henderson General Division, Hamilton Civic Hospitals, Hamilton, Ontario.
Address correspondence to: Dr. Coleman Rotstein, McMaster Medical Unit, Henderson General Division, Hamilton Civic Hospitals, 711 Concession Street, Hamilton, Ontario L8V 1C3.
Acknowledgements: The authors express their gratitude to Miss Virginia Hammill and Mrs. Lois Deck for secretarial assistance and the Hamilton Civic Hospitals Research Centre for statistical analysis expertise.

INTRODUCTION

Although numerous potent beta-lactam antimicrobial agents have emerged in the last decade, aminoglycosides and vancomycin remain commonly utilized parenteral agents. The aminoglycosides continue to be the mainstay of therapy for serious gram-negative infections and resistant organisms.[1] In fact, aminoglycoside-beta-lactam combinations are still considered to be the "gold standard" of therapy for all types of systemic *Pseudomonas aeruginosa* infections with the possible exception of infections of the urinary tract.[2] Despite this documented efficacy, some prescribers refrain from using aminoglycosides due to their narrow therapeutic-toxic ratio and their poten-

tial for oto- and nephrotoxicity.[3,4]

Increased vancomycin utilization has paralleled the increasing prevalence of methicillin-resistant staphylococcal infections.[5] In particular, the proliferation of coagulase-negative staphylococcal nosocomial bacteremias has greatly augmented vancomycin use.[6] However, vancomycin administration is also associated with certain toxicities. While vancomycin's ability to induce ototoxicity is controversial,[7] it has been documented to produce nephrotoxicity in 0 to 17% of patients.[8-13] Because of increasing resistance in nosocomial pathogens affecting oncology and critical care patients, concurrent administration of vancomycin and aminoglycosides is more common and concerns have arisen regarding the nephrotoxic potential of the coadministration of these antibacterial agents.[8,10] Studies, however, have provided conflicting results. The incidence of nephrotoxicity due to the combination of vancomycin with an aminoglycoside has ranged from 7% to 35%.[8-14] These studies have suffered from the problems of retrospective bias and the failure to adequately address confounding factors such as concomitant medications.

In a prospective fashion, we have attempted to examine the issue of nephrotoxicity associated with aminoglycoside, vancomycin, and the combination of vancomycin and aminoglycoside therapies. Risk factors potentially associated with nephrotoxicity in each of the groups were also explored.

Patients and Methods

At the Henderson General Division of the Hamilton Civic Hospitals, a 600-bed teaching hospital, consecutive patients receiving aminoglycoside, vancomycin, or combined aminoglycoside and vancomycin therapy over a period of six months from September 1990 to March 1991, were prospectively followed. Patients were excluded if they received either drug or the combination of drugs for less than 48 hours or were under 15 years of age. The following patient characteristics were recorded: age, sex, weight, underlying diagnosis, and baseline serum creatinine value.

The aminoglycosides (tobramycin, gentamicin or amikacin) were administered intravenously at a dose of 1-2 mg/kg of body weight per dose for tobramycin and gentamicin and 7.5-10 mg/kg per dose for amikacin. Doses were initially given every 8-12 hours empirically based on age, body weight and serum creatinine values. Aminoglycoside peak concentrations were obtained 0.5 hours after the end of the infusion which took place over 0.5 hours, while trough serum concentrations were drawn 10 minutes prior to antibiotic administration. When peak samples were not obtained in accordance with this guideline, the values were extrapolated to 0.5 hours after the end of the infusion to obtain the peak value. Peak and trough values used in the calculations were mean serum concentrations of the corresponding values (varied from 1-10 levels) obtained for each patient during the course of therapy.

Vancomycin was administered initially at a dose of 0.5-1 g every 12-24 hours intravenously based on age, body weight and serum creatinine values. Vancomycin peak serum concentrations were usually obtained one hour after the end of an infusion which occurred over one hour, while trough serum concentrations were drawn ten minutes prior to dose administration. The dosage interval was sometimes prolonged if serum vancomycin concentrations or serum creatinine values dictated that an increased dosage interval was warranted.

Serum creatinine was measured by spectrophotometry and recorded every one to four days during each course of therapy. Serum antibiotic concentrations were analyzed using a fluorescence-polarization immunoassay. Nephrotoxicity associated with antibiotic therapy was defined as a 50% or more decrease in the patient's baseline calculated creatinine clearance using the method of Cockroft and Gault.[15]

All therapeutic interventions were performed as necessary by the pharmacokinetic services of the Pharmacy Department or by the attending Infectious Diseases consultation service. Pharmacokinetic adjustments in antibiotic dose or dosage time interval using a one compartment model were made as appropriate, to ensure that the respective drug concentrations were in the therapeutic range. The desired aminoglycoside trough and peak serum concentrations were ≤ 2 mg/L and 5-10 mg/L, respectively, for tobramycin and gentamicin and ≤ 10 mg/L and 20-30 mg/L for amikacin, respectively. Attempts were made to maintain vancomycin trough concentrations at ≤ 10 mg/L and peak concentrations at 20-40 mg/L.

The following data regarding therapy were also recorded: the dose and frequency of the aminoglycoside and vancomycin administration; trough and peak serum concentrations approximately every three days; the duration of therapy; and a list of concurrent potentially nephrotoxic drugs administered including amphotericin B, acyclovir, cephalosporins, penicillins, cisplatinum, diuretics and amethopterin.[16]

In order to assess the effect of the combination of vancomycin and aminoglycosides, patients were divided into three groups: Group A-patients receiving aminoglycosides only; Group B-pa-

tients receiving vancomycin only; and Group C-patients receiving vancomycin and aminoglycosides concomitantly. Data regarding those patients determined to be nephrotoxic were compared with pooled information from non-nephrotoxic patients. Mean values were calculated for each parameter. Each individual group was also analyzed separately wherein nephrotoxic patients were compared with non-nephrotoxic patients using Fisher's Exact test. The association of nephrotoxicity with patient factors and pharmacokinetic information was performed using Chi-square analysis and Student's t-test as appropriate.

Based on the results of the univariate analysis, factors demonstrated to be significant for the development of nephrotoxicity were then loaded in a stepwise fashion to determine their significance in a multiple logistic regression analysis (BMDP — Stepwise Logistic Regression, BMDP Statistical Software Inc., Los Angeles, California). In addition, another multivariate analysis was performed using all variables studied (age, sex, weight, baseline serum creatinine, aminoglycoside and/or vancomycin mean daily dose, duration of therapy, peak and trough serum concentrations, and the number of concomitant potentially nephrotoxic drugs). Each patient was assigned to a malignant or non-malignant group and this dichotomous variable was entered into the analysis.

RESULTS

A total of 492 patients who received 507 therapeutic courses were included in the study. Not included in the analyses were 15 multiple courses of therapy in the same patients. Thus, one therapeutic course in each of 492 patients was analyzed. An overall comparison of the patient demographic characteristics between the non-nephrotoxic (458 patients) and nephrotoxic (34 patients) groups is found in Table I. Significant differences were noted between the non-nephrotoxic and nephrotoxic groups for underlying diagnosis (i.e., malignant vs. non-malignant), duration of vancomycin and aminoglycoside therapy and mean aminoglycoside trough concentration. In the nephrotoxic group, malignant conditions outnumbered non-malignant ones. Similarly, the duration of therapy with vancomycin or an aminoglycoside in the nephrotoxic group exceeded that of the non-nephrotoxic group (19.2 ± 9.4 vs. 11.5 ± 7.2 days, respectively, for vancomycin, and 13.6 ± 9.7 vs. 8.3 ± 6.5 days, respectively, for the aminoglycosides). In addition, the mean aminoglycoside trough serum concentration was significantly higher in the nephrotoxic group compared to that in the non-nephrotoxic group. Twelve percent of all the patients had trough aminoglycoside concentrations of >2 mg/L. No other differences were observed between the groups with regard to vancomycin trough and peak concentrations and aminoglycoside peak concentrations. Only two patients were treated with amikacin and one of them became nephrotoxic.

When the patients were categorized according to the antibiotic(s) administered, significant differences in demographic data emerged among Groups A, B and C with regard to age and underlying diagnosis (Table II). Group B (vancomycin therapy alone) contained significantly older patients than Groups A (aminoglycoside alone) and C (combined aminoglycoside and vancomycin), but Group C had a significantly greater proportion of patients with malignancy than Groups A and B. The incidence of nephrotoxicity among Groups A, B and C is shown in Table III. For Group A patients, 4.5% became nephrotoxic whereas no patients developed nephrotoxicity in Group B. However, combined therapy with aminoglycosides and vancomycin resulted in 25.0% of the patients developing

Table I: Characteristics of non-nephrotoxic patients compared with nephrotoxic patients

	Non-Nephrotoxic Patients n=458	Nephrotoxic Patients n=34	p Value
Age (years)	54.4±19.2	57.4±19.3	0.39
Sex (number of men/number of women)	185/272	17/17	0.28
Weight (kg)	70.5±15.8	67.8±16.3	0.36
Baseline Serum Creatinine (μmol/L)	86.3±30.5	91.2±32.5	0.37
Underlying Diagnosis (malignant/non-malignant)	123/311	19/15	0.0015
Antibiotic Daily Dose (mg)			
Vancomycin	1420±555	1444±527	0.88
Aminoglycoside	230±49	217±79	0.15
Length of Course (days)			
Vancomycin	11.5±7.2	19.2±9.4	0.0006
Aminoglycoside	8.3±6.5	13.6±9.7	<0.0001
Serum Levels of Antibiotics mg/L			
Vancomycin peak	32.1±11.9	35.1±9.3	0.40
Vancomycin trough	8.8±6.0	10.0±5.4	0.50
Aminoglycoside peak	5.0±1.8	5.1±1.4	0.71
Aminoglycoside trough	1.2±0.9	1.6±1.1	0.010

Values are expressed as mean ± SD unless otherwise stated

nephrotoxicity. The nephrotoxicity rate among Group C patients was higher than the rates exhibited by Groups A ($p < 0.05$) and B ($p < 0.05$). There was a trend with respect to underlying diagnosis (malignant vs. non-malignant) in association with the development of nephrotoxicity in Group C compared to Group A. No statistically significant difference in the incidence of nephrotoxicity was observed in Groups A and C between gentamicin and tobramycin use [Group A 9/174 (5.2%) gentamicin use vs. 10/226 (4.4%) tobramycin use and Group C 3/17 (17.6%) gentamicin use vs. 11/46 (23.9%) tobramycin use].

The administration of concomitant nephrotoxic drugs had a marked effect on the development of nephrotoxicity among our patients. For the pooled information on all patients with nephrotoxicity, an increasing number of concomitant nephrotoxic drugs (up to four) produced a higher incidence of nephrotoxicity among the patients (Table IV). In the Group A nephrotoxic patients, the following concomitant drugs were used: acyclovir (one patient), amphotericin B (one patient), cephalosporins (nine patients), penicillins (twelve patients), cisplatinum (one patient), and diuretics (six patients). Similarly, in the nephrotoxic Group C patients the concomitant drugs included: acyclovir (five patients), amphotericin B (seven patients), cephalosporins (ten patients), penicillins (sixteen patients), cisplatinum (two patients), diuretics (two patients), and amethopterin (one patient). Another analysis of the concomitant nephrotoxic drugs excluding penicillins and cephalosporins demonstrated that: 4.4% (19/428), 14.9% (10/67), 55.6% (5/9) and 66.6% (2/3) of patients receiving no, one, two and three concomitant nephrotoxic drugs, respectively, developed nephrotoxicity.

Table II: Demographic Data for Groups A, B and C

	GROUP A (Aminoglycoside) (n=401)	GROUP B (Vancomycin) (n=27)	GROUP C (Aminoglycoside-Vancomycin) (n=64)	p-VALUE
Age (years)	54.9±19.3	62.4±18.6	49.9±18.4	0.0152
Sex (number of men/ number of women)	159/242	10/17	34/30	0.110
Weight (kg)	70.8±16.3	67.1±14.6	68.9±14.6	0.48
Baseline Serum Creatinine (μmol/L)	87.8±30.4	75.5±14.3	86.5±32.3	0.184
Baseline Creatinine Clearance (ml/s)	1.4±0.65	1.27±0.45	1.54±0.64	0.29
Underlying Diagnosis (malignant/non-malignant)	90/291	9/15	43/21	p<0.00005

Values are expressed as mean ± SD unless otherwise stated.

Table III: Incidence of nephrotoxicity for aminoglycoside, vancomycin and combined aminoglycoside and vancomycin therapy

	Non-Nephrotoxic	Nephrotoxic	%
GROUP A (Aminoglycoside)	383	18	4.5
GROUP B (Vancomycin)	27	0	0.0
GROUP C (Aminoglycoside + Vancomycin)	48	16	25.0*+
TOTAL	**458**	**34**	

* Significantly different from Group A ($p<0.05$)
\+ Significantly different from Group B ($p<0.05$)

Table IV: Effect of the number of concomitant drugs* on the development of nephrotoxicity

Number of Drugs	Non-Nephrotoxic	Nephrotoxic	Percent Nephrotoxic
0	186	2	1.1
1	190	11	5.0
2	57	8	12.3
3	18	7	28.0
4	5	6	54.5
5	0	0	-
6	1	0	0

* Potentially nephrotoxic drugs monitored: cephalosporins, amphotericin B, acyclovir, penicillins, amethopterin, cisplatinum and diuretics.

The patient's underlying diagnosis (malignant vs. non-malignant), the duration of vancomycin and/or aminoglycoside therapy and the mean serum aminoglycoside trough level which significantly contributed to the development of nephrotoxicity in Groups A, B and C were analyzed in a stepwise fashion by a multiple logistic regression. It was hoped that one or more factors would emerge as predominant when these factors were combined with the number of concomitant nephrotoxic drugs in this type of analysis. The number of concomitant nephrotoxic drugs emerged as the most significant

factor predisposing patients to nephrotoxicity in all groups. In particular, this finding was further verified when vancomycin was included in the analysis as one of the concomitant nephrotoxic drugs. The results of this analysis are shown in Table V.

Our data on the incidence of nephrotoxicity with concomitant aminoglycoside and vancomycin therapy were contrasted with the results of other investigators in Table VI.[8-14,17] The incidence of nephrotoxicity ranged from 7 to 35%. Little variation was noted between retrospective and prospective studies.

DISCUSSION

The potential development of nephrotoxicity is an unwanted side effect of aminoglycoside and vancomycin therapy. It may interfere with planned therapy and lead to alternative antibiotic selection which may be less effective and more costly. In addition, the development of nephrotoxicity due to these antimicrobial agents may impose a significant economic burden on the health care system.[18] Therefore, efforts to prevent the development of aminoglycoside and/or vancomycin-induced nephrotoxicity are worthy of pursuit.

The incidence of aminoglycoside-associated nephrotoxicity has been extensively reported and summarized. It has ranged from 0 to 44%.[19] We observed a rate of 4.5% which is in the lower end of this range but comparable with rates of other investigators. However, contrasting rates may be hampered by the differences in patient population characteristics, study design including small numbers of subjects, and differences in the definition of nephrotoxicity. The most pressing of these problems is the study design because of the introduction of bias in retrospective analyses, and the difficulty in drawing conclusions from small numbers of subjects. We overcame these problems by performing a prospective trial incorporating larger patient numbers.

Although the risk of vancomycin-induced nephrotoxicity appeared to be a problem with earlier preparations of the drug, it has not emerged as one with the more recent formulation.[20] In fact, the incidence of nephrotoxicity in recent publications has varied from 0 to 17%.[8-13] Once more, these data are problematic due to retrospective study designs and small number of patients. Although our data failed to demonstrate any nephrotoxic potential associated with vancomycin, this conclusion was limited by low patient numbers receiving vancomycin alone.

Controversy still exists about the nephrotoxic potential of vancomycin when administered concurrently with aminoglycosides. Although Cook and Farrar cautioned readers about the additive nephrotoxicity of vancomycin and an aminoglycoside used in combination, this was not well substantiated.[21] Some human trials have suggested augmented nephrotoxicity with the combination[8,12-14] while others do not concur.[9,10] Our results point to enhanced nephrotoxicity with concomitant aminoglycoside and vancomycin treatment.

A more complete understanding of the rates of nephrotoxicity associated with the drugs individually and in combination comes from

Table V: Factors associated with nephrotoxicity for aminoglycoside and combined aminoglycoside and vancomycin therapy by logistic regression analysis

Factor	p Value
Underlying Diagnosis	0.0318
Duration of Therapy	0.3218
Aminoglycoside Mean Trough Concentration	0.2568
Concomitant Medication	<0.0005
Age	0.0702
Vancomycin included with Concomitant Medication	<0.0005

Table VI: Aminoglycoside and Vancomycin Nephrotoxicity

	Farber & Moellering 1983 (8)	Mellor et al 1985 (9)	Sorrell & Colignon 1985 (10)	Cimino et al 1987 (11)	Downs et al 1989 (12)	Smith et al 1989 (17)	Rybak et al 1990 (13)	Pauly et al 1990 (14)	Current Study
Type of study	retrospective	prospective	prospective	retrospective	prospective	prospective	prospective	retrospective	prospective
No. of Courses of concomitant aminoglycoside and vancomycin therapy	100	27	50	40	12	35	63	105	64
Nephrotoxicity (%)	35	7	8	15	25	14	22	27	25

an evaluation of risk factors for nephrotoxicity. Previously, elevated trough serum aminoglycoside and vancomycin concentrations,[11] cephalothin usage,[22] liver disease, age, sex, shock,[23] and furosemide therapy[24] have been implicated as significant risk factors.

We focused on pharmacokinetic parameters and concomitant drugs in an attempt to establish risk factors for the nephrotoxicity of aminoglycosides and vancomycin. It was felt that pharmacokinetic parameters and other concomitant drugs would be most amenable to change if they were verified as risk factors for nephrotoxicity. We found in our univariate analysis that a diagnosis of malignant disease, the duration of therapy, and mean aminoglycoside trough concentrations were associated with nephrotoxicity. Although there was a significant difference among Groups A, B and C with respect to age, this was not a significant predictor of nephrotoxicity in the pooled data analysis. Furthermore, even though the vancomycin alone group had the highest mean age, no patients in this group became nephrotoxic. Moreover, in our multiple logistic regression analysis the number of concomitant nephrotoxic drugs (particularly two or more) emerged as the most significant factor.

Cephalosporins and penicillins were included among our potentially nephrotoxic agents, because these drugs have been implicated as causes of interstitial nephritis leading to renal insufficiency.[25] It is possible that the development of even a minor degree of interstitial nephritis may enhance the propensity of producing nephrotoxicity with aminoglycosides in combination with vancomycin. Of note, our findings were unchanged even when both cephalosporin and penicillin concomitant medications were excluded from the analysis.

There are, however, three caveats to our conclusions. First, a randomized trial of adequate sample size comparing the aminoglycoside-vancomycin combination to another drug in combination with an aminoglycoside for specific clinical indications in patient populations at risk for nephrotoxicity would produce results least subject to bias. Second, the inclusion of more factors such as the type of infecting organism, liver disease, shock or previous aminoglycoside and vancomycin exposure in the logistic regression analysis may have an effect on our results. Finally, the inclusion of all concomitant medications would be advantageous in assessing the nephrotoxic potential of this factor.

The results of this study suggest that there is increased nephrotoxicity associated with the concurrent administration of aminoglycosides and vancomycin. From our data, there is no difference in the nephrotoxic potential of either gentamicin or tobramycin. Moreover, vancomycin, when administered alone, does not appear to cause nephrotoxicity. Also, one should be cognizant of the increased risk of the combination of aminoglycosides and vancomycin when two or more other nephrotoxic drugs are administered concurrently. In such situations, it would be prudent to substitute other less nephrotoxic antimicrobials such as broad spectrum cephalosporins or fluoroquinolones to prevent aminoglycoside- and vancomycin-induced nephrotoxicity.

REFERENCES

1. John JF Jr. What price success? The continuing saga of the toxic: therapeutic ratio in the use of aminoglycoside antibiotics. *J Infect Dis* 1988; 158:1-6.
2. Siegenthaler WE, Bonetti A, Luthy R. Aminoglycoside antibiotics in infectious diseases: an overview. *Am J Med* 1986; 80 (Suppl 6B):2-14.
3. Brummett RE, Fox KE. Aminoglycoside-induced hearing loss in humans. *Antimicrob Agents Chemother* 1989; 33:797-800.
4. Meyer R. Risk factors and comparisons of clinical nephrotoxicity of aminoglycosides. *Am J Med* 1986; 80 (Suppl 6B):119-25.
5. Chambers HF. Methicillin-resistant staphylococci. *Clin Microbiol Rev* 1988; 1:173-86.
6. Schaberg DR, Culver DH, Gaynes RP. Major trends in the microbial etiology of nosocomial infection. *Am J Med* 1991; 91 (Suppl 3B):72S-5S.
7. Brummett RE, Fox KE. Vancomycin- and erythromycin-induced hearing loss in humans. *Antimicrob Agents Chemother* 1989; 33:791-6.
8. Farber BF, Moellering RC. Retrospective study of the toxicity of preparations of vancomycin from 1974 to 1981. *Antimicrob Agents Chemother* 1983; 23:138-41.
9. Mellor JA, Kingdom J, Cafferkey M, et al. Vancomycin toxicity: a prospective study. *J Antimicrob Chemother* 1985; 15:773-80.
10. Sorrell TC, Collingnon PJ. A prospective study of adverse reactions associated with vancomycin therapy. *J Antimicrob Chemother* 1985; 16:235-41.
11. Cimino MA, Rotstein C, Slaughter RL, et al. Relationship of serum antibiotic concentrations to nephrotoxicity in cancer patients receiving concurrent aminoglycoside and vancomycin therapy. *Am J Med* 1987; 83:1091-7.
12. Downs NJ, Neihart RE, Dolezal M, et al. Mild nephrotoxicity associated with vancomycin use. *Arch Intern Med* 1989; 149:1777-81.
13. Rybak MJ, Albrecht LM, Boike SC, et al. Nephrotoxicity of vancomycin alone and with an aminoglycoside. *J Antimicrob Chemother* 1990; 25:679-87.
14. Pauly DJ, Musa DM, Lestico MR, et al. Risk of nephrotoxicity with combination vancomycin-aminoglycoside antibiotic therapy. *Pharmacotherapy* 1990; 10:378-82.
15. Cockroft DW, Gault MN. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; 16:31-41.
16. Koren G. The nephrotoxic potential of drugs and chemicals: pharmacological basis and clinical relevance. *Medical Toxicology* 1989; 4:59-72.
17. Smith SR, Cheesbrough J, Spearing R, et al. Randomized prospective study comparing vancomycin with teicoplanin in the treatment of

infections associated with hickman catheters. *Antimicrob Agents Chemother* 1989; 33:585-8.
18. Eisenberg JM, Koffeiz H, Glick HA, et al. What is the cost of nephrotoxicity associated with aminoglycosides? *Ann Intern Med* 1987; 107:900-9.
19. McCormack JP, Jewesson PJ. A critical reevaluation of the "therapeutic range" of aminoglycosides. *Clin Infect Dis* 1992; 14:320-39.
20. McHenry MC, Gavin TL. Vancomycin. *Pediatr Clin North Am* 1983; 30:31-47.
21. Cook FV, Farrar WE Jr. Vancomycin revisited. *Ann Intern Med* 1978; 88:813-8.
22. Wade JC, Smith CR, Petty BG, et al. Cephalothin plus an aminoglycoside is more nephrotoxic than methicillin plus an aminoglycoside. *Lancet* 1978; 1:604-6.
23. Moore RD, Smith CR, Lipsky JJ, et al. Risk factors for nephrotoxicity in patients treated with aminoglycosides. *Ann Intern Med* 1984; 100:352-7.
24. Kahn T. Effect of furosemide on gentamicin and netilmicin nephrotoxicity. *Kidney Int* 1977; 12:527.
25. Manian FA, Stone WJ, Alford RH. Adverse antibiotic effects associated with renal insufficiency. *Rev Infect Dis* 1990; 12:236-49.