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Combination therapy with an aminoglycoside for *Staphylococcus aureus* endocarditis and/or persistent bacteremia is associated with a decreased rate of recurrent bacteremia: a cohort study

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Abstract

Purpose—Although limited data exist on the efficacy and potential risk of synergistic aminoglycoside therapy for persistent *Staphylococcus aureus* bacteremia and endocarditis, aminoglycosides are frequently used in clinical practice.

Methods—As our study population, we included subjects fulfilling the modified Duke criteria for *S. aureus* endocarditis and/or having greater than 72 h of *S. aureus* bacteremia. Among these subjects, we compared patients who did and did not receive aminoglycoside therapy for their *S. aureus* bloodstream infection. These groups were compared for the primary outcome of recurrent bacteremia, as well as for the duration of bacteremia, mortality, complication rate, and incident renal failure.

Results—Eighty-seven subjects fulfilled the inclusion criteria. Of these, 49 received aminoglycoside therapy, whereas 38 did not. There were no significant differences in the baseline characteristics when comparing groups who did or did not receive aminoglycoside therapy. Four (8.2%) subjects treated with aminoglycoside therapy experienced recurrent bacteremia versus nine (23.7%) who did not receive aminoglycoside therapy [relative risk and 95% confidence interval [RR (95% CI)] = 0.51 (0.22–1.17), $p = 0.04$]. In multivariable analyses, aminoglycoside use remained significantly associated with a decrease in recurrent bacteremia [adjusted odds ratio (OR) (95% CI) = 0.26 (0.07–0.98), $p = 0.046$]. No significant differences were seen between groups treated with and without an aminoglycoside in terms of the 6-month all-cause mortality (51.0 vs. 42.1%, $p = 0.41$), complication rate (71.4 vs. 73.7%, $p = 0.82$), or incident renal failure (54.5 vs. 46.9%, $p = 0.54$).

Conclusions—The use of combination therapy with an aminoglycoside in persistent *S. aureus* bacteremia and/or endocarditis may be associated with a lower rate of recurrent bacteremia without significant differences in the incident renal failure.

Background

Persistent *Staphylococcus aureus* bacteremia and endocarditis has a high morbidity and mortality. Mortality rates of *S. aureus* endocarditis have been cited to range from 26% to more than 70% [1, 2]. Despite the increasing incidence of *S. aureus* bacteremia and infective endocarditis, with *S. aureus* now the leading cause of infective endocarditis in many areas worldwide [3–5], optimal therapeutic regimens have not been well defined. Combination therapy with an aminoglycoside is frequently used in clinical practice for the treatment of persistent *S. aureus* bacteremia and endocarditis, despite limited data to support its use [6]. In vitro experimental models of *S. aureus* endocarditis have shown synergy with the use of combination therapy including a glycopeptide or β -lactam with an aminoglycoside [2, 7, 8]. Animal models of endocarditis have also shown that combination therapy including an aminoglycoside has increased bactericidal activity compared with monotherapy, with a reduction in bacterial density within vegetations and an increased rate of vegetation sterilization [9, 10].

Clinical studies have not shown overall improved clinical outcomes or mortality, however, with the addition of an aminoglycoside to standard monotherapy [11–13]. The use of combination therapy has been most studied in the subgroup of *S. aureus* endocarditis in intravenous drug users (IVDU). The only, to our knowledge, prospective randomized study of synergistic aminoglycoside therapy in both IVDU and non-IVDU populations with endocarditis showed only a shorter duration of bacteremia with combination therapy, but no difference in the mortality or cure rates [14]. It is based on this study that many experts recommend the use of a cell wall-active agent with an aminoglycoside for the first 3–5 days of therapy to possibly decrease the duration of bacteremia [6]. In this study, we aimed to determine if combination therapy with an aminoglycoside is associated with a reduction in recurrent bacteremia.

Methods

A retrospective cohort study was performed at the Philadelphia Veterans Affairs Medical Center (PVAMC). The study was approved by the institutional review board (IRB) at the PVAMC. Microbiologic records were used to identify all patients with a positive blood culture for *S. aureus* from January 1997 to December 2007. Patient records were then examined using the PVAMC Computerized Patient Record System (CPRS) to determine if they met the inclusion criteria.

Subjects were included in the study if they: (1) had sustained bacteremia with blood cultures positive for *S. aureus* for ≥ 72 h (positive blood cultures on a minimum of two separate dates at least 72 h apart) and/or (2) met modified Duke criteria for the diagnosis of definite *S. aureus* infective endocarditis [15]. In order to determine the efficacy of aminoglycoside therapy specifically on patients treated only after a diagnosis of persistent bacteremia was made, patients with ≥ 72 h of bacteremia (but without the diagnosis of definite infective endocarditis) treated with any aminoglycoside therapy in the first 72 h of bacteremia were excluded from the study. Any subject meeting the inclusion criteria treated with ≥ 1 dose of an aminoglycoside was considered to be in the aminoglycoside-exposed cohort; subjects were considered to be unexposed if they received no aminoglycoside therapy.

Clinical data collected for the study included demographic data (age, sex, and race), presence of co-morbid conditions [including diabetes mellitus, IVUD, stage 2 or higher chronic kidney disease (glomerular filtration rate [GFR] ≤ 89 mL/min/1.73 m²)[16], and end-stage renal disease (ESRD) on dialysis], chronic steroid use (defined by daily steroid use >5 mg prednisone or equivalent), Charlson Index [17], treatment of *S. aureus* bacteremia (use, dose, and duration of any antistaphylococcal antibiotic), presence of an indwelling central venous catheter at the initial onset of bacteremia and date of removal, and any intensive care unit (ICU) admission during bacteremia.

The primary outcome for the study was the incidence of recurrent (either relapse or re-infection) *S. aureus* bacteremia, defined as the return of *S. aureus* bacteremia (any positive blood culture) after: (1) the documentation of negative blood cultures, but without a positive blood culture in the 96 h preceding the new positive blood culture (to avoid labeling patients with sustained bacteremia who have transient negative blood cultures as a recurrence) and/or (2) clinical improvement after completing a course of an antistaphylococcal antibiotic. This definition of recurrence is based on previous studies [18, 19]. Any recurrent bacteremia within 6 months of the initial bacteremia was included.

Secondary outcomes for the study included: the total duration of bacteremia (defined as the total number of days of positive blood cultures), 6-month all-cause mortality, incidence of complications of persistent bacteremia or infective endocarditis, and incident renal failure in the 6 months following the initial bacteremia (defined as an increase in the serum creatinine ≥ 2 times the baseline value, GFR loss of greater than 50% of the baseline based on the Cockcroft–Gault equation measurement, or requiring dialysis). Complications evaluated included stroke, septic pulmonary emboli, major arterial or other emboli phenomenon, septic arthritis, osteomyelitis, epidural abscess, pyomyositis or muscle abscess, septic thrombophlebitis, visceral abscess, and infection of the dialysis graft or fistula.

The baseline characteristics of the study subjects were compared using a Chi-square test for dichotomous variables and a Mann–Whitney *U*-test for non-parametric continuous variables. Bivariable analyses were conducted to determine the association between the primary exposure of interest (i.e., aminoglycoside therapy) and the primary and secondary outcomes (i.e., recurrent bacteremia). All tests were two-sided, and a *p* value of ≤ 0.05 was considered to be statistically significant. Potential confounding variables were evaluated in the same way. A relative risk (RR) and 95% confidence interval (CI) were calculated to evaluate both the strength of any association, as well as the precision of the estimate of the effect. Adjusted odds ratios (OR) were calculated using multiple logistic regression analysis with recurrent bacteremia as the dependent outcome [20]. In addition to the primary exposure of interest (i.e., aminoglycoside therapy), variables were considered for inclusion in a multivariable model if they were found to be associated with recurrent bacteremia on bivariable analysis (*p* value ≤ 0.20) or if they were involved in confounding on stratified analysis [21]. These variables remained in the final multivariable model if their inclusion in

the model resulted in a 15% change in the effect size of the primary association of interest (i.e., the association between aminoglycoside therapy and recurrence) [22, 23].

Results

A total of 506 episodes of *S. aureus* bacteremia were evaluated from January 1997 through December 2007. Eighty-seven subjects fulfilled the inclusion criteria and were included in the study (Fig. 1) by endocarditis (51%) and persistent bacteremia (68%). Sixteen patients (18%) had both endocarditis and persistent bacteremia. The baseline clinical characteristics of the study patients are described in Table 1. There was no statistically significant difference in any of the baseline clinical characteristics between the group receiving combination aminoglycoside therapy and the group who did not. Subjects were treated with a variety of non-aminoglycoside antimicrobials; most commonly, an antistaphylococcal beta-lactam and/or vancomycin were prescribed. The overall median duration of beta-lactam antimicrobial therapy was 19 days (range 1–377 days) and the median duration of vancomycin therapy was 16 days (range 1–68 days). The median durations of therapy for beta-lactams and vancomycin included patients who received any amount of either therapy, even if this was not given for the entire duration of treatment. The aminoglycosides prescribed in the study were either gentamicin or tobramycin; the median duration of aminoglycoside therapy was 5 days (range 1–40 days). Of the 87 *S. aureus* isolates, four were resistant to aminoglycosides. One subject in the aminoglycoside-treated group had an aminoglycoside-resistant isolate.

The median overall duration of bacteremia was 5 days (range 1–41 days), with no significant difference between the groups treated with and without an aminoglycoside (median 5 days for both groups, $p = 0.49$). In assessing the duration of bacteremia, 50 (57%) patients had at least one negative blood culture within 48 h of the last positive blood culture. Among all 87 subjects, 13 experienced the primary outcome of recurrent bacteremia. Significantly fewer patients in the group treated with an aminoglycoside experienced recurrence, 4 (8.2%), compared to the group not receiving an aminoglycoside, 9 (23.7%) [RR (95% CI) = 0.51 (0.22–1.17), $p = 0.04$]. The median time to recurrent bacteremia was 53 days (range 2–185 days) and the median duration of initial bacteremia in those patients who developed recurrence was 7 days (range 1–15 days). Eleven (85%) of the patients experiencing recurrence had an MRSA isolate. The characteristics in Table 1 were used in the multivariable model to evaluate factors associated with recurrence. In the final multivariable model, aminoglycoside use remained significantly associated with a decrease in recurrence [adjusted OR (95% CI) = 0.26 (0.07–0.98), $p = 0.046$] (Table 2). In addition, methicillin resistance in the *S. aureus* isolates was associated with recurrence (Table 2). We also examined the primary outcome stratified by inclusion criteria, although 16 patients (18%) met the inclusion criteria for both endocarditis and persistent bacteremia. For patients enrolled by meeting the endocarditis inclusion criterion ($n = 44$), fewer had recurrence in the group receiving an aminoglycoside, 2 (6.9%), compared to those not receiving an aminoglycoside, 4 (26.7%), but this difference was no longer statistically significant [RR (95% CI) = 0.47 (0.15–1.48), $p = 0.09$]. For those patients exclusively with persistent bacteremia ($n = 43$), 2 (10.0%) had recurrence in the aminoglycoside-treated group versus 5 (21.7%) in the group not treated with an aminoglycoside [RR (95% CI) = 0.57 (0.17–1.93), $p = 0.42$].

The 6-month all-cause mortality was 47.1%, with no significant difference between the groups treated with and without an aminoglycoside [51.0 vs. 42.1%, RR (95% CI) = 1.17 (0.81–1.69), $p = 0.41$]. Overall, 72.4% of subjects experienced at least one complication of bacteremia, with no significant difference between the group treated with an aminoglycoside (71.4%) and the group treated without an aminoglycoside (73.7%) [RR (95% CI) = 0.95

(0.64–1.43), $p = 0.82$]. The baseline serum creatinine for patients not on dialysis was 0.9 mg/dL (range 0.4–3.1) and the baseline GFR was 95 mL/min/1.73 m² (range 22–185). There was no significant difference in incident renal failure between the group who received an aminoglycoside and the group who did not [54.5 vs. 46.9%, RR (95%CI) = 1.16 (0.72–1.89), $p = 0.54$].

Discussion

In this study, with a primary outcome of recurrent bacteremia, significantly fewer patients treated with combination aminoglycoside therapy experienced recurrence compared to those who did not receive an aminoglycoside. Aminoglycoside use remained significantly associated with decreased recurrence after controlling for important confounders. For the other secondary efficacy endpoints, no statistically significant difference was observed in the overall duration of bacteremia, 6-month all-cause mortality, or complication rate between those who received and those who did not receive an aminoglycoside. There was also no difference between the groups in terms of incident renal failure as a measure of nephrotoxicity.

We chose to evaluate recurrent bacteremia as the primary outcome related to the efficacy of combination aminoglycoside therapy given that recurrence is common in patients with *S. aureus* bacteremia, with rates ranging from 5 to 23% [18, 19, 24–29]. Recurrent bacteremia is associated with significant morbidity and, potentially, higher mortality, and patients such as our study population with persistent *S. aureus* bacteremia and/or endocarditis are at higher risk for recurrence [19]. In the current study, we noted a significantly lower rate of recurrent bacteremia in the cohort of patients treated with aminoglycoside therapy. This finding demonstrates a potential role for the use of synergistic aminoglycoside therapy in this select group of patients who are at particularly high risk for recurrence.

Korzeniowski et al. [14] previously noted in a randomized study, a decreased duration of bacteremia with the use of combination aminoglycoside therapy for *S. aureus* endocarditis in IVDUs and non-IVDUs. In our study, however, we did not find a significant difference in the duration of bacteremia between the groups treated with and without an aminoglycoside. Our study was unable to fully assess the impact of aminoglycoside therapy on the initial duration of bacteremia due to the inclusion of patients with ≥ 72 h of bacteremia as part of our inclusion criteria, therefore, making our study population inherently different than that of Korzeniowski et al.'s cohort.

Consistent with other studies [1, 2, 30], our patient population with persistent *S. aureus* bacteremia and endocarditis had a high overall mortality, with a 6-month all-cause mortality of 47.1%. There was no significant difference in the mortality between the cohorts; however, the study's small sample size may have precluded the ability to distinguish a significant difference. Our results, though, were similar to other studies that have not shown an improved mortality with the use of combination aminoglycoside therapy [11–14]. Similarly, there was no significant difference in the complication rate between the groups, but the overall rate of patients experiencing at least one complication was quite high at 72.4%. Interestingly, the overall rate of incident renal failure was higher than expected at 50.8% compared with a prior study by Conlon et al. [31], in which one-third of patients with definite bacterial endocarditis developed acute renal failure. However, we found no statistically significant difference in the incident renal failure between those treated with aminoglycoside therapy and those who did not receive an aminoglycoside. This is in contrast to a study by Cosgrove et al. demonstrating significantly higher nephrotoxicity in patients treated with initial low-dose gentamicin for *aureus* bacteremia and endocarditis versus those who did not. This suggests that aminoglycoside therapy as well as other factors,

such as sepsis, metastatic infection to the kidney, and immune complex-mediated glomerulonephritis, are likely to be important in predicting renal dysfunction in this population with prolonged bacteremia or endocarditis.

There are several limitations to this study. First, the use of aminoglycoside therapy was at the discretion of the treating physician, raising the possibility of confounding by indication. Although we controlled for confounding using a multivariable logistic regression model, the potential for unmeasured confounding remains. Second, the definition of our primary outcome, recurrent *S. aureus* bacteremia within 6 months of the initial bacteremia, would encompass both relapse and re-infection. Our intent was to primarily include relapsed bacteremia, which would likely be related to therapy for initial bacteremia and its complications, rather than re-infection. In this study, we were unable to distinguish between relapse and re-infection, which may have led to the misclassification of some recurrences as being as being related to initial treatment when, in fact, they were re-infections unrelated to the initial bacteremia and its therapy. However, our a priori decision to define a recurrence within 6 months of the initial bacteremia was made to include relapses and fewer re-infections, and was based on prior data that relapse tends to occur much earlier after the completion of antibiotic therapy than re-infection (median 32 vs. 99 days) [19]. In addition, it is unlikely that misclassification would preferentially affect one cohort more than another. Lastly, the sample size of our study may have limited our ability to demonstrate differences in the 6-month mortality, complication rate, and incident renal failure.

Conclusions

In summary, combination aminoglycoside therapy may play a role in the treatment of patients with persistent *Staphylococcus aureus* bacteremia and/or infective endocarditis in the prevention of recurrent bacteremia. In this study, no significant additional nephrotoxicity was found with the use of aminoglycoside therapy, but the overall rates of incident renal failure in this population were high.

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References

1. Shurland S, Zhan M, Bradham DD, et al. Comparison of mortality risk associated with bacteremia due to methicillin-resistant and methicillin-susceptible *Staphylococcus aureus*. *Infect Control Hosp Epidemiol.* 2007; 28:273–279. [PubMed: 17326017]
2. Graham JC, Gould FK. Role of aminoglycosides in the treatment of bacterial endocarditis. *J Antimicrob Chemother.* 2002; 49:437–444. [PubMed: 11864943]
3. Petti CA, Fowler VG Jr. *Staphylococcus aureus* bacteremia and endocarditis. *Infect Dis Clin North Am.* 2002; 16:413–435. x–xi. [PubMed: 12092480]
4. Cabell CH, Jollis JG, Peterson GE, et al. Changing patient characteristics and the effect on mortality in endocarditis. *Arch Intern Med.* 2002; 162:90–94. [PubMed: 11784225]
5. Fowler VG Jr, Miro JM, Hoen B, et al. *Staphylococcus aureus* endocarditis: a consequence of medical progress. *JAMA.* 2005; 293:3012–3021. [PubMed: 15972563]
6. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: endorsed by the Infectious Diseases Society of America. *Circulation.* 2005; 111:e394–e434. [PubMed: 15956145]

7. McGrath BJ, Kang SL, Kaatz GW, et al. Bactericidal activities of teicoplanin, vancomycin, and gentamicin alone and in combination against *Staphylococcus aureus* in an in vitro pharmacodynamic model of endocarditis. *Antimicrob Agents Chemother.* 1994; 38:2034–2040. [PubMed: 7811015]
8. Watanakunakorn C, Glotzbecker C. Enhancement of the effects of anti-staphylococcal antibiotics by aminoglycosides. *Antimicrob Agents Chemother.* 1974; 6:802–806. [PubMed: 4451352]
9. Sande MA, Johnson ML. Antimicrobial therapy of experimental endocarditis caused by *Staphylococcus aureus*. *J Infect Dis.* 1975; 131:367–375. [PubMed: 1117194]
10. Sande MA, Courtney KB. Nafcillin–gentamicin synergism in experimental staphylococcal endocarditis. *J Lab Clin Med.* 1976; 88:118–124. [PubMed: 1047088]
11. Abrams B, Sklaver A, Hoffman T, et al. Single or combination therapy of staphylococcal endocarditis in intravenous drug abusers. *Ann Intern Med.* 1979; 90:789–791. [PubMed: 434682]
12. Ribera E, Gómez-Jimenez J, Cortes E, et al. Effectiveness of cloxacillin with and without gentamicin in short-term therapy for right-sided *Staphylococcus aureus* endocarditis. A randomized, controlled trial. *Ann Intern Med.* 1996; 125:969–974. [PubMed: 8967707]
13. Watanakunakorn C, Baird IM. Prognostic factors in *Staphylococcus aureus* endocarditis and results of therapy with a penicillin and gentamicin. *Am J Med Sci.* 1977; 273:133–139. [PubMed: 871133]
14. Korzeniowski O, Sande MA. Combination antimicrobial therapy for *Staphylococcus aureus* endocarditis in patients addicted to parenteral drugs and in nonaddicts: a prospective study. *Ann Intern Med.* 1982; 97:496–503. [PubMed: 6751182]
15. Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis.* 2000; 30:633–638. [PubMed: 10770721]
16. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis.* 2002; 39:S1–S266. [PubMed: 11904577]
17. Librero J, Peiró S, Ordiñana R. Chronic comorbidity and outcomes of hospital care: length of stay, mortality, and readmission at 30 and 365 days. *J Clin Epidemiol.* 1999; 52:171–179. [PubMed: 10210233]
18. Fowler VG Jr, Kong LK, Corey GR, et al. Recurrent *Staphylococcus aureus* bacteremia: pulsed-field gel electrophoresis findings in 29 patients. *J Infect Dis.* 1999; 179:1157–1161. [PubMed: 10191218]
19. Chang FY, Peacock JE Jr, Musher DM, et al. *Staphylococcus aureus* bacteremia: recurrence and the impact of antibiotic treatment in a prospective multicenter study. *Medicine (Baltimore).* 2003; 82:333–339. [PubMed: 14530782]
20. Hosmer, DW.; Lemeshow, S. *Applied logistic regression.* New York: John Wiley & Sons; 1989.
21. Sun GW, Shook TL, Kay GL. Inappropriate use of bivariable analysis to screen risk factors for use in multivariable analysis. *J Clin Epidemiol.* 1996; 49:907–916. [PubMed: 8699212]
22. Greenland S. Modeling and variable selection in epidemiologic analysis. *Am J Public Health.* 1989; 79:340–349. [PubMed: 2916724]
23. Robins JM, Greenland S. The role of model selection in causal inference from nonexperimental data. *Am J Epidemiol.* 1986; 123:392–402. [PubMed: 3946386]
24. Kreisel K, Boyd K, Langenberg P, et al. Risk factors for recurrence in patients with *Staphylococcus aureus* infections complicated by bacteremia. *Diagn Microbiol Infect Dis.* 2006; 55:179–184. [PubMed: 16631340]
25. Johnson LB, Almoujahed MO, Ilg K, et al. *Staphylococcus aureus* bacteremia: compliance with standard treatment, long-term outcome and predictors of relapse. *Scand J Infect Dis.* 2003; 35:782–789. [PubMed: 14723349]
26. Gottlieb GS, Fowler VG Jr, Kong LK, et al. *Staphylococcus aureus* bacteremia in the surgical patient: a prospective analysis of 73 postoperative patients who developed *Staphylococcus aureus* bacteremia at a tertiary care facility. *J Am Coll Surg.* 2000; 190:50–57. [PubMed: 10625232]
27. Marr KA, Kong L, Fowler VG, et al. Incidence and outcome of *Staphylococcus aureus* bacteremia in hemodialysis patients. *Kidney Int.* 1998; 54:1684–1689. [PubMed: 9844145]

28. Raad II, Sabbagh MF. Optimal duration of therapy for catheter-related *Staphylococcus aureus* bacteremia: a study of 55 cases and review. Clin Infect Dis. 1992; 14:75–82. [PubMed: 1571466]
29. Ehni WF, Reller LB. Short-course therapy for catheter-associated *Staphylococcus aureus* bacteremia. Arch Intern Med. 1989; 149:533–536. [PubMed: 2919931]
30. Chang FY, MacDonald BB, Peacock JE Jr, et al. A prospective multicenter study of *Staphylococcus aureus* bacteremia: incidence of endocarditis, risk factors for mortality, and clinical impact of methicillin resistance. Medicine (Baltimore). 2003; 82:322–332. [PubMed: 14530781]
31. Conlon PJ, Jefferies F, Krigman HR, et al. Predictors of prognosis and risk of acute renal failure in bacterial endocarditis. Clin Nephrol. 1998; 49:96–101. [PubMed: 9524779]
32. Cosgrove SE, Vigliani GA, Fowler VG Jr, et al. Initial low-dose gentamicin for *Staphylococcus aureus* bacteremia and endocarditis is nephrotoxic. Clin Infect Dis. 2009; 48:713–721. [PubMed: 19207079]

Fig. 1.
Flowchart of patient inclusion

Table 1

Baseline clinical characteristics

	Aminoglycoside use (<i>n</i> = 49)	No aminoglycoside use (<i>n</i> = 38)	<i>p</i> value
Age (years), median (range)	58 (50–70)	57 (53–71)	0.68
Male sex	47 (96)	36 (95)	0.79
Black race	33 (67)	26 (68)	0.68
Inclusion criteria			
Endocarditis	29 (59)	15 (39)	0.07
Bacteremia	31 (63)	28 (74)	0.30
DM	22 (45)	20 (53)	0.47
IVDU	9 (18)	5 (13)	0.51
CKD	7 (14)	9 (24)	0.26
ESRD	16 (33)	6 (16)	0.07
HIV	5 (10)	2 (5)	0.40
Steroid use	3 (6)	1 (3)	0.44
ESLD	2 (4)	4 (11)	0.24
MRSA isolate	27 (55)	21 (55)	0.99
ICU stay during bacteremia	32 (65)	21 (55)	0.34
Charlson index, median (range)	4 (2–6)	4 (2–6)	0.87
Presence of central venous catheter	20 (41)	12 (32)	0.38

Data are no. of patients (%), unless otherwise indicated *DM* diabetes mellitus, *IVDU* current intravenous drug use, *CKD* chronic kidney disease, *ESRD* end-stage renal disease on dialysis, *HIV* human immunodeficiency virus, *ESLD* end-stage liver disease, *MRSA* methicillin-resistant *Staphylococcus aureus*, *ICU* intensive care unit

Table 2

Multivariable analysis of clinical variables associated with recurrent bacteremia

Variable	Unadjusted OR	Adjusted OR (95% CI)	<i>p</i> value
Aminoglycoside therapy	0.29	0.26 (0.07–0.98)	0.046
MRSA isolate	5.50	5.93 (1.19–29.47)	0.030

OR odds ratio, *CI* confidence interval