MAJOR ARTICLE

Initial Low-Dose Gentamicin for *Staphylococcus aureus* Bacteremia and Endocarditis Is Nephrotoxic

Sara E. Cosgrove,[1] Gloria A. Vigliani,[2] Marilyn Campion,[a] Vance G. Fowler, Jr.,[5] Elias Abrutyn,[7,b] G. Ralph Corey,[5,6] Donald P. Levine,[8] Mark E. Rupp,[9] Henry F. Chambers,[10] Adolf W. Karchmer,[3] and Helen W. Boucher[4]

[1]Division of Infectious Diseases, Johns Hopkins University School of Medicine, Baltimore, Maryland; [2]Vigliani Consulting, Waban, and [3]Division of Infectious Diseases, Beth Israel Deaconess Medical Center, and [4]Division of Infectious Diseases, Tufts Medical Center, Boston, Massachusetts; [5]Division of Infectious Diseases, Duke University Medical School, and [6]Duke Clinical Research Institute, Durham, North Carolina; [7]Drexel University College of Medicine, Philadelphia, Pennsylvania; [8]Wayne State University, University Health Center, Detroit, Michigan; [9]Division of Infectious Diseases, University of Nebraska Medical Center, Omaha; and [10]Division of Infectious Diseases, University of California, San Francisco

(See the editorial commentary by Bayer and Murray on pages 722–4)

Background. The safety of adding initial low-dose gentamicin to antistaphylococcal penicillins or vancomycin for treatment of suspected *Staphylococcus aureus* native valve endocarditis is unknown. This study evaluated the association between this practice and nephrotoxicity.

Methods. We performed a prospective cohort study of safety data from a randomized, controlled trial of therapy for *S. aureus* bacteremia and native valve infective endocarditis involving 236 patients from 44 hospitals in 4 countries. Patients either received standard therapy (antistaphylococcal penicillin or vancomycin) plus initial low-dose gentamicin ($n = 116$) or received daptomycin monotherapy ($n = 120$). We measured renal adverse events and clinically significant decreased creatinine clearance in patients (1) in the original randomized study arms and (2) who received any initial low-dose gentamicin either, as a study medication or ⩽2 days before enrollment.

Results. Renal adverse events occurred in 8 (7%) of 120 daptomycin recipients, 10 (19%) of 53 vancomycin recipients, and 11 (17%) of 63 antistaphylococcal penicillin recipients. Decreased creatinine clearance occurred in 9 (8%) of 113 of evaluable daptomycin recipients, 10 (22%) of 46 vancomycin recipients, and 16 (25%) of 63 antistaphylococcal penicillin recipients. An additional 21 patients received initial low-dose gentamicin ⩽2 days before study enrollment. A total of 22% of patients who received initial low-dose gentamicin versus 8% of patients who did not receive initial low-dose gentamicin experienced decreased creatinine clearance ($P = .005$). Independent predictors of a clinically significant decrease in creatinine clearance were age ⩾65 years and receipt of any initial low-dose gentamicin.

Conclusions. Initial low-dose gentamicin as part of therapy for *S. aureus* bacteremia and native valve infective endocarditis is nephrotoxic and should not be used routinely, given the minimal existing data supporting its benefit.

The practice of adding initial low-dose gentamicin to antistaphylococcal penicillins or to vancomycin in patients with possible *Staphylococcus aureus* endocarditis is common but remains of uncertain value. Current American Heart Association guidelines recommend considering the addition of initial low-dose gentamicin to antistaphylococcal penicillins or cefazolin for treatment of native valve endocarditis caused by methicillin-susceptible *S. aureus* (MSSA) [1]. Many physicians view the addition of initial low-dose gentamicin as useful in achieving earlier clearance of blood cultures in patients with methicillin-resistant *S. aureus* (MRSA) bacteremia [2].

The use of initial low-dose gentamicin in the management of suspected *S. aureus* endocarditis is based on in vitro data demonstrating that synergistic doses of aminoglycosides, in combination with antistaphylococcal penicillins or vancomycin, result in more rapid bactericidal activity against *S. aureus* and on in vivo data from a rabbit model of endocarditis showing more rapid eradication of *S. aureus* from cardiac vegetations

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[a] Consultant, Newton, Massachusetts.

[b] Deceased.

Reprints or correspondence: Dr. Sara E. Cosgrove, The Johns Hopkins Hospital, Osler 425, 600 N. Wolfe St., Baltimore, MD 21287 (scosgro1@jhmi.edu).

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Table 1. Characteristics of patients in the study.

Characteristics	Receipt of any gentamicin	
	Yes (n = 130)	No (n = 106)
Age		
Median years (range)	52 (21–91)	53 (22–87)
⩾65 years	38 (29)	30 (28)
Male sex	77 (59)	65 (61)
Weight, median kg (range)	76.7 (49.9–124.8)	80.5 (52.0–131.4)
Baseline creatinine level, mg/dL		
Mean ± SD	1.12 ± 0.434	1.13 ± 0.392
Median (range)	1.00 (0.3–2.9)	1.10 (0.5–2.3)
Creatine clearance, median mL/min (range)	86.3 (18–277)	82.7 (28–247)
Median creatine clearance		
<30 mL/min	3 (2)	2 (2)
30 to <50 mL/min	18 (14)	18 (17)
50 to 80 mL/min	38 (29)	31 (29)
>80 mL/min	71 (55)	55 (52)
Risk factor		
Diabetes mellitus	46 (35)	40 (38)
HIV infection	3 (2)	6 (6)
SIRS	100 (77)	77 (73)
Study agent		
Daptomycin	22 (17)	98 (92)
Antistaphylococcal penicillins	59 (45)	4 (4)
Vancomycin	49 (38)	4 (4)
Final diagnosis, per adjudication committee		
Left-side endocarditis	12 (9)	7 (7)
Right-side endocarditis	25 (19)	10 (9)
Complicated bacteremia	66 (51)	55 (52)
Uncomplicated bacteremia	27 (21)	34 (32)
Receipt of any concomitant nephrotoxic drug[a]		
All	68 (52)	58 (55)
ACE-Is or ARBs	36 (28)	42 (40)
NSAIDs or COX-2 inhibitors	36 (28)	20 (19)
Amphotericin B	0 (0)	1 (1)
Contrast media	6 (5)	3 (3)
High-dose gentamicin	1 (1)	4 (4)
Initial low-dose gentamicin		
Before study enrollment		
No. (%) of patients	43 (33)	NA
Median days (range)	2.0 (1–12)	NA
Daily dose, median mg/kg (range)	2.9 (0.9–5.6)	NA
As a study drug		
No. (%) of patients	109 (84)	NA
Median days (range)	4.0 (1–12)	NA
Daily dose, median mg/kg (range)	2.1 (0.8–3.5)	NA
Overall exposure		
No. (%) of patients	130 (100)	NA
Median days (range)	4.0 (1–13)	NA
Daily dose, median mg/kg (range)	2.2 (0.8–5.6)	NA

NOTE. ACE-Is, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; COX-2, cyclooxygenase 2; NA, not applicable; NSAIDs, nonsteroidal anti-inflammatory drugs; SIRS, systemic inflammatory response syndrome.

[a] Receipt of drug means that the patient received it ⩽7 days before study enrollment until the occurrence of either a clinically significant decrease in creatine clearance or the day before the last day of study treatment, whichever came first.

Table 2. Numbers of patients receiving study drugs and gentamicin.

Patients	No. of patients			
	Daptomycin (n = 120)	Vancomycin (n = 53)	ASP (n = 63)	Total (n = 236)
Evaluable for adverse events	120	53	63	236
Received any gentamicin				
All	22	49	59	130
Before study drug treatment	21	7[a]	15[a]	43
As study drug treatment	1	49	59	109
Had adequate clearance data[b]				
All	113	46	63	222
Received no gentamicin	93	3	4	100
Received any gentamicin				
All	20	43	59	122
Before study drug treatment	19	6	15	40
As study drug treatment	1	43	59	103

NOTE. ASP, antistaphylococcal penicillin.

[a] All also received gentamicin as study drug treatment.

[b] Defined as having a baseline and at least 1 postbaseline creatinine value.

with antistaphylococcal penicillins plus initial low-dose gentamicin compared with antistaphylococcal penicillins alone [3, 4]. Initial low-dose gentamicin use in the treatment of *S. aureus* endocarditis became commonplace after Korzeniowski and Sande [5] demonstrated that combination therapy decreased time to clearance of MSSA bacteremia by 1 day in non–injection drug using patients with predominantly left-side endocarditis, although it did not affect morbidity or mortality.

In the study, nafcillin was administered for 6 weeks with or without low-dose gentamicin for the first 2 weeks of therapy. Because patients who received gentamicin experienced significant renal impairment, the authors concluded that gentamicin should only be considered during the first 3–5 days of treatment. Unfortunately, this practice has not been reevaluated in the intervening 25 years, during which time patients have become older, have experienced more frequent comorbid diseases, are infected more commonly with MRSA, and are treated more often with vancomycin [6].

Recently, an international, open-label, randomized trial demonstrated that, in patients with *S. aureus* bacteremia and endocarditis, daptomycin monotherapy is not inferior to standard therapy with initial low-dose gentamicin plus an antistaphylococcal penicillin or vancomycin [7]. In that study, patients in the standard therapy arm experienced significantly more cases of renal impairment than those in the daptomycin arm. This investigation focuses on safety data from the 236 patients enrolled in the original study and aims to evaluate the renal impairment seen in the standard therapy arm and to assess the clinical impact of initial low-dose gentamicin on renal function.

METHODS

Therapeutic agents. In the original study, patients were randomized to receive daptomycin monotherapy or standard therapy with either vancomycin (1 g every 12 h with appropriate dose adjustment) or an antistaphylococcal penicillin (nafcillin, oxacillin, or flucloxacillin; 2 g every 4 h). Choice of standard therapy was based on the susceptibility of the causative organism to methicillin. All patients in the standard therapy group and patients with a high likelihood of left-side endocarditis who received daptomycin were to receive initial low-dose gentamicin (1 mg/kg every 8 h, with appropriate dose adjustment) for the first 4 days of therapy. These medications, including initial low-dose gentamicin, are considered study medications in this article. In addition, medications given to patients before enrollment into the study were reviewed to determine which patients received initial low-dose gentamicin $\leq$2 days before randomization. The institutional review board at each site approved the protocol, and all patients or their authorized representatives provided written informed consent.

Definitions. Renal impairment clinical adverse events recorded by the investigators included interstitial nephritis, toxic nephropathy, acute prerenal failure, acute or chronic renal failure, renal impairment, or renal tubular necrosis. Creatinine clearance was calculated using the Cockcroft-Gault equation [8]. In addition, the glomerular filtration rate was calculated using the Modification of Diet in Renal Disease equation [9]. Analyses presented use the Cockcroft-Gault equation.

A clinically significant decrease in creatinine clearance was defined as having a decrease in creatinine clearance to <50 mL/

Table 3. Renal toxic effects, as determined from adverse events and laboratory evaluations in the original randomized treatment arms.

Toxic effect	Daptomycin arm	Standard therapy arm			
		Overall	P^a	Vancomycin	ASP
Renal impairment adverse events					
Overall population	8/120 (7)	21/116 (18)	.01	10/53 (19)	11/63 (17)
Patients aged ⩾65 years	2/30 (7)	12/38 (32)	.02	6/16 (38)	6/22 (27)
Patients with diabetes	3/44 (7)	12/42 (29)	.01	5/21 (24)	7/21 (33)
Clinically significant decrease in CrCl					
Overall population	9/113 (8)	26/109 (24)	.002	10/46 (22)	16/63 (25)
Patients aged ⩾65 years	3/27 (11)	15/35 (43)	.01	5/13 (39)	10/22 (45)
Patients with diabetes	3/44 (7)	12/40 (30)	.01	5/19 (26)	7/21 (33)
Sustained 50% decrease in CrCl					
Overall population	0/113	7/109 (6)	.01	3/46 (7)	4/63 (6)
Patients aged ⩾65 years	0/27	3/35 (9)	.25	1/13 (8)	2/22 (9)
Patients with diabetes	0/44	6/40 (15)	.01	3/19 (16)	3/21 (14)
Sustained 25% decrease in CrCl					
Overall population	11/113 (10)	24/109 (22)	.02	15/46 (33)	9/63 (14)
Patients aged ⩾65 years	2/27 (7)	9/35 (26)	.09	3/13 (23)	6/22 (27)
Patients with diabetes	3/44 (7)	10/40 (25)	.03	6/19 (32)	4/21 (19)

NOTE. Data are proportion of patients (%), unless otherwise indicated. ASP, antistaphylococcal penicillin; CrCl, creatinine clearance.

[a] Determined by Fisher's exact test, compared with daptomycin.

min if the baseline creatinine clearance was ⩾50 mL/min or having a decrease in creatinine clearance of ⩾10 mL/min if the baseline creatinine clearance was <50 mL/min [6]. A sustained decrease in creatinine clearance was defined as having ⩾2 sequential measurements of decreased creatinine clearance. This was determined for both 25% and 50% reductions from baseline creatinine clearance.

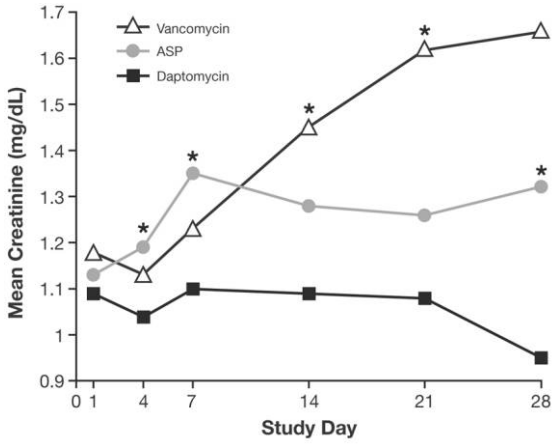
Collection of laboratory data. Laboratory data, including serum creatinine level, were obtained on days 1, 4, and 7 and then weekly until the end of therapy, as well as at the 6-week posttherapy safety visit. All analyses of renal function included laboratory data collected from baseline through the end of treatment with study agents. Patients had to have a baseline and at least 1 postbaseline creatinine value to be deemed evaluable and to be included in the analyses evaluating laboratory evidence of renal dysfunction.

We conducted 2 separate sets of analyses. First, we assessed the occurrence of adverse events and changes in renal function in the original randomized study arms. Second, to better characterize the impact of initial low-dose gentamicin on renal function, we conducted analyses in which patients were classified as having received initial low-dose gentamicin or not, regardless of whether the gentamicin was received as a study medication or ⩽2 days before study enrollment. These analyses included comparison of the occurrence of and time to a clinically significant decrease in creatinine clearance, the percentage of patients experiencing a sustained 25% or 50% reduction in creatinine clearance, and an assessment of the relationship between renal function and gentamicin dose and duration. We conducted a multivariate analysis to determine the impact of risk factors in the development of clinically significant decreases in creatinine clearance.

Statistical analysis. Categorical data were analyzed using Fisher's exact test, and continuous data were analyzed using analysis of covariance for continuous data. We assessed time to a clinically significant decrease in creatinine clearance using the Kaplan-Meier method. Logistic regression was performed using a forward stepwise procedure. Variables with $P < .10$ in the univariate analysis were candidates for the multivariable analysis. All predictors were checked for colinearity and confounding. We evaluated effect modification among variables by testing appropriate interaction terms for statistical significance. The final regression models were analyzed for overfitting by the bootstrap method (1000 bootstrap samples of all the data were used). All tests were 2-sided; adjustments were not made for multiple analyses. We conducted all analyses using SAS software, version 9.1 (SAS Institute).

RESULTS

Patient characteristics. Baseline characteristics were comparable in patients who did and did not receive initial low-dose gentamicin (table 1) and across the original randomized antibiotic treatment groups, as detailed elsewhere [6]. In the



Number of Patients Each Study Day

	Day 1	Day 4	Day 7	Day 14	Day 21	Day 28
Vancomycin	53	39	40	24	19	8
ASP	63	58	54	35	25	12
Daptomycin	120	101	102	39	31	13

Figure 1. Mean serum creatinine levels, by treatment group, over time. *$P \leq .05$, compared with daptomycin, for change from baseline (analysis of covariance). ASP, antistaphylococcal penicillin.

original randomized groups, baseline creatinine levels were similar among patients receiving daptomycin, vancomycin, or antistaphylococcal penicillins (mean, 1.09, 1.18, and 1.13 mg/dL, respectively; $P = .35$). Baseline creatinine clearance was also similar among these 3 groups (median, 86, 77, and 87 mL/min, respectively; $P = .25$). Similar numbers of patients in all 3 groups had diabetes mellitus, and similar numbers received therapy with concomitant nephrotoxic agents.

Receipt of antibiotics. Sixty-three patients received antistaphylococcal penicillins as a study drug: 27 (43%) received only an antistaphylococcal penicillin for the duration of the study, 35 (56%) received initial empirical vancomycin treatment (most for only 1 or 2 days), with a change to an antistaphylococcal penicillin once the isolate was determined to be MSSA, and 1 patient (2%) infected with MRSA inappropriately received an antistaphylococcal penicillin for 9 days before being switched to vancomycin.

Most patients randomized to standard therapy received treatment with initial low-dose gentamicin as a study medication (108 [93%] of 116), including 49 (92%) of 53 patients who received vancomycin and 59 (94%) of 63 patients who received an antistaphylococcal penicillin (table 2). In contrast, only 1 (1%) of the 120 patients assigned to receive daptomycin received initial low-dose gentamicin as study medication. The median length of gentamicin administration was 5 days (range, 1–7 days) in patients treated with vancomycin and 4 days (range, 2–12 days) in patients treated with antistaphylococcal penicillins.

Overall, 43 (18%) of 236 patients received initial low-dose gentamicin before study enrollment (21 in the daptomycin arm and 22 in the standard therapy arm). None of the 21 patients receiving daptomycin received initial low-dose gentamicin as a study medication, whereas all the patients in the standard therapy arm did. Thus, a total of 130 patients received any initial low-dose gentamicin (table 2), 122 of whom were evaluable for analysis. One hundred two evaluable patients were in the standard therapy arm and received a median of 5 days of initial low-dose gentamicin (range, 1–13 days) at a mean daily dose of 2.1 mg/kg. Twenty evaluable patients were in the daptomycin arm and received a median of 2 days of initial low-dose gentamicin (range, 1–12 days) at a mean daily dose of 3.1 mg/kg; 19 of these patients received gentamicin only before study enrollment. Of all patients receiving initial low-dose gentamicin, only 3 patients received a total exposure of >4 mg/kg of gentamicin per day. Of 106 patients who did not receive any gentamicin, 100 patients were evaluable for analysis (93 in the daptomycin arm and 7 in the standard therapy arm).

Evidence of renal dysfunction in the original randomized treatment arms. Renal impairment adverse events were more commonly reported in the standard therapy arm than in the daptomycin arm, regardless of comparator agent (table 3). Eight (7%) of 120 patients who received daptomycin experienced at

Table 4. Incidence of decrease in creatinine clearance (CrCl), by receipt of any initial low-dose gentamicin.

	Received gentamicin, no. (%) of patients		
Decrease	Yes[a] (n = 122)	No[a] (n = 100)	P[b]
Clinically significant decrease in CrCl	27 (22)	8 (8)	.005
Sustained 50% decrease in CrCl	7 (6)	0 (0)	.02
Sustained 25% decrease in CrCl	26 (21)	9 (9)	.02
Discontinuation of use of study medication because of renal events	4 (3)	1 (1)	.38

[a] Number of patients with both baseline and at least 1 postbaseline value during treatment.
[b] Determined by Fisher's exact test.

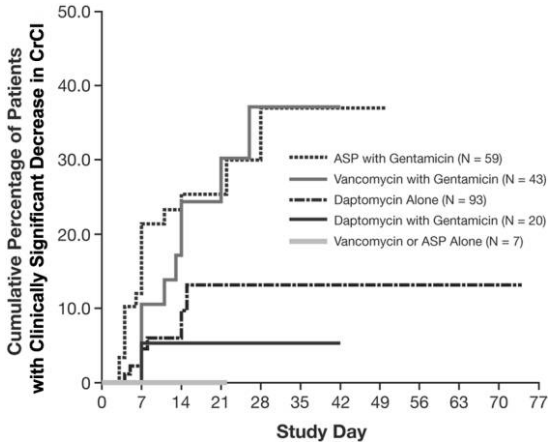


Figure 2. Time to a clinically significant decrease in creatinine clearance (CrCl). ASP, antistaphylococcal penicillin.

least 1 renal adverse event, compared with 10 (19%) of 53 patients who received vancomycin and 11 (17%) of 63 patients who received antistaphylococcal penicillins. The difference in rates of renal impairment adverse events was most pronounced in elderly patients and patients with diabetes (table 3).

The mean serum creatinine measurements among patients in the standard therapy group were higher than those in the daptomycin group during treatment with the study drug (figure 1). The significant changes from baseline creatinine level occurred early in therapy for patients receiving antistaphylococcal penicillins (days 4 and 7) and later in therapy for patients receiving vancomycin (days 14, 21, and 28).

Clinically significant decreases in creatinine clearance were more common in the standard therapy arm relative to the daptomycin arm (24% vs. 8%, $P = .002$) (table 3) and were similarly distributed among patients who received an antistaphylococcal penicillin (16 [25%] of 63) and vancomycin (10 [22%] of 46). Again, patients in the standard therapy arm who were ⩾65 years old and patients with diabetes were more likely to experience a clinically significant decrease in creatinine clearance than were those in the daptomycin arm (table 3).

Impact of gentamicin on renal impairment. Overall, 27 (22%) of 122 patients who received any initial low-dose gentamicin versus 8 (8%) of 100 patients who did not receive any initial low-dose gentamicin experienced a clinically significant decrease in creatinine clearance ($P = .005$) (table 4). Patients with a baseline creatinine clearance >80 mL/min experienced a clinically significant decrease in creatinine clearance relatively infrequently (5 [7.2%] of 69 who received initial low-dose gentamicin vs. 2 [3.8%] of 53 who did not; $P = .70$). In contrast, those with a baseline creatinine clearance of 50–80 mL/min were more likely to develop a clinically significant decrease in creatinine clearance when exposed to initial low-dose gentamicin (15 [44.1%] of 34 vs. 4 [14.3%] of 28; $P = .014$). The percentage of patients who experienced either a sustained 50% or a sustained 25% decrease in creatinine clearance was also significantly higher in the group that received initial low-dose gentamicin (table 4).

Clinically significant decreases in creatinine clearance occurred earlier ($P = .01$, by Wilcoxon test) and were sustained through the end of therapy ($P = .009$, by log rank test) in patients who received initial low-dose gentamicin than in patients who received no gentamicin (figure 2). None of the 7 patients who received standard therapy alone experienced a decrease in renal function (figure 2).

We conducted a multivariate analysis to determine the impact of risk factors in the development of a clinically significant decrease in creatinine clearance in this cohort of patients who received any initial low-dose gentamicin. Age ⩾65 years and receipt of any initial low-dose gentamicin were independently associated with a clinically significant decrease in creatinine clearance (table 5). Although a slight statistical association was found between duration of gentamicin therapy and renal impairment (table 5), the clinical association between dose and duration of gentamicin and nephrotoxicity appeared minimal in this cohort (figure 3).

All analyses presented herein were repeated using Modification of Diet in Renal Disease equations to calculate the glomerular filtration rate. No important differences in the results were noted (data not shown).

DISCUSSION

Our findings suggest that receipt of even a few days of initial low-dose gentamicin in combination with vancomycin or an antistaphylococcal penicillin in the treatment of *S. aureus* bacteremia and native valve endocarditis is frequently associated with renal dysfunction. These findings were consistent when different measures of renal dysfunction, such as increase in mean creatinine level, decrease and sustained decrease in creatinine clearance, and time to decrease in creatinine clearance, were evaluated. Although data are not available on the frequency with which physicians in practice add initial low-dose gentamicin to standard therapy in the treatment of *S. aureus* bacteremia and endocarditis, we suspect that it occurs commonly, given that 43 (18.2%) of 236 patients in this study had been prescribed initial low-dose gentamicin before study enrollment.

Several reports have demonstrated that, when vancomycin and standard doses of gentamicin are administered concomitantly, the incidence of nephrotoxicity is greater than when either drug is administered alone [10, 11]. No studies, however, have evaluated nephrotoxicity associated with the combination of initial low-dose gentamicin and vancomycin for the treatment of *S. aureus* bacteremia or endocarditis.

Furthermore, although nephrotoxicity associated with gen-

Table 5. Potential individual predictors of clinically significant decrease in creatinine clearance.

Characteristic	OR (95% CI)	
	Univariate	Multivariable
Age ⩾65 years[a]	3.44 (1.64–7.24)	3.56 (1.66–7.65)
Receipt of any gentamicin as study medication or before enrollment[a]	3.27 (1.41–7.57)	3.39 (1.43–8.00)
Treatment group		
Vancomycin vs. daptomycin	3.21 (1.21–8.53)	…
Antistaphylococcal penicillin vs. daptomycin	3.93 (1.62–9.54)	…
Weight (per 1-kg increase)[a]	0.97 (0.95–0.99)	…
Receipt of any nephrotoxic medication[b]	1.11 (0.54–2.30)	…
Receipt of ACE-Is or ARBs[b]	1.03 (0.48–2.20)	…
Receipt of NSAIDs/COX-2 inhibitors[b]	1.26 (0.56–2.83)	…
Receipt of contrast media[a,b]	4.70 (1.20–18.46)	…
Duration of gentamicin as study medication (days)[a]	1.17 (1.02–1.35)	…
Total days of gentamicin use[a]	1.14 (1.01–1.30)	…
Average dose of gentamicin as study medication (per 1-mg/kg daily increase)[a]	1.37 (0.98–1.90)	…
SIRS present	0.72 (0.32–1.63)	…
Diabetes	1.28 (0.62–2.67)	…
MSSA infection	0.88 (0.42–1.85)	…

NOTE. ACE-Is, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; COX-2, cyclooxygenase-2; MSSA, methicillin-susceptible *Staphylococcus aureus;* NSAIDs, nonsteroidal anti-inflammatory drugs; SIRS, systemic inflammatory response syndrome.

[a] $P \leqslant .05$ in a univariate model.

[b] Receipt ⩽7 days before study enrollment to the occurrence of either a clinically significant decrease in creatinine clearance or the day before the last day of study treatment, whichever came first.

tamicin has been observed in patients receiving 2-week courses of low-dose gentamicin in conjunction with antistaphylococcal penicillins, compared with patients receiving antistaphylococcal penicillins alone for the treatment of endocarditis [4, 12], it has not been reported in patients receiving short courses of initial low-dose gentamicin. The amounts and durations of gentamicin received by patients in this study were low, with a median exposure of only 4 days at a daily dose of 2–3 mg/kg, a schedule not expected to produce significant serum peaks or troughs. The decline in renal function seen was clinically relevant, with discontinuation of study medication use in 4 (3%) of 122 patients, sustained 25% decreases in creatinine clearance in 26 (21%) of 122 patients, and sustained 50% decreases in creatinine clearance in 7 (6%) of 122 patients. Although no patients died or required long-term hemodialysis as a result of renal dysfunction in the cohort, elevations in serum creatinine levels and decreased creatinine clearance can lead to additional laboratory and imaging studies, nephrology consultation, changes in medication and doses, prolonged hospitalization, and increased mortality [13–15]. In addition, renal dysfunction occurred frequently in this cohort, despite the fact that a large proportion of patients had uncomplicated bacteremia and right-side endocarditis—infections that are generally considered less severe. We did not find an important relationship between dose or duration of gentamicin and the incidence of renal impairment in this cohort. This may be because relatively few patients received higher doses or longer therapy or because of the tendency to stop gentamicin therapy if evidence of renal impairment developed.

The results of this investigation also suggest that other situations in which patients receive low-dose and/or short-course gentamicin, such as surgical prophylaxis in the penicillin-allergic patient, should undergo scrutiny for safety. Indeed, nephrotoxicity has been reported to occur in 17 (20%) of 87

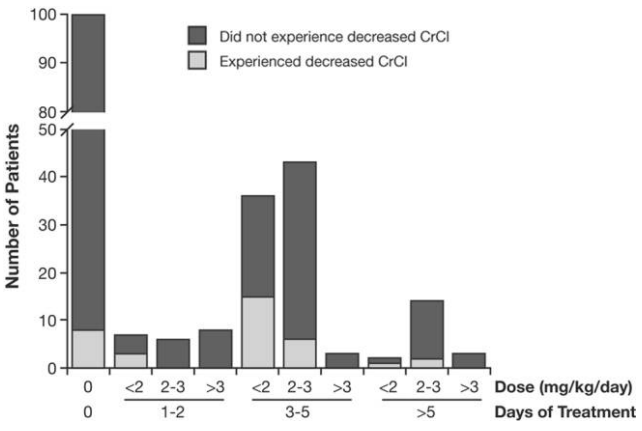


Figure 3. Occurrence of decreased creatinine clearance (CrCl), by gentamicin exposure, expressed as number of patients versus the average total daily dose and the duration of treatment.

patients who received a single 2-g dose of dicloxacillin and 240 mg of gentamicin as surgical prophylaxis for the repair of intertrochanteric hip fractures, compared with only 4 (5%) of 76 patients who received no prophylactic antibiotics [16].

Surprisingly, no differences were apparent in the incidence of renal dysfunction between patients receiving an antistaphylococcal penicillin and those receiving vancomycin. If either of these agents is given as monotherapy, the incidence of nephrotoxicity is generally low, suggesting that the addition of gentamicin plays a role in the nephrotoxicity that we observed [17–20]. Nephrotoxicity was also observed earlier in patients receiving antistaphylococcal penicillins, with a mean serum creatinine level peak on study day 7, compared with patients receiving vancomycin, in whom the mean serum creatinine level began to increase on day 7 and continued to increase throughout the study. This finding may relate to the earlier and more rapid lysis of *S. aureus* seen with β-lactam antibiotics relative to vancomycin, leading to earlier antigen-immune complex deposition. Alternatively, the finding may suggest that the synergistic nephrotoxicity seen with vancomycin and gentamicin is more sustained.

The impact of initial low-dose gentamicin on renal function appears to be greater in individuals with underlying but underappreciated renal dysfunction, such as persons aged $\geqslant$65 years and those with diabetes. Unfortunately, *S. aureus* bacteremia and endocarditis now occur frequently in persons with these risk factors [5, 21, 22]. Other studies have also demonstrated an association between gentamicin and renal dysfunction in these populations, but generally not with the initial low-dose gentamicin used in this study [23–25].

This study has limitations. The data are from a randomized, controlled trial that was not designed to assess the effect of gentamicin on renal dysfunction. The secondary analyses presented in this study, however, provide a consistent picture suggestive of an association between gentamicin and renal dysfunction. Accounting for the impact of potentially nephrotoxic agents on individual patient outcomes is challenging because individual patients may respond to these agents differently. For example, patients may have concurrent conditions, such as volume depletion, that predispose them to nephrotoxicity, particularly in the context of concomitant administration of a nephrotoxic drug. However, these differences were to some degree controlled for through the randomization process and were assessed in part via the risk factor analysis. The open-label design of the original trial could have affected investigator reports of renal adverse events, but observations based on objective laboratory data are unlikely to be affected by this potential bias.

We were unable to assess the impact of the addition of initial low-dose gentamicin on the efficacy of therapy with antistaphylococcal penicillins or vancomycin, given that only 7 patients in the standard therapy group did not receive gentamicin. However, early studies examining initial low-dose gentamicin combination therapy in patients with MSSA bacteremia and endocarditis showed either no benefit [3, 26] or minimal benefit (reduction in the duration of bacteremia by 1 day) [4]. More recent studies also show no significant benefit to adding low-dose aminoglycosides for injection drug users with MSSA right-side endocarditis who are undergoing 2-week short-course therapy [12] or in sterilizing valves in patients with native valve *S. aureus* endocarditis undergoing surgery [27].

In conclusion, initial low-dose gentamicin appears to result in significant renal dysfunction when used with either vancomycin or antistaphylococcal penicillins for the treatment of *S. aureus* bacteremia and native valve endocarditis. Recent American Heart Association guidelines for the management of endocarditis state that the addition of gentamicin in the treatment of native valve MSSA endocarditis should be considered optional. On the basis of evidence of potential harm and the lack of evidence for clinically significant benefit, we recommend against the routine use of initial low-dose gentamicin in the management of most cases of *S. aureus* bacteremia and native valve endocarditis, particularly in elderly and diabetic patients and in patients with even mild baseline renal dysfunction.

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she has not been on any speakers' bureaus since December 2007 and has sold all her shares of Cubist and Pfizer.

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