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REVIEW ARTICLE

# Nephrotoxicity with Combination Vancomycin-Aminoglycoside Therapy

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**OBJECTIVES** The purpose of this paper is to review the medical literature regarding vancomycin-aminoglycoside induced nephrotoxicity in the pediatric population.
**METHODS** MEDLINE (1966 through June 2005), EMBASE (1980 through 1st quarter 2005), and International Pharmaceutical Abstracts databases were reviewed using appropriate search terms for articles related to nephrotoxicity with vancomycin and aminoglycoside use. Case reports, letters to editors, retrospective and prospective studies evaluating nephrotoxicity with the agents in pediatric patients were compiled and summarized. Studies in animals and adults were also briefly reviewed.
**RESULTS** One case report, two letters to editors, one retrospective study, and two prospective studies evaluated the nephrotoxicity of combination aminoglycoside and vancomycin therapy in pediatric patients. The collective number of patients in the reports was 165. Patients ranged in age from 3 days to 19 years old. Four out of the six reports, including all of the prospective studies, concluded that combination therapy does not potentiate nephrotoxicity.
**CONCLUSIONS** Although vancomycin and the aminoglycosides have been associated with drug induced nephrotoxicity, reports in the literature do not appear to support the idea that the combination of vancomycin and an aminoglycoside is more nephrotoxic than either medication alone.

**KEYWORDS:** adverse effect, aminoglycoside, drug interaction, nephrotoxicity, pediatric, vancomycin

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## INTRODUCTION

Vancomycin is commonly used in pediatric patients as empiric therapy for suspected methicillin-resistant *Staphylococcus aureus* (MRSA) or for confirmed treatment of MRSA infections that show no inducible resistance to vancomycin.[1,2] In order to increase the bactericidal activity of vancomycin, aminoglycosides may be added for synergistic activity, especially in resistant strains. The combination may also be used in the treatment of multibacterial infections or empiric treatment of nosocomial infections.[3] Although long considered nephrotoxic, the potential of vancomycin to cause kidney damage remains unclear. More recent information has suggested that data regarding the nephrotoxicity of combined vancomycin and an aminoglycoside are conflicting.[1,4-8] The

**ABBREVIATIONS** AAP, alanine aminopeptidase; BUN, blood urea nitrogen; MRSA, methicillin-resistant *Staphylococcus aureus*; NAG, N-acetyl-beta-D-glucosaminidase

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purpose of this paper is to review literature regarding vancomycin-aminoglycoside induced nephrotoxicity in the pediatric population.

## BACKGROUND

A search was conducted in MEDLINE (1966 through June 2005), EMBASE (1980 through 1st quarter 2005), and International Pharmaceutical Abstracts databases for articles related to nephrotoxicity with vancomycin and aminoglycoside use. The search strategy involved various combinations of the terms aminoglycoside(s), vancomycin, kidney failure, and nephrotoxicity, related articles searches, and bibliography searches. Case reports, letters to editors, retrospective studies, and two prospective studies evaluating nephrotoxicity with combination aminoglycoside and vancomycin therapy in pediatric patients were compiled and summarized. Studies in animals and adults are also briefly reviewed.

Vancomycin-induced nephrotoxicity has been reported when vancomycin is given alone. Sorrell and Collignon did not note any nephrotoxicity in 25 adult and adolescent hospitalized patients.[9] Likewise, in a retrospective study by Farber et al., only 5% of adult and elderly patients at Massachusetts General Hospital receiving vancomycin alone developed renal impairment, which reversed when vancomycin was discontinued.[10] Rybak et al. reported similar findings in a prospective study of 168 adult patients in the hospital with no predisposing or underlying factors that might affect renal function.[11] Conversely, higher rates of nephrotoxicity have been noted by other authors. Incidences of 13% and 19% were reported in two studies of elderly patients,[12,13] and a 15% incidence was reported in adults with cancer.[4] Only one study has noted a rise in serum creatinine in 2 of 19 children treated with vancomycin.[14]

Many practitioners believe that reports of nephrotoxicity with vancomycin prior to 1980 were due to impurities in the preparations available, though the manufacturer states that it is unknown whether impurities were nephrotoxic or not.[1,10,15] After 1980, the incidence of vancomycin-induced nephrotoxicity has ranged from 0–25% (median 5%).[16] Additional variables include concurrent administration of other nephrotoxic agents (particularly aminoglycosides and radiographic contrast media), hypotension and underlying medical conditions. When it does present, vancomycin-induced nephrotoxicity is thought to occur by two mechanisms that affect proximal tubular cells. The first mechanism involves the basolateral membrane of the kidney where vancomycin is actively transported from the blood to the tubular cell. The second mechanism involves the reabsorption of vancomycin in the proximal tubules, though this is not thought to be a primary cause of nephrotoxicity. It is hypothesized that when vancomycin is present at these sites in the kidney, the agent may be toxic to the cells and may result in tubular necrosis.[1,17]

Aminoglycosides bind to the brush border in the proximal tubule of the kidney where they are stored in lysosomes that then bind to phospholipids. Structural damage to the proximal tubule, including cell necrosis, may occur when these lysosomes rupture. Aminoglycosides may also impair epidermal growth factor, which then impedes cellular repair. Tubular damage from aminoglycoside antibiotics may result in increased N-acetylglucosaminidase (NAG) excretion and increased serum creatinine.[18] Alanine aminopeptidase (AAP) is an enzyme present in the brush border that signifies structural damage to the kidney when levels appear increased in the urine.[1] To improve aminoglycoside safety yet retain efficacy, many institutions have moved to using extended interval dosing in neonates and once daily dosing in pediatric and adult patients rather than 2–3 divided doses daily.[1] Renal damage due to aminoglycoside therapy not in combination with vancomycin has an incidence of approximately 3%–26% in studies in adults and approximately 0%–10% in studies in neonates.[1,10] Hailemeskel et al. and Rybak et al. reported 2.7% and 15.4% incidences of nephrotoxicity in adult and elderly patients receiving monotherapy with an aminoglycoside, respectively.[19,20] Goetz evaluated aminoglycoside therapy in elderly patients and found a 12% incidence of nephrotoxicity.[13] Cimino and colleagues reported an incidence of 18% in a study of adult cancer patients.[4] Data is conflicting regarding nephrotoxicity with aminoglycosides in neonates. Gordjani et al. did not find any signs of glomerular dysfunction in neonates treated with tobramycin.[21] Tessin

et al. also found no statistically significant changes in AAP or NAG when tobramycin treated patients were compared to those who had received ceftazidime.[22] Fanos et al. did, however, find an increase in tubular dysfunction in neonatal patients given amikacin.[23]

Although concern has been expressed about an increased risk of nephrotoxicity when vancomycin and an aminoglycoside are used concurrently, this controversy continues as to whether or not this combination causes more nephrotoxicity than that noted for of either agent alone.[10] Some have hypothesized that, if it occurs, an increase in nephrotoxicity may be due to the damaging affects caused by both drugs in the proximal tubule.[1]

### *Animal studies*

Studies have been conducted in animals evaluating nephrotoxicity when the two antibiotics are combined. Similar to studies in humans, the animal studies have also resulted in conflicting evidence. Two studies found no increased nephrotoxic effect when vancomycin was combined with an aminoglycoside in rats compared to either agent alone. The first study by Torel et al. evaluated ten rats injected with 100 mg/kg of vancomycin and 80 mg/kg of amikacin for 15 days, and compared this group to a group of 10 rats injected with amikacin 80 mg/kg and a group of 5 untreated rats. Renal changes were noted in the treated groups; however changes in serum creatinine, urea and nitrogen concentrations, and morphological changes were similar in both treated groups.[24] Kacew et al. found that nephrotoxicity due to vancomycin 100 mg/kg or 500 mg/kg plus gentamicin 20 mg/kg or 100 mg/kg for 4 days was no different than that noted with gentamicin 20 mg/kg or 100 mg/kg alone.[25] Alternatively, 2 animal studies conducted by Fauconneau et al. and one by Wold and Turnipseed found increased nephrotoxic effects when vancomycin 200–300 mg/kg was given in combination with gentamicin 100-200 mg/kg or tobramycin 80 mg/kg compared to any of the agents alone.[26-28]

### *Adult reports*

Several retrospective[19,29] and prospective studies[4,11-13] have evaluated the nephrotoxicity of concomitantly administered vancomycin-aminoglycoside therapy in hospitalized adults. These reports have noted the incidence of nephrotoxicity to be between 4.4%–35%.[4,10-13,19,29] When vancomycin was added to therapy with an aminoglycoside, Farber et al. reported a 35% incidence of nephrotoxicity in adults[10] and Pauly et al. reported an incidence of 27%.[10] Downs et al. compared combination therapy to vancomycin alone and found the incidence of nephrotoxicity was 33% in patients receiving both an aminoglycoside and vancomycin compared to 13% with vancomycin only.[12] Hailemeskel et al., Goetz et al., and Rybak et al. all compared the incidence of nephrotoxicity with aminoglycosides and vancomycin combined to either agent alone in hospitalized adults. All three studies found an increased incidence of nephrotoxicity with combination therapy compared to aminoglycoside or vancomycin therapy alone; however, this difference was only statistically significant in the study by Rybak and colleagues ($P < .0001$).[11,13,19] The incidence of nephrotoxicity with combination therapy was 4.4%, 24%, and 22%, respectively in the studies by Hailemeskel et al., Goetz et al., and Rybak et al. Nephrotoxicity occurred in 2.7%–2.8%, 12%, and 11% of patients on aminoglycoside therapy alone, and in 1.1%, 19%, and 5% of patients, respectively, on vancomycin alone.[11,13,19] Cimino and colleagues, however, found that cancer patients receiving aminoglycoside therapy alone had a higher incidence of nephrotoxicity (18%), compared to those receiving either vancomycin alone (15%) or combination aminoglycoside and vancomycin therapy (15%).[4] Concern has arisen that nephrotoxicity may actually have been overestimated since some studies included only patients exposed to high concentrations of the antibiotics.[1,30] A meta-analysis evaluating data on renal dysfunction from vancomycin and aminoglycoside therapy in adults concluded that combination therapy is associated with an increase in nephrotoxicity compared to either agent alone.[13]

### *Pediatric reports*

Several reports including one case report,[30] two letters to the editor,[5,14] one retrospective study[6] and two prospective studies[7,8] have been published evaluating nephrotoxicity due to vancomycin and aminoglycoside combination therapy in pediatric patients (Table). Nephrotoxicity is thought to be less common in the

**Table.** Summary of Literature Reports in Pediatric Patients

| Reference (Report Type) | Number of Patients (Ages) | Drugs | Conclusions |
|---|---|---|---|
| 30 (case series) | 4 (3–10 yrs) | Patients 1 & 2: gentamicin 7.5 mg/kg/days + vancomycin 40 mg/kg/days<br>Patient 3: amikacin 22.5 mg/kg/days + vancomycin 40 mg/kg/days<br>Patient 4: tobramycin 5.5 mg/kg/days + vancomycin 40 mg/kg/days | Serum creatinine should be monitored in patients receiving vancomycin-aminoglycoside therapy.<br>The aminoglycoside should be discontinued if the serum creatinine increases by ≥ 0.5 mg/dL. |
| 7 (prospective) | 90 (5 days to 19 yrs) | Vancomycin: mean dose 35 mg/kg/days (range 20–60 mg/kg/days) AND Gentamicin (n = 76): mean dose 6.5 mg/kg/days (range 2.5–14 mg/kg/days) OR Tobramycin (n = 14): mean dose 6.5 mg/kg/days (range 2.5–14 mg/kg/days) | Combination vancomycin-aminoglycoside therapy may be safe when serum concentrations remain in "therapeutic" range. |
| 8 (randomized, double-blind, placebo controlled) | 14 (2–14 yrs) | Vancomycin: 300 mg/m$^2$ after each amikacin dose + Amikacin: 800 mg/m$^2$/days q 6 hrs + Ticarcillin: 2.25 g/m$^2$ after each dose of vancomycin + Nystatin q 6 hrs OR Amikacin: 800 mg/m$^2$/days q 6 hrs + Ticarcillin and clavulanate (3 g ticarcillin/100 mg clavulanate) 2.25 g/m$^2$ after each dose of placebo + placebo after each amikacin dose + Nystatin every 6 hrs | Vancomycin does not potentiate the nephrotoxicity of amikacin. |
| 6 (retrospective observational) | 47 (3–55 days) | 15 mg/kg of vancomycin: q 24 hrs if PCA < 30 wks q 18 hrs if PCA 30–33 wks q 12 hrs if PCA ≥ 34 wks q 8 hrs if PCA ≥ 34 wks and chronological age ≥ 1 wk ± Gentamicin | Vancomycin, even at high concentrations, is relatively safe in low birth weight infants. Clinically important nephrotoxicity was absent with the combination. |
| 14 (observational) | 345 courses of therapy | Vancomycin: doses not specified Aminoglycoside: doses and drugs not specified or avoiding nephrotoxicity with these agents | Monitoring of aminoglycoside and vancomycin concentrations may be beneficial in decreasing |
| 5 (retrospective observational) | 10 (14 mo–14 yrs) | Vancomycin and gentamicin doses not specified | Vancomycin and gentamicin may be used safely in combination in pediatric patients with routine serum concentration monitoring. |

*PCA, postconceptional age*

neonatal population than in adult patients.[1,7] It is theorized that because neonates have immature proximal tubular cells they have a decreased uptake of the antibiotics; hence, they may exhibit renal protection from these antibiotics.[1]

## Case report

The first report evaluating nephrotoxicity with combination vancomycin-aminoglycoside therapy was described by Odio et al. and involved a case series of four children.[30] The patients' diagnoses included: disseminated *Staphylococcus aureus* osteomyelitis (patient 1, 10 years old), presumptive suppurative arthritis and endocarditis (patient 2, 10 years old), *Staphylococcus aureus* pneumonia (patient 3, 13 years old), and presumptive intra-abdominal abscess (patient 4, 3 years old). All patients received vancomycin 40 mg/kg/day. Patients 1 and 2 also received gentamicin (7.5 mg/kg/day) in combination for 31 and 10 days, respectively; patient 3 received amikacin (22.5 mg/kg/day) in combination for 3 days; and patient 4 received tobramycin (5.5 mg/kg/day) in combination for 7 days. Serum concentrations of the antibiotics were not reported. All four children experienced nephrotoxicity, defined as greater than or equal to a two-fold increase in serum creatinine from baseline. The increased serum creatinine and blood urea nitrogen (BUN) concentrations returned to baseline within 3 to 6 days following discontinuation of the aminoglycoside in 3 of the 4 patients. The fourth patient's serum creatinine eventually returned to baseline; however, the BUN remained elevated beyond

six days. Patient 3 was admitted to the hospital with an elevated BUN and serum creatinine and was thought to possibly have had a preexisting renal function abnormality. The authors failed to note how the patients were identified for inclusion in the report or how many children received combination therapy without renal effects during the same time period. Dosing frequencies of the aminoglycosides and concomitant nephrotoxic medications were not reported. The authors urged physicians to monitor serum creatinine in patients on vancomycin-aminoglycoside therapy and to discontinue the aminoglycoside if the serum creatinine increases by ≥ 0.5 mg/dL.[30]

**Letters to Editor**

Two letters to editors have also reported cases of nephrotoxicity following combined therapy in pediatric patients. Dean et al. reported two cases of aminoglycoside-induced nephrotoxicity out of 345 courses of therapy (0.6%), two cases of vancomycin-induced nephrotoxicity in 19 patients receiving only vancomycin therapy (10.2%), and two cases of nephrotoxicity out of 9 patients receiving at least 1 week of vancomycin plus an aminoglycoside (22%).[14] Nephrotoxicity was defined as an increase in serum creatinine of ≥ 0.5 mg/dL. In all cases, the serum creatinine returned to baseline when the antibiotic doses were adjusted in response to peak and trough serum concentrations (vancomycin peak 20–40 mg/L; vancomycin trough 5–10 mg/L; gentamicin peak 5–8 mg/L; gentamicin trough < 2 mg/L). Serum concentrations of the antibiotics were reported to have increased prior to an increase in serum creatinine in all patients with nephrotoxicity. It was suggested that monitoring aminoglycoside and vancomycin concentrations may be beneficial in decreasing or avoiding nephrotoxicity with these agents.[14]

In a second letter, ten patients, 14 months to 14 years of age, who received combination vancomycin-gentamicin therapy for at least 3 days (mean 8 days) were retrospectively studied by Swinney et al.[5] Antibiotic serum concentrations were reported to remain within reference ranges. None of the patients developed nephrotoxicity, which was defined as an increase in serum creatinine of 0.3 mg/dL if the serum creatinine was < 3 mg/dL, or 0.7 mg/dL if the serum creatinine was > 3 mg/dL. It was concluded that combination therapy was not associated with nephrotoxicity.[5]

**Retrospective studies**

Linder and colleagues conducted a retrospective study of 47 patients aged 3 to 55 days (mean ± SD, 14 ± 10 days) who received vancomycin and had elevated serum concentrations (peak > 30 mg/L or trough > 10 mg/L).[6] All of the neonates had hyaline membrane disease and were born at ≤ 37 weeks gestation. The patients received a vancomycin dose of 15 mg/kg given every 24 hours if postconceptional age was < 30 weeks, every 18 hours if postconceptional age ranged from 30–33 weeks, every 12 hours in those with a postconceptional age ≥ 34 weeks, and every 8 hours in patients ≥ 34 weeks postconceptional age and chronological age ≥ 1 week. Sixty-five treatment courses were evaluated from 47 patients. The mean vancomycin peak and trough concentrations were 36.8 ± 9.6 mg/L and 13.5 ± 7.1 mg/L, respectively. Several patients had trough concentrations that exceeded 10 mg/L (44 treatment courses, 68%), and 15 mg/L (23 treatment courses, 36%). Peak vancomycin concentrations above 40 mg/L were reported in 47 treatment courses (72%).

Thirty-five of the 65 treatment courses included concomitant gentamicin therapy (mean peak 6.28 ± 1.99 mg/L; mean trough 1.69 ± 1.01 mg/L). Patients were treated for a median of 7 days (range, 3–60 days). No statistically significant differences were found in BUN and serum creatinine concentrations in patients treated with vancomycin alone versus combination therapy with gentamicin. An 8.6% (3 of 35) incidence of decreased renal function (serum creatinine increase of ≥ 0.5 mg/dL from baseline) was reported in patients receiving combination vancomycin-aminoglycoside therapy. None of the patients receiving vancomycin monotherapy had symptoms of nephrotoxicity, defined as an increase in serum creatinine of ≥ 0.5 mg/dL. Overall, nephrotoxicity was reported in 4 out of 65 treatment courses. In all cases, the increases in serum creatinine significantly decreased within 14 days of discontinuation of therapy. The authors reported an absence of clinically important nephrotoxicity with this combination.[6]

**Prospective studies**

In a prospective study, Nahata et al. evaluated the nephrotoxicity of vancomycin plus an aminoglycoside in 90 pediatric patients.[7] Patients ranged from 5 days to 19 years, with 30 patients younger than 1 month of age, 31 patients ranged from 1 month to 1 year old, and 29 patients were > 1 year of age. Antibiotics were prescribed for documented methicillin-resistant staphylococci and gram-negative rods. Patients received vancomycin (mean dose, 35 mg/kg/day; range, 20–60 mg/kg/day) and gentamicin (n = 76) or tobramycin (n = 14) (mean dose, 6.5 mg/kg/day; range, 2.5–14 mg/kg/day) for documented methicillin-resistant staphylococci and gram-negative rods. All patients receiving combination vancomycin-aminoglycoside therapy were included in the study. Specific diseases and concomitant medications were not reported. The duration of therapy ranged from 3–18 days with a mean of 9 days. Peak serum vancomycin concentrations ranged from 10–55 mg/L and trough concentrations ranged from 2–18 mg/L. Nine patients had a peak vancomycin serum concentration above 40 mg/L and 20 patients had values above 30 mg/L. Gentamicin and tobramycin serum concentrations were within the normal reference (peaks 4–9 mg/L; troughs ≤ 2 mg/L). There were no statistically significant increases in serum creatinine from baseline. The average serum creatinine concentration was 0.42 mg/dL prior to therapy, 0.40 mg/dL during therapy, and 0.43 mg/dL post therapy. The authors concluded that combination vancomycin-aminoglycoside therapy may be safe when serum concentrations remain in reference range.[7]

A randomized, double-blind, placebo controlled trial evaluated the nephrotoxicity of vancomycin combined with amikacin and ticarcillin compared to amikacin and ticarcillin/clavulanate plus placebo in 14 children with febrile neutropenia.[8] Patients randomized to receive vancomycin were given vancomycin (300 mg/m$^2$ every 6 hours following each amikacin dose), amikacin (800 mg/m$^2$/day every 6 hours), and ticarcillin (2.25 g/m$^2$ after each dose of vancomycin). Patients randomized to placebo were administered amikacin (800 mg/m$^2$/day, every 6 hours), ticarcillin and clavulanate as 3 g ticarcillin/100 mg clavulanate (2.25 g/m$^2$ of ticarcillin after each dose of placebo) plus placebo (following each amikacin dose). Antibiotic doses were adjusted after the fourth dose to ensure that the peak vancomycin serum concentration was between 20–40 mg/L and the trough serum concentration was below 8 mg/L. All patients also received oral nystatin every 6 hours.[8]

Nephrotoxicity was evaluated using measures of total urinary protein excretion, renal tubular enzymes N-acetyl-beta-D-glucosaminidase (NAG) and alanine aminopeptidase before therapy and every 8 hours for 7 days during therapy. Serum creatinine was measured on days 5 and 10 of therapy. Patients ranged in age from 2–14 years. Eight patients were randomized to the vancomycin group, with the remaining six patients to the placebo group. Concentrations of NAG and AAP increased in both treatment groups during the study period; however, no statistically significant differences were found between the groups. Concentrations of NAG ranged from 2.4 units/g creatinine on the first day to 20 units/g creatinine on day 6 in the vancomycin group; and from 3.2 units/g creatinine on the first day to 17 units/g creatinine on day 6 in the placebo group. Concentrations of AAP ranged from 4.1 units/g creatinine on the first day to 63 units/g creatinine on day 7 of therapy in the vancomycin group. The AAP in the placebo group ranged from 12 units/g creatinine on the first day to 28 units/g on day 6 of therapy. One patient developed a 0.2 mg/dL increase in serum creatinine. The patient's treatment group and serum creatinine concentrations were not reported. Amikacin clearance did not differ significantly between the groups. The authors concluded that vancomycin does not potentate the nephrotoxicity of amikacin in children with febrile neutropenia. It was further hypothesized that the lack of nephrotoxicity illustrated in this study may be due to increased serum concentration monitoring.[8]

## DISCUSSION

The available data concerning nephrotoxicity of combined vancomycin and aminoglycosides comes from one case report of four patients,[30] two letters to editors involving 345 treatment courses in one letter and 10 patients in the second,[5,14] one retrospective study of 47 patients,[6] and two prospective studies involving 104 patients.[7,8] There are several limitations to the

available literature. The collective number of patients reported is only 165 and a number of patients were included more than once. While all included pediatric patients' ages ranged from as young as 3 days to as old as 19 years. Forty-seven of the patients were neonates, including premature newborns. Patients had a variety of concurrent diseases including cancer. Diseases, including documented infections, were treated for a variety of reasons. Patients received a variety of dosages for 3 to 30 days. Most studies used a magnitude change in serum creatinine to define nephrotoxicity; however, a clinically significant change was not uniform. The studies provided the mean total daily dose of the antibiotics; however, in most cases the authors did not state whether the aminoglycosides were given in a single daily dose versus divided doses.

Four of the six reports and all of the prospective studies concluded that the combination of vancomycin and an aminoglycoside does not potentiate nephrotoxicity of aminoglycosides. When an increase in serum creatinine was noted, the value returned to baseline when doses were adjusted to maintain serum concentrations within the reference range. In all reported cases of nephrotoxicity, the adverse effect was completely reversed upon discontinuation of the antibiotic or upon decrease in dose to obtain the recommended peak and trough concentrations.

Regardless of whether nephrotoxicity was noted, most authors speculated that a decrease or lack of nephrotoxicity may have been related to monitoring of aminoglycoside and vancomycin serum concentrations and adjusting dosage to maintain concentrations within the specified reference range for each drug. This recommendation is controversial.[31-34]

Little evidence supports a correlation between vancomycin peak (20–40 mg/L) serum concentrations and toxicity.[9,15,35-36] Likewise, there is conflicting evidence that a correlation exists between clinical cure or in vitro killing rates and trough (5–15 mg/L) serum vancomycin concentrations.[4,11,15] Studies in hospitalized infants and children concluded that the routine monitoring of aminoglycosides[37,38] and vancomycin[39-43] is not warranted in patients receiving normal doses for age and who have normal serum creatinine.

## CONCLUSIONS

Although vancomycin and the aminoglycosides have been associated with drug induced nephrotoxicity, reports in the literature do not appear to support the idea that the combination of vancomycin and an aminoglycoside is more nephrotoxic than either medication alone. The evidence in the literature is limited due to the small number of patients and limited information presented in the cases and letters to editors. Larger prospective studies would be necessary to conclusively establish the association between increased nephrotoxicity and combination therapy.

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