Recurrent *Staphylococcus aureus* Bacteremia: Pulsed-Field Gel Electrophoresis Findings in 29 Patients

Vance G. Fowler, Jr., Li Kuo Kong, G. Ralph Corey, Geoffrey S. Gottlieb, R. Scott McClelland, Daniel J. Sexton, Diane Gesty-Palmer, and Lizzie J. Harrell

Department of Medicine, Division of Infectious Diseases, Department of Microbiology and Clinical Microbiology Laboratory, Duke University Medical Center, Durham, North Carolina

To identify risk factors for relapse among 309 prospectively identified cases of *Staphylococcus aureus* bacteremia, patients with recurrent *S. aureus* bacteremia were identified, and pulsed-field gel electrophoresis (PFGE) was performed on isolates from both episodes. PFGE banding patterns from both isolates were identical in 23 patients, consistent with relapsed infection. Patients with PFGE-confirmed relapse were more likely by both univariate and multivariate analyses to have an indwelling foreign body (odds ratio [OR] = 18.2, 95% confidence interval [CI] = 7.6–43.6; $P < .001$), to have received vancomycin therapy (OR = 4.1, 95% CI = 1.5–11.6; $P = .008$), or be hemodialysis-dependent (OR = 4.1, 95% CI = 1.8–9.3; $P = .002$) than patients who did not develop recurrent bacteremia. These results suggest that recurrent episodes of *S. aureus* bacteremia are primarily relapses and are associated with an indwelling foreign body, receiving vancomycin therapy, and hemodialysis dependence.

Recurrent *Staphylococcus aureus* bacteremia is a common phenomenon. A second episode of *S. aureus* bacteremia in a patient may represent relapse of a persistent infection or reinfection unrelated to prior staphylococcal disease. Although the ability to identify *S. aureus* bacteremia as relapse or reinfection has important implications for patient management, surprisingly little has been written about this problem. Thus, many features of recurrent *S. aureus* bacteremia remain incompletely defined.

Pulsed-field gel electrophoresis (PFGE) offers a potential tool for distinguishing different *S. aureus* strains by identifying a genetic pattern unique to each isolate. We hypothesized that by performing PFGE on *S. aureus* isolates from multiple episodes of bacteremia in the same patient and comparing the genetic patterns from these different isolates, we could distinguish patients with relapsed staphylococcal infection from those reinfected with a new strain. The purpose of this study was to use PFGE to differentiate relapses from new infections in patients with recurrent *S. aureus* bacteremia and to identify clinical features associated with PFGE-confirmed relapses of *S. aureus* bacteremia.

Received 3 August 1998; revised 28 December 1998.

Presented in part: 37th Interscience Conference on Antimicrobial Agents and Chemotherapy, September 1997, Toronto, Canada (abstract no. LM-11).

Research guidelines of Duke University were followed in the conduct of the clinical research of this report.

Financial support: Health Services Research and Development Fellowship from the Veterans Administration Medical Center, Durham, North Carolina (to V.G.F.).

Reprints or correspondence: Dr. Vance G. Fowler, Jr., Box 3824, Division of Infectious Diseases, Duke University Medical Center, Durham, NC 27710 (fowle007@mc.duke.edu).

The Journal of Infectious Diseases 1999; 179:1157–61

0022-1899/99/7905-0015$02.00

Materials and Methods

Subjects and setting. Between September 1994 and December 1996, we received daily reports from the clinical microbiology laboratory on all patients at Duke University Medical Center with one or more blood culture(s) positive for *S. aureus.* Patients were then evaluated within 36 h of the detection of bacteremia for clinical evidence of infection. Recurrent bacteremia was defined as a subsequent episode of *S. aureus* bacteremia after the completion of an antibiotic course of therapy yielding an apparent clinical cure. Patients were excluded from the study for the following reasons: age <18 years, polymicrobic infection, neutropenia (white blood cell count $<10^9$/L), death prior to the return of positive blood cultures, or outpatient status.

Clinical features. Each patient was evaluated by a member of the infectious diseases team for signs suggestive of infective endocarditis and for clinical evidence of a source of the bacteremia. Infective endocarditis was defined according to the Duke criteria [1]. Staphylococcal tissue infection was considered the source of bacteremia if clinical signs of a known or suspected soft-tissue infection antedated the bacteremia. An intravascular catheter was considered to be the portal of entry for *S. aureus* bacteremia if (1) there was evidence of inflammation at the catheter insertion site and/or (2) semiquantitative culture of the vascular catheter tip was positive for ⩾15 colonies of *S. aureus,* and (3) there was no clinical evidence of another source for the bacteremia [2]. A foreign body was defined as any device that was inserted for an extended period of time (e.g., tunneled intravascular catheter, synthetic intravascular graft, arthroplasty, orthopedic hardware).

Treatment. Patients were classified as having received vancomycin therapy if this agent was prescribed for the entire treatment

period or if therapy was converted to vancomycin within 2 days of initiating another antibiotic type [3].

Patient outcome. Follow-up was attempted for all living patients. Twelve weeks after the date of the first positive blood culture, telephone contact was made with the patient, a family member, or the patient's primary care physician to inquire about the patient's current condition. In the event of a second hospitalization within 12 weeks of the first hospitalization, all pertinent medical records were reviewed.

Bacterial isolates. Isolates were identified by standard microbiologic technique [4], and antimicrobial susceptibility testing was performed by disk diffusion according to National Committee for Clinical Laboratory Standards criteria [5, 6]. Isolates were frozen (−70°C) from the time of identification until they were subcultured to sheep blood agar for PFGE. Methicillin resistance was confirmed by using a salt-screen plate.

PFGE. For each episode of bacteremia, at least 1 isolate from each patient was analyzed by PFGE. The molecular technique is described elsewhere [7]. Briefly, single colonies of fresh isolates (18–24 h) were transferred to 5 mL of trypticase soy broth and grown overnight at 37°C on a shaker (250 rpm). A 60-μL aliquot of the turbid broth was centrifuged, resuspended in cold cell suspension buffer, and embedded in an agarose plug. The agarose-embedded cells were then lysed, and chromosomal DNA was purified (GenePath Group 1 Reagent Kit; Bio-Rad Laboratories, Hercules, CA). The DNA samples were then restricted with *Sma*1, and slices of the plugs with the embedded DNA were loaded into the wells of a 1% molecular biology grade agarose gel (Bio-Rad) and analyzed by PFGE using the Bio-Rad Gene Path strain typing instrument with settings for *S. aureus.* The gel was stained with ethidium bromide and photographed under ultraviolet light.

PFGE patterns were compared by visual inspection and interpreted using established guidelines [8] by a single experienced investigator (L.J.H.)blinded to clinical data. Isolates with no differences in PFGE banding patterns of chromosomal fragments were defined as indistinguishable, those with three or fewer fragment differences were defined as closely related, and those with four or greater fragment differences were defined as different. Recurrent bacteremia was defined as a relapse if the PFGE banding patterns of the isolates were indistinguishable or closely related and a new infection if the paired isolates demonstrated different banding patterns.

Statistical analysis. Descriptive statistics for continuous variables were summarized in terms of medians and interquartile ranges. Categorical variables were reported in terms of the number and percent of patients affected. Comparisons between the group with relapsed *S. aureus* bacteremia and the group reinfected with a separate strain of *S. aureus* were made with Wilcoxon rank sum tests for continuous variables and with Fisher's exact tests for categorical variables. Relationships were considered significant when the 2-sided P value was $\leq .05$. Because characteristics identified as risk factors for PFGE-confirmed relapse might be interrelated, Spearman correlation analysis was performed on all candidate variables found to be significant by univariate analysis. Relationships between these variables were described using coefficient values ranging from −1 to +1 (strongest negative to strongest positive correlation).

To explore the independent contribution of various risk factors for relapsed infection, multivariate logistic regression was performed using clinically relevant variables and PFGE-confirmed relapse as the outcome. Because of the small number of outcomes ($n = 23$), only two variables were included in each model. To fully explore the relationship between variables, all possible 2-variable combinations were evaluated. All calculations were performed in SAS software licensed by the Duke University Medical Center.

Results

From September 1994 to December 1996, 310 consecutive patients with *S. aureus* bacteremia were prospectively identified. Of these 310 patients, 309 were followed for at least 12 weeks after the initial positive blood culture. Thirty-eight patients (12.3%) developed recurrent *S. aureus* bacteremia. The isolates from 8 patients were unavailable for analysis: 4 were identified in an outside hospital and discarded, and 4 were identified at our institution but not found. We were unable to adequately lyse the isolate of 1 patient for PFGE analysis.

Among the remaining 29 patients, there were 49 episodes of recurrent *S. aureus* bacteremia. The mean age was 48 years, and 15 (51.7%) were men. Fifteen (51.7%) patients were hemodialysis-dependent, 7 (24.1%) had diabetes mellitus, and 5 (17.2%) had a malignancy (3 hematologic, 2 solid tumors). Metastatic infections were common, occurring in 10 (34.5%) patients. Seven patients (24.1%) eventually died of staphylococcal infection (6 relapse patients, 1 reinfection patient). Ten (34.5%) of 29 patients had methicillin-resistant *S. aureus* (MRSA), 7 of whom (70.0%) were in the relapse group.

Relapse group. *S. aureus* bacteremia in 23 patients (82.1%) was due to PFGE-confirmed relapse (table 1). At the time of relapse, all 23 patients had an identifiable focus of persistent staphylococcal infection that had been present at the time of a previous episode of bacteremia. An unremoved foreign body was present in 19 patients (82.6%). The remaining 4 patients had persistent deep-tissue infections as the presumed source of their relapsed bacteremia (1 patient each with septic arthritis,

Table 1. Characteristics of 29 patients with recurrent *S. aureus* bacteremia according to PFGE analysis of paired isolates.

	Patients with	
	Relapse (PFGE identical)	Reinfection (PFGE different)
n	23	6
Age	55 (41–68)	38 (35–47)
Male sex	14 (60.9%)	1 (16.7%)
Race (black)	15 (65.2%)	5 (83.3%)
Unremoved foreign bodies	19 (82.6%)	4 (66.7%)
Deep-tissue source for bacteremia	4 (17.4%)	0
Injection drug use[a]	0	3 (50.0%)
MRSA (%)	7 (30.4%)	3 (50.0%)
Vancomycin use	19 (82.6%)	3 (50.0%)
Metastatic infection	7 (30.4%)	3 (50.0%)
Died of *S. aureus* infection	6 (26.1%)	1 (16.7%)

NOTE. MRSA, methicillin-resistant *S. aureus.*

[a] $P = .005$, Fisher's exact test. All other comparisons in table were not statistically significant.

abscess, mediastinitis, and infectious endocarditis). None of the 23 patients in the relapse subset were known to be injection drug users. Metastatic infection at the time of the initial episode of bacteremia was common. Seven (30.4%) of the 23 patients had at least 9 metastatic infections at the time of their initial bacteremia (arthritis in 4 patients, soft-tissue abscesses in 3 patients, endocarditis in 2 patients). Six patients (26.1%) died of relapsing staphylococcal bacteremia.

Risk factors for PFGE-confirmed relapse. Because relapsed infection is a concern faced by clinicians caring for patients infected with *S. aureus,* we sought to identify risk factors for relapsed bacteremia by univariate analysis. We compared select characteristics of 23 patients with PFGE-confirmed relapse with 271 patients simultaneously registered into our database who did not develop recurrent *S. aureus* bacteremia during the 12-week follow-up period (table 2). Patients with PFGE-confirmed relapse were more likely to have an indwelling prosthetic device (odds ratio [OR] = 18.2, 95% confidence interval [CI] = 7.6–43.6; $P < .001$), be hemodialysis-dependent (OR = 4.1, 95% CI = 1.8–9.3; $P = .002$), or have received vancomycin-based therapy (OR = 4.1, 95% CI = 1.5–11.6; $P = .008$).

Results of multivariate models were all consistent with results of the univariate models, with the presence of an indwelling foreign body having the largest effect. The model most predictive of PFGE-confirmed relapse (*c* statistic = 0.86) included the variables "presence of an unremoved foreign body" (OR = 16.9, 95% CI = 6.0–60.6; $P < .001$) and "vancomycin therapy" (OR = 3.5, 95% CI = 1.2–12.7; $P = .04$).

The OR for hemodialysis dependence changed from 4.1 to 1.6 in the model with "presence of an indwelling foreign body" and to 2.9 in the model with "vancomycin therapy." The Spearman correlation coefficient between "hemodialysis dependence" and "indwelling foreign body" was 0.36 ($P < .001$), between "hemodialysis dependence" and "vancomycin therapy" was 0.32 ($P < .001$), and between "indwelling foreign body" and "vancomycin therapy" was 0.11 ($P = .054$). These results suggest that significant correlation exists between these three variables.

Table 2. Univariate analysis of select patient characteristics for 294 consecutive patients with *S. aureus* bacteremia seen at Duke University Medical Center from September 1994 until December 1996.

	No. (%) with			
	No recurrence ($n = 271$)	Relapse ($n = 23$)	OR (95% CI)	*P*
Diabetes mellitus	63 (23.2)	7 (30.4)	1.4 (0.6–3.7)	NS
Hemodialysis dependence	75 (27.7)	14 (60.9)	4.1 (1.8–9.3)	.002
Indwelling foreign body	56 (20.7)	19 (82.6)	18.2 (7.6–43.6)	<.001
Vancomycin-based therapy	145 (53.5)	19 (82.6)	4.1 (1.5–11.6)	.008
Metastatic infection	79 (29.2)	6 (26.1)	0.9 (0.3–2.3)	NS
Infection with MRSA	85 (31.4)	7 (30.4)	1.0 (0.4–2.4)	NS

NOTE. NS, not significant, $P > .05$. A total of 271 patients had no evidence of recurrent *S. aureus* bacteremia 12 weeks after initial positive blood culture, and 23 patients had relapsed *S. aureus* bacteremia confirmed by PFGE. Six patients with PFGE-confirmed reinfection are not included in this comparison.

New infection group. Reinfection with a different strain of *S. aureus* occurred in 6 patients. Patients with reinfection had predisposing factors for recurrent staphylococcal infection: 3 patients were felt to be reinfected with *S. aureus* as a consequence of their injection drug use, 2 patients as a result of their severe dermatitis, and 1 patient as a consequence of multiple surgical wounds. Foreign bodies were present but uninfected in 3 patients: 2 hemodialysis-dependent patients had nonfunctional intravascular grafts, and 1 patient had an indwelling intravascular catheter. A fourth patient had an infected foreign body (hip arthroplasty). Patients reinfected with a different strain of *S. aureus* were significantly more likely to be injection drug users than patients with PFGE-confirmed relapsed bacteremia ($P = .005$). Metastatic infection at the time of the initial episode of bacteremia was common: 3 patients (50%) had at least 5 infectious complications of their bacteremia (arthritis in 2 patients and septic pulmonary embolus, pericarditis, and endocarditis in 1 patient each). One patient (16.7%) died of reinfection with a new *S. aureus* isolate.

Unremoved foreign bodies. Twenty-three patients (83%) had an unremoved foreign body present at the time of recurrence that had been in place at the time of the initial episode of bacteremia (intravascular grafts in 14 patients, tunneled catheters in 5 patients, and orthopedic devices in 4 patients). Most of these foreign bodies (19 of these 23 patients, 82.6%) were infected at the time of recurrence. Infection involving the foreign body was confirmed either microbiologically (11 patients) or clinically (8 patients). In 18 of these 19 patients with infected foreign bodies, relapsed infection was confirmed by PFGE.

The median length of time to recurrence after the first detected bacteremic episode was 69 days (interquartile range = 35–89 days). Twenty-two (76%) of 29 patients developed their initial recurrences within 90 days of their first positive culture. Of these 22 patients, 19 patients had PFGE-confirmed relapses. By contrast, 4 of the 7 patients who developed their initial recurrence after >90 days had PFGE-confirmed relapse (OR = 4.8, 95% CI = 0.73–30.8; $P = .13$).

Multiple recurrences. Ten patients were found to have more than one recurrence of bacteremia. Most (8) of these 10 patients had PFGE-confirmed relapse, including 1 who had 5 bacteremia relapses associated with multiple deep-tissue infections over a 15-month period (figure 1). The identification of multiple episodes of *S. aureus* bacteremia in a patient was prognostically important: Among patients with more than one recurrence of *S. aureus* bacteremia, 6 of 10 ultimately died of staphylococcal sepsis. In contrast, only 1 (5.3%) of 19 patients with a single episode of recurrent *S. aureus* bacteremia died of their infections ($P = .002$).

Therapy. Twenty-two patients were treated with a predominantly vancomycin-based antimicrobial regimen. The primary reason for vancomycin administration was infection with MRSA in 10 patients and convenience in hemodialysis-dependent patients in 12 patients. Six patients were treated with a β-

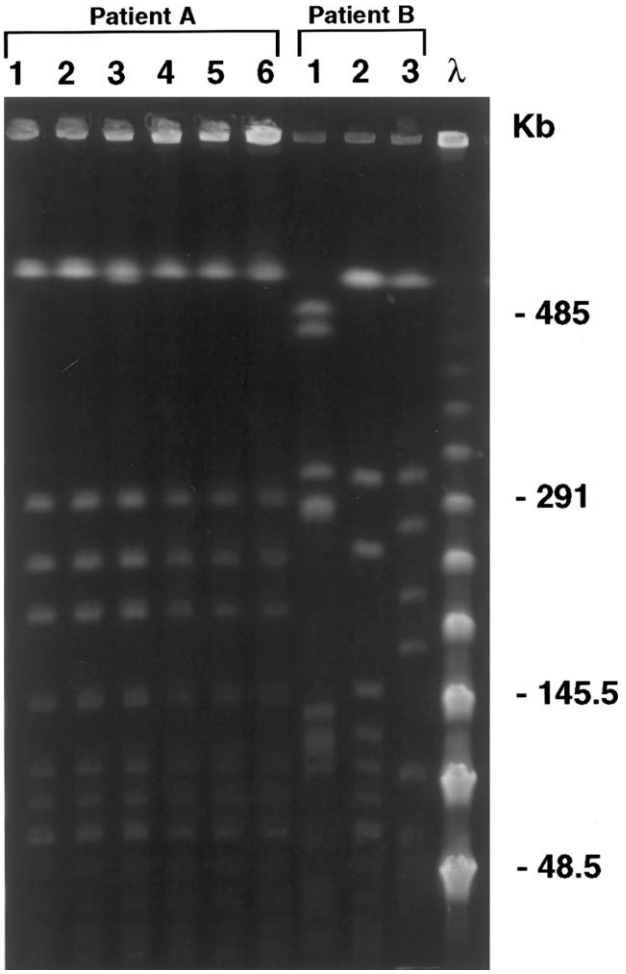

Figure 1. PFGE patterns of *Sma*1-digested chromosomal DNA from 2 patients with recurrent *S. aureus* bacteremia. Isolates from patient A (lanes 1–6) have indistinguishable banding patterns and were defined as relapsed infections. This patient had 6 episodes of relapsed bacteremia associated with multiple deep-tissue infections (paraspinous abscess, vertebral osteomyelitis, and endocarditis) and ultimately died of *S. aureus* endocarditis. Isolates from patient B (lanes 1–3) had different banding patterns between the 3 episodes of bacteremia and were defined as new infections. This patient presumably was reinfected as consequence of continued injection drug use.

lactam antibiotic–based regimen, and 1 patient did not receive therapy. The median duration of therapy in the initial course was 28 days (interquartile range = 14–42).

Most of the hemodialysis-dependent patients (13/15, 86.7%) relapsed from a previous infection. Of these hemodialysis patients, 13 (86.7%) had an unremoved foreign object, and 14 (93.3%) were treated with vancomycin. Three of these patients were infected with MRSA.

Discussion

This investigation is the largest molecular analysis of isolates from patients with recurrent *S. aureus* bacteremia, and, to our knowledge, represents the first such analysis using PFGE. Using both univariate and multivariate logistic regression analyses, we found that patients with PFGE-confirmed relapse were significantly more likely to have an indwelling foreign body, received vancomycin therapy, or be hemodialysis-dependent than patients who did not develop recurrent bacteremia.

Patients with PFGE-confirmed relapse were 18.2 times more likely to have an unremoved foreign body than patients who did not develop recurrent *S. aureus* bacteremia. This finding agrees with previous observations. For example, Hartstein et al. [9] typed the isolates of 8 patients with nonconsecutive recurrent *S. aureus* bacteremia collected over a 3.5-year period. They used restriction endonuclease analysis of plasmid DNA and immunoblotting and found that relapsing infections were strongly associated with the presence of an intravascular foreign body. Unfortunately, their small patient size limited the power of their findings. Other investigators have demonstrated in both a retrospective [10] and prospective [11] study design that infected unremoved foreign bodies carry a high risk for relapsing infection. We also found that patients with a prosthetic device who develop recurrent *S. aureus* bacteremia have a very high risk of *S. aureus* prosthetic device infection. In 82.6% of patients with recurrent *S. aureus* bacteremia and an unremoved foreign body present at the time of the initial bacteremia, the foreign body was infected at the time of recurrence. These results suggest that foreign bodies are often infected in patients with recurrent *S. aureus* bacteremia.

The use of vancomycin for the treatment of *S. aureus* bacteremia was significantly associated with PFGE-confirmed relapse. This finding is consistent with the observations of others [9, 12–14]. As suggested by the Spearman correlation coefficients, our findings may be due in part to confounding interactions. For example, most patients who received vancomycin were also hemodialysis-dependent patients with unremoved foreign bodies. Thus, the question of the comparative efficacy of vancomycin versus β-lactam antibiotics awaits a randomized trial for resolution. Nevertheless, these results should discourage the inappropriate use of vancomycin, as has been suggested elsewhere [15].

Hemodialysis dependence was also significantly associated with PFGE-confirmed relapse in our analysis. There are several possible explanations for this finding. First, unremoved foreign bodies (hemodialysis access sites) were particularly common among these patients. Clinicians often attempted to save a synthetic dialysis graft site or tunneled intravascular catheter in patients with limited dialysis access. Second, the infrequent vancomycin dosing strategy often used among hemodialysis-dependent patients because of convenience and cost may not maintain an adequate trough level in high-flux, large pore–size artificial kidneys [16]. Finally, the significant association between hemodialysis dependence and PFGE-confirmed relapse may be due in part to interactions with other variables (e.g., presence of foreign body, vancomycin therapy).

In the subset of patients with reinfection, factors predisposing patients to chronic *S. aureus* colonization were associated with the development of a new *S. aureus* infection. For example, half of the patients with new infections were injection drug users, a patient group with high *S. aureus* colonization rates [17, 18]. Two other patients had severe dermatitis, another condition promoting staphylococcal colonization. Our findings suggest that patients with conditions promoting chronic *S. aureus* colonization often develop multiple staphylococcal infections, often with different strains.

The time to recurrence has been associated with whether the infection represents relapse or reinfection [9]. In our study, 86% of the patients who developed a second episode of *S. aureus* bacteremia within 90 days of their initial infection had PFGE-confirmed relapses. Although this trend was not statistically significant ($P = .13$), it is consistent with the findings of a previous investigation that early recurrence represents a relapse, whereas later recurrences are more likely to be reinfection [9]. Of importance, however, patients with multiple relapses of *S. aureus* bacteremia due to a persistent source of infection may relapse several times over many months.

Our study has several limitations. First, we cannot exclude the possibility that patients with identical isolates by PFGE (categorized as relapse in this study) were not simply reinfected with the same isolate on several occasions. However, we doubt that this is likely because of the fact that all of the patients we categorized as relapse on the basis of PFGE results had an identifiable source of their bacteremia that had been present at the time of their previous episode of bacteremia (e.g., infected foreign body or persistent deep-tissue infection). Second, it is possible that the appearance of a different isolate of *S. aureus* by PFGE may reflect a change in the population size of 2 (or more) strains initially present in the patient rather than reinfection. However, the small number of paired isolates with different PFGE banding patterns limited our ability to draw conclusions about this important clinical phenomenon.

In conclusion, we have shown by molecular techniques that most episodes of recurrent *S. aureus* bacteremia represent relapse of a previous infection and often of an infected foreign body. Because of the high rate of foreign body infection among patients with recurrent *S. aureus* bacteremia, most foreign bodies in these patients should be considered as infected until proven otherwise. Furthermore, all patients with recurrent *S. aureus* bacteremia should undergo a thorough evaluation for deep-tissue sites of infection. Only in this way can the high rate of associated complications and death be minimized.

Acknowledgment

The authors gratefully acknowledge statistical assistance from L. M. McIntyre.

References

1. Durack DT, Lukes AS, Bright DK. New criteria for diagnosis of infective endocarditis:utilization of specific echocardiographic findings. Duke Endocarditis Service. Am J Med **1994**;96:200–9.
2. Libman H, Arbeit RD. Complications associated with *Staphylococcus aureus* bacteremia. Arch Intern Med **1984**;144:541–5.
3. Mylotte JM, Aeschlimann JR, Rotella DL. *Staphylococcus aureus* bacteremia: factors predicting hospital mortality. Infect Control Hosp Epidemiol **1996**;17:165–8.
4. Balows A, Hausler W, Herrman KL, et al. Manual of clinical microbiology. Washington, DC: American Society for Microbiology, **1991**.
5. National Committee for Clinical Laboratory Standards. Performance standards for antimicrobial disk susceptibility tests—6th ed. NCCLS document M2-A6 (ISBN 1-56238-308-6). Wayne, PA: NCCLS, **1997**.
6. National Committee for Clinical Laboratory Standards. Performance standards for antimicrobial susceptibility testing—eighth informational supplement. NCCLS document M100-S8 (ISBN 1-56238-337-X). Wayne, PA: NCCLS, **1998**.
7. Zaidi AK, Harrell LJ, Rost JR, Reller LB. Assessment of similarity among coagulase-negative staphylococci from sequential blood cultures of neonates and children by pulsed-field gel electrophoresis. J Infect Dis **1996**; 174:1010–4.
8. Tenover FC, Arbeit RD, Goering RV, et al. Interpreting chromosomal DNA restriction patterns produced by pulsed-field gel electrophoresis: criteria for bacterial strain typing. J Clin Microbiol **1995**;33:2233–9.
9. Hartstein AI, Mulligan ME, Morthland VH, Kwok RY. Recurrent *Staphylococcus aureus* bacteremia. J Clin Microbiol **1992**;30:670–4.
10. Dugdale DC, Ramsey PG. *Staphylococcus aureus* bacteremia in patients with Hickman catheters. Am J Med **1990**;89:137–41.
11. Marr KA, Sexton DJ, Conlon PJ, Corey GR, Schwab SJ, Kirkland KB. Catheter-related bacteremia and outcome of attempted catheter salvage in patients undergoing hemodialysis. Ann Intern Med **1997**;127:275–80.
12. Levine DP, Fromm BS, Reddy BR. Slow response to vancomycin or vancomycin plus rifampin in methicillin-resistant *Staphylococcus aureus* endocarditis. Ann Intern Med **1991**;115:674–80.
13. Mortara LA, Bayer AS. *Staphylococcus aureus* bacteremia and endocarditis. New diagnostic and therapeutic concepts. Infect Dis Clin North Am **1993**;7:53–68.
14. Small PM, Chambers, HF. Vancomycin for *Staphylococcus aureus* endocarditis in intravenous drug users. Antimicrob Agents Chemother **1990**;34: 1227–31.
15. Recommendations for preventing the spread of vancomycin resistance: recommendations of the Hospital Infection Control Practices Advisory Committee (HICPAC). Am J Infect Control **1995**;23:87–94.
16. Barth RH, DeVincenzo N. Use of vancomycin in high-flux hemodialysis: experience with 130 courses of therapy. Kidney Int **1996**;50:929–36.
17. Berman DS, Schaefler S, Simberkoff MS, Rahal JJ. *Staphylococcus aureus* colonization in intravenous drug abusers, dialysis patients, and diabetics [letter]. J Infect Dis **1987**;155:829–31.
18. Tuazon CU, Sheagren JN. Increased rate of carriage of *Staphylococcus aureus* among narcotic addicts. J Infect Dis **1974**;129:725–7.