ORIGINAL INVESTIGATION

Treatment and Outcome of *Staphylococcus aureus* Bacteremia

A Prospective Study of 278 Cases

Allan G. Jensen, MD; Carsten H. Wachmann, MSc, PhD; Frank Espersen, MD, PhD; Jens Scheibel, MD; Peter Skinhøj, MD, PhD; Niels Frimodt-Møller, MD, PhD

Background: *Staphylococcus aureus* bacteremia is still a serious problem, and the optimal treatment is under debate. Only a few studies concerning treatment are available.

Methods: The study population was all patients with a positive blood culture result for *S aureus* in Copenhagen County, Denmark, from May 1994 through April 1996. Of 278 patients with *S aureus* bacteremia, 186 were evaluated according to outcome in a prospective, observational follow-up study. The time above the minimum inhibitory concentration was estimated for dicloxacillin sodium for each treatment regimen and evaluated by logistic regression along with other potential risk factors.

Results: The following variables were statistically associated with death: the presence of an uneradicated focus (odds ratio [OR], 6.7; 95% confidence interval [CI], 2.1-21.0); the presence of septic shock (OR, 3.7; 95% CI, 1.5-9.1); the total daily dose of penicillinase-stable penicillin less than 4 g (OR, 3.7; 95% CI, 1.3-11.1); and age 60 years or older (OR, 2.4; 95% CI, 1.1-5.3). The following variables were significantly associated with recurrence: the total daily dose of penicillinase-stable penicillin less than 3 g (OR, 3.9; 95% CI, 1.6-10.0) and the presence of a secondary focus (OR, 3.2; 95% CI, 1.3-7.7). Among 155 patients with observation time longer than duration of treatment, this factor (duration of treatment, <14 days) was significantly related to mortality (OR, 0.84; 95% CI, 0.76-0.94).

Conclusions: Focus eradication and the dosing of penicillinase-stable penicillin are important to the outcome of *S aureus* bacteremia. We recommend treatment with at least 1 g of penicillinase-stable penicillins 4 times daily for longer than 14 days.

Arch Intern Med. 2002;162:25-32

From the Sector for Microbiology (Drs Jensen, Espersen, and Frimodt-Møller) and Biostatistical Unit (Dr Wachmann), Statens Serum Institut; the Department of Clinical Microbiology, Herlev University Hospital (Dr Scheibel); and the Department of Infectious Diseases, Rigshospitalet (Dr Skinhøj), Copenhagen, Denmark.

STAPHYLOCOCCUS AUREUS is still one of the most important pathogens of bacteremia.[1-5] Despite the availability of potent antistaphylococcal antibiotics, *S aureus* bacteremia (SAB) is still an important problem with a high mortality,[6-9] and studies are already available on this condition.[6,8,10-13] Some data on the importance of focus identification and focus eradication in the treatment of SAB are available,[7,10] and (based on primarily experimental evidence) the time the serum drug concentration remains above the minimal inhibitory concentration (MIC) is an important pharmacokinetic parameter for the effect of β-lactam antibiotics[14-18] when determining the appropriate dosage. However, very few clinical studies have investigated the optimal dosing strategy of β-lactam antibiotics in the treatment of SAB. One study[19] showed equal efficacy with continuous infusion compared with intermittent infusion of 2 g of oxacillin 6 times daily; however, a significantly less amount of the drug was used with continuous infusion.

In the present study of consecutive SAB cases, we compare outcomes in hospital-acquired SAB vs community-acquired SAB and specifically address the role of the bacterial focus and the administration of penicillinase-stable penicillin in multiple regression analysis.

RESULTS

INCIDENCE

From 236 136 patients admitted to the 4 hospitals during the study period, 296 episodes of SAB were detected. Of these, 18 (6%) were regarded as contaminations, and of the remaining 278 true bacteremia cases, 147 (53%) were hospital acquired and 131 (47%) community acquired. Thus, the total incidence rate of true bacteremia cases was 1.18 per 1000 admissions (0.62 for hospital-acquired cases and 0.56 for community-acquired cases).

POPULATION, MATERIALS, AND METHODS

STUDY POPULATION, MICROBIOLOGICAL METHODS, AND COLLECTION OF DATA

The study period was from May 1, 1994, to April 30, 1996, and comprised 236 136 admissions to 4 community hospitals (2404 somatic beds), which serve 604 762 inhabitants in Copenhagen County, Denmark. The Department of Clinical Microbiology at Herlev University Hospital, Copenhagen, received all clinical samples from this area. All specimens were routinely registered in a microbiological database system (ADBakt, Autonik AB; Ramsta, Sköldinge, Sweden) running on a digital minicomputer (model VAX 4200; Compaq Computer Corp, Houston, Tex) with 40 connected terminals.[20] The blood culture system used was Colorbact (Statens Serum Institut).[21,22] All *S aureus* strains isolated were phage typed according to the method of Blair and Williams[23] using the current international set of typing phages. The phages were used in concentrations of routine dilution: 100× and 1000× routine dilution. The subdivision into phage groups and complexes was done according to Parker.[24]

Susceptibility to antibiotics of the infecting strains was determined by a disk diffusion method.[25] The testing comprised susceptibility to penicillin, streptomycin, tetracycline, erythromycin, methicillin, and gentamicin. When a blood culture was detected as positive for *S aureus* in the clinical microbiology laboratory, the patient was seen by one of us (A.G.J.), in most cases within 24 hours. After receiving informed consent, the patient was examined at bedside, and clinical data were obtained from the chart. From reviewing medical records, the following data were extracted: source of infection, sex, age, underlying disease and/or condition, type and time of symptoms, and clinical findings (ie, primary and secondary foci; hospital investigations, such as echocardiography, radiography, bone scintigraphy, and computed tomography scanning; and type, duration, and daily dosage of antibiotic treatment). All medical records were reviewed by the same person (A.G.J.) 3 months after a blood culture was found positive for *S aureus* to establish time of hospital admission and 3-month survival and recurrence outcome.

DEFINITIONS

Based on the history of the patient, physical examination findings, body temperature, clinical course, and results of cultures from other body sites, it was decided whether the bacteremia was a true bacteremia or if it had to be regarded as a contamination according to Weinstein et al.[26] True bacteremia cases were subdivided into hospital- and community-acquired cases. A hospital-acquired bacteremia was defined as a patient with a positive blood culture result and clinical evidence of infection that developled later than 48 hours after admission.[26] Episodes in patients with infections of implanted foreign bodies were considered hospital acquired. Underlying condition was any disease and/or underlying condition recorded prior to or at admission. Onset of infection was the time of first appearance of symptoms. Primary focus of infection was based on evident clinical signs and/or symptoms that were later confirmed by the cultivation of a bacterial strain with the same resistance pattern as the blood culture strain. Endocarditis, osteomyelitis, arthritis, and meningitis were considered secondary foci if the patients had not received surgical intervention prior to the onset of SAB. Finding *S aureus* in the urinary tract was considered secondary to SAB if the patient did not have signs

PHAGE TYPING AND ANTIBIOTIC RESISTANCE

Strains belonging to phage type group II and type 95 were isolated most frequently (65 [23%] and 54 [19%], respectively). Of 278 *S aureus* strains isolated, 57 (21%) were susceptible to all antibiotics tested, 186 (67%) were resistant to penicillin alone, and 35 (13%) were resistant to more than 1 antibiotic. Only 3 (1%) of the isolated *S aureus* strains were resistant to methicillin. Community-acquired strains did not differ significantly from hospital-acquired strains in accordance to phage type distribution or resistance pattern (data not shown). Thus, no strains seemed especially related to hospital infection in this study.

PATIENT CHARACTERISTICS

The median age (70 years) for patients with community-acquired SAB was higher than the median age (62 years) for patients with hospital-acquired SAB; however, the sex distribution was not significantly different (**Table 1**). Patients with malignancies and patients receiving immunosuppressive therapy were most frequently found among the hospital-acquired cases (Table 1). These patients and patients receiving hemodialysis more often had hospital-acquired SAB, while intravenous drug abusers had primarily community-acquired infection compared with other patients.

SYMPTOMS AND INFECTIOUS FOCI

Fever was registered in nearly all patients (97%) (Table 1). Septic shock was recorded in 70 cases (25%), and when further analyzed it did not relate to source of infection or primary foci (Table 1, data not shown).

PORTAL OF ENTRY

Intravenous catheters and postoperative wounds were most often the primary foci of SAB infection (90 [61%]) in hospital-acquired cases, while skin lesions predominated in community-acquired cases (53 [40%]) (Table 1). The number of cases with an unknown portal of entry was much higher for community-acquired cases vs hospital-acquired cases (Table 1). Patients with community-acquired SAB had a higher frequency of secondary infection, especially endocarditis and osteomyelitis (Table 1).

and/or symptoms of urinary tract infection and a primary focus of infection other than in the urinary tract was demonstrated. Foci of infection were divided into identified and not identified. Identified foci were further subdivided into eradicable and not eradicable, and eradicable foci were further subdivided into eradicated and not eradicated. Eradicable foci included drainable abscesses and foci with indwelling foreign bodies, such as peripheral and central intravenous catheters, urinary tract catheter, subcutaneous arteriovenous fistula, transvenous pacemaker, pleural drain, Hoffmann apparatus, and endoprosthesis. Noneradicable foci included skin, respiratory tract, urinary tract, gastrointestinal tract, endocarditis, osteomyelitis, meningitis, and arthritis. Eradicated foci included foci in which cases abscesses and indwelling foreign bodies, such as intravenous catheters, urinary tract catheters, had been drained or removed, respectively. Unknown foci were considered not eradicable. Septic shock included both severe sepsis and septic shock as defined by Muchardt et al.[27] Death was considered attributable to SAB if the patient died within 5 weeks after a blood culture was found positive or if the patient died in connection with recurrence of SAB. Recurrence was defined as a new blood culture result positive for *S aureus* with the same resistance pattern and phage type within 3 months from the onset of SAB and after antibiotic treatment had been stopped.

TREATMENT

Patients who died within 3 days after a blood culture was found positive for *S aureus* and patients who survived without treatment were excluded from the analysis. To evaluate the importance of dose and dosing interval, only patients (n=186) treated with dicloxacillin sodium were included in the present statistical analysis.

Based on simple pharmacokinetic principles and under the assumption that the dicloxacillin sodium kinetics fit an open 2-compartment model, the time above the MIC ($T_{>MIC}$) was estimated for dicloxacillin sodium for each treatment regimen. In accordance to Löfgren et al,[28] the MIC of dicloxacillin sodium for *S aureus* was 0.4 mg/L and peak concentrations of dicloxacillin 30 minutes after intravenous administration (1 hour after oral administration) were 100 mg/L(oral, 30 mg/L) and 200 mg/L (oral, 60 mg/L) for 1 and 2 g, respectively. The serum elimination half-life was estimated to be 2 hours with a 3% free concentration of dicloxacillin sodium assumed throughout. Set in relation to the total time of treatment (T_{total}), the $T_{>MIC}/T_{total}$ of the protein-free fraction was estimated to be 78% for intravenous dicloxacillin sodium, 1 g three times daily, and 100% for intravenous dicloxacillin sodium, 1 g four times daily and 2 g three times daily. Similarly, the area under the free serum dicloxacillin concentration curve (AUC) above the MIC (AUC/MIC) was estimated for the 3 dosage regimens (data not shown).

STATISTICAL METHODS

The following potential risk factors associated with survival and recurrence in this study were evaluated by logistic regression analysis: age, sex, the origin of infection, the time from onset of symptoms to SAB, underlying malignancy, the presence of a septic shock, the eradication of a primary focus, the presence of a secondary focus, the total daily dose, the $T_{>MIC}/T_{total}$, and the total AUC. Statistical analysis was performed with computer software (SAS/STAT; SAS Institute Inc, Cary, NC), using the GENMOD procedure to account for overdispersion and PHREG procedure for Kaplan-Meier estimates of survival and recurrence functions.

TREATMENT

Patients who died within 3 days after a positive blood culture finding (n=38) and patients who survived without treatment (n=5) were excluded from the analysis. Of the resulting 235 patients, 186 (79%) were treated with penicillinase-stable penicillin (dicloxacillin sodium); 24 (10%), with penicillin G or ampicillin sodium; 13 (6%), with a second-generation cephalosporin; 8 (3%), with vancomycin hydrochloride; and 2 (0.85%), with aminoglycoside either alone or with erythromycin base. None of the patients were treated with a third-generation cephalosporin.

Of the 186 patients treated with dicloxacillin sodium, 162 were treated with dicloxacillin sodium intravenously followed by oral treatment. Of these patients, 16 (10%) received less than 3 g/d; 101 (62%), 3 g/d; 22 (14%), 4 g/d; and 23 (14%) above 4 g/d. Of the resulting 24 patients (13%) who received oral dicloxacillin sodium only, most received 1.5 g/d or 3 g/d (11 [46%] and 10 [42%], respectively).

OUTCOME

The overall mortality rate was 34% and was nonsignificantly higher in patients with community-acquired SAB compared with patients with hospital-acquired SAB (Table 1). The overall recurrence rate was 12% and possibly higher for hospital-acquired SAB (Table 1). Neither the mortality rate nor the recurrence rate was statistically associated to the type of primary or secondary focus (data not shown). The respiratory tract as the portal of entry was associated with a relatively high mortality (27 [63%]of 43 patients), especially for hospital-acquired SAB (14 [74%] of 19 cases), compared with community-acquired SAB (13 [54%] of 24 cases); however, this finding was not significant ($P=.32$). The mortality rate of patients with no secondary infection was 36% (79 of 218 patients). For these patients, the mortality rate was higher for community-acquired SAB compared with hospital-acquired SAB (41 [49%] of 83 vs 38 [28%] of 135; $P=.002$). Mortality was higher in patients with septic shock (46 [66%] of 70) compared with patients without septic shock (49 [24%] of 208; $P<.001$), and patients receiving hemodialysis had a lower mortality rate (3 [10%] of 30) than the remaining patients (92 [37%] of 248; $P=.002$). However, mortality rates for patients with malignancy (24 [36%] of 67), patients receiving immunosuppressive therapy (26 [40%] of 65), and patients who abuse alcohol (17 [45%] of 38) did not differ signifi-

Table 1. Clinical Data for Patients With Community-Acquired SAB Compared With Hospital-Acquired SAB*

Parameter	All Patients (N = 278)	Community (n = 131)	Hospital (n = 147)
Age, median (range), y	64 (0-94)	70 (0-94)†	62 (0-92)
Male	157 (56)	77 (59)	80 (54)
Underlying conditions			
Malignancy	67 (24)	13 (10)	54 (37)§
Immunosuppressive therapy	65 (23)	18 (14)	47 (32)§
Alcohol abuse	38 (14)	22 (17)	16 (11)
Hemodialysis	30 (11)	2 (2)	28 (19)
Intravenous abuse	21 (8)	20 (15)‡	1 (1)
Type 2 diabetes mellitus	23 (8)	10 (8)	13 (9)
Type 1 diabetes mellitus	21 (8)	10 (8)	11 (7)
Symptoms			
Fever	271 (97)	128 (98)	143 (97)
Septic shock	70 (25)	32 (24)	38 (26)
Primary foci			
Intravenous catheter	68 (24)	2 (2)	66 (45)§
Skin	57 (21)	53 (40)‡	4 (3)
Respiratory tract	43 (15)	24 (18)	19 (13)
Urinary tract	36 (13)	19 (15)	17 (12)
Postoperative wound	24 (9)	0	24 (16)
Other	18 (6)	7 (5)	11 (7)
Unknown	32 (12)	26 (20)‡	6 (4)
Secondary foci			
None	233 (84)	93 (71)	140 (95)§
Endocarditis	22 (8)	18 (14)‡	4 (3)
Osteomyelitis	20 (7)	17 (13)‡	3 (2)
Meningitis	3 (1)	3 (2)	0
Outcome			
Mortality	95 (34)	52 (40)‖	43 (29)
Recurrence	33 (12)	17 (5)	16 (11)

*Data are given as the number (percentage) of patients unless otherwise specified. SAB indicates *Staphylococcus aureus* bacteremia.
†Higher ($P = .03$) compared with hospital-acquired cases.
‡More frequent ($P < .001$) compared with hospital-acquired cases.
§More frequent ($P < .001$) compared with community-acquired cases.
‖More frequent ($P = .07$) compared with hospital-acquired cases.

cantly from patients without these characteristics (Table 1). The recurrence rate was higher for patients with osteomyelitis (7 [35%] of 20) than for patients without a secondary focus (19 [9%] of 218; $P = .002$). Patients with endocarditis also had a higher recurrence rate (3 [14%] of 22) than patients without a secondary focus; however, this finding was not significant ($P = .45$).

OUTCOME VS FOCUS IDENTIFICATION, REMOVABILITY, AND REMOVAL

The mortality and recurrence rates related to focus identification, eradicability, and eradication are given in **Table 2**. Of the remaining 235 patients, the mortality rate and the recurrence rate of patients with an identified focus were not significantly higher compared with that of patients with an unidentified focus ($P = .36$ and $P = .43$, respectively) (Table 2). The mortality rate was lower for patients with an eradicable focus than for other patients ($P = .002$) (Table 2).

Of the 87 patients with an eradicable focus, both the mortality rate and the recurrence rate were significantly

Table 2. Outcome Related to Focus Treatment for Patients With SAB*

Focus	No. of Patients	Mortality	Recurrence
Not identified	24	4 (17)	2 (8)
Identified	211	53 (25)	30 (14)
Not eradicable	148	46 (31)†	22 (15)
Eradicable	87	11 (13)	10 (11)
Not eradicated	13	6 (46)‡	4 (31)§
Eradicated	74	5 (7)	6 (8)

*Data are given as the number (percentage) of patients unless otherwise specified. SAB indicates *Staphylococcus aureus* bacteremia.
†Increased frequency ($P = .002$) compared with SAB cases with an eradicable focus.
‡Increased frequency ($P = .001$) compared with SAB cases with an eradicated focus.
§Increased frequency ($P = .04$) compared with SAB cases with an eradicated focus.

lower for cases in which the focus had been eradicated compared with cases in which the focus was not eradicated ($P = .001$ and $P = .04$, respectively) (Table 2). The same findings were observed when patients with endocarditis were excluded in accordance to Iannini et al.[7] The outcome was not related to time of focus identification, type of drug administration, or time of treatment (data not shown).

FACTORS SIGNIFICANTLY ASSOCIATED WITH OUTCOME

Factors associated with death and recurrence in a logistic regression analysis are presented in **Table 3** and **Table 4**, respectively. The presence of an uneradicated focus, the presence of septic shock, age 60 years or older, and a total daily dose of dicloxacillin sodium less than 4 g were factors significantly associated with death (Table 3), and the presence of a secondary focus and a total daily dose of dicloxacillin sodium less than 3 g were associated with recurrence (Table 4). Both $T_{>MIC}/T_{total}$ and the AUC/MIC percentages were significantly associated with outcome, but the logistic regression analysis did not allow the selection of either parameter as the most important. This lack of distribution between the 2 parameters may be explained by the high correlation between the $T_{>MIC}/T_{total}$ and AUC/MIC percentages. The importance of focus eradication for patient survival and presence of a secondary focus for SAB recurrence are illustrated by Kaplan-Meier plots in **Figure 1** and **Figure 2**, respectively. The importance of the latter factor could be evaluated because the observation period was longer than the duration of treatment for 155 patients. The mortality was 23% (17 of 74 patients) for patients treated for less than 14 days and 4% (3 of 81 patients) for patients treated for 14 days or more ($P < .001$). Variation in duration of treatment among these patients somewhat obscures these observations. Among the 155 patients, the total daily dose of dicloxacillin sodium was no longer significant: less than 4 g/d intravenously (mortality, 18 [16%] of 116) vs 4 g/d or more intravenously (mortality, 2 [5%] of 39) ($P = .1$). If duration of treatment was included in the logistic re-

Table 3. Univariate and Regression Analyses of Mortality Related to SAB in 186 Patients*

Risk Factor	Present Risk Factor, Died/Total (%)	Absent Risk Factor, Died/Total (%)	Univariate	*P* Value	Logistic Regression† OR (95% CI)	*P* Value
Focus not eradicated	42/125 (34)	4/61 (7)	7.2	<.001	6.7 (2.1-21.0)	<.001
Septic shock	18/38 (47)	28/148 (19)	3.9	.001	3.7 (1.5-9.1)	.004
Total daily dose <4 g	40/142 (28)	6/44 (14)	2.5	.07	3.7 (1.3-11.1)	.02
Age ≥60 y	32/96 (33)	14/90 (16)	2.7	.006	2.4 (1.1-5.3)	.03
Community-acquired	26/84 (31)	20/102 (20)	1.8	NS	NI	NS
Male	29/111 (26)	17/75 (23)	1.2	NS	NI	NS
Time >3 d‡	21/80 (26)	25/106 (24)	1.2	NS	NI	NS
Malignancy	10/42 (24)	36/144 (25)	0.9	NS	NI	NS
Secondary focus	9/46 (20)	37/140 (26)	0.7	NS	NI	NS

*SAB indicates *Staphylococcus aureus* bacteremia; OR, odds ratio; CI, confidence interval; NS, not significant; and NI, not included in the final regression model.
†C-index of model, 0.81.
‡Time from onset of symptoms to finding a positive blood culture for SAB.

Table 4. Univariate and Regression Analyses of Recurrence Following SAB in 186 Patients*

Risk Factor	Positive Risk Factor Recurrence/Total (%)	Negative Risk Factor Recurrence/Total (%)	Univariate	*P* Value	Logistic Regression† OR (95% CI)	*P* Value
Total daily dose <3 g	11/37 (30)	17/149 (11)	3.3	.009	3.9 (1.6-10.0)	.004
Secondary focus	12/46 (26)	16/140 (11)	2.7	.03	3.2 (1.3-7.7)	.009
Community-acquired	14/84 (17)	14/102 (14)	1.3	NS	NI	NS
Male	18/111 (16)	10/75 (13)	1.3	NS	NI	NS
Time >3 d‡	14/80 (18)	14/106 (13)	1.4	NS	NI	NS
Malignancy	8/42 (19)	20/144 (14)	1.5	NS	NI	NS
Uneradicated focus	23/125 (18)	5/61 (8)	2.5	NS	NI	NS
Septic shock	4/38 (11)	24/148 (16)	0.6	NS	NI	NS
Age ≥60 y	13/96 (14)	15/90 (17)	0.8	NS	NI	NS

*SAB indicates *Staphylococcus aureus* bacteremia; OR, odds ratio; CI, confidence interval; NS, not significant; and NI, not included in the final regression model.
†C-index of model, 0.66.
‡Time from onset of symptoms to finding a positive blood culture for SAB.

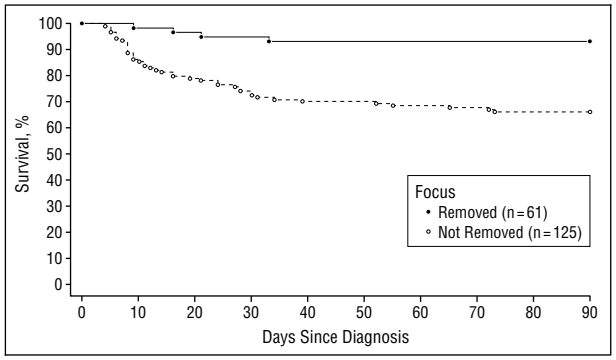


Figure 1. Kaplan-Meier estimate of the survival function in *Staphylococcus aureus* bacteremia cases according to focus removal.

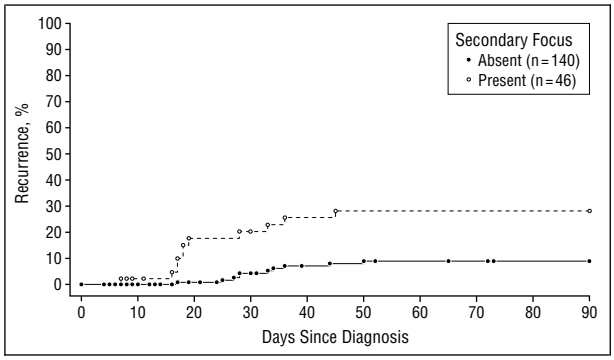


Figure 2. Kaplan-Meier estimate of the recurrence fraction according to secondary focus.

gression analysis with all the factors mentioned in Table 3, only 2 factors were significantly correlated with outcome: duration of treatment (OR, 0.84; 95% CI, 0.76-0.94; *P*=.001) and focus removal (OR, 15; 95% CI, 1.9-121; *P*=.01).

COMMENT

In the present study, 53% of the SAB cases were hospital acquired, which is in the lower range compared with other studies (46%-87%).[6,8,29-38] This is probably because of the large number of patients admitted directly from the community in contrast to other studies from larger tertiary hospitals or referral centers in United States.[39] However, this is similar to our previous 1-year case-control study,[40] the SAB cases of which were included in this 2-year study. The total incidence rate of bacteremia cases was 1.18 per 1000 admissions.

The role of *S aureus* as a potential contamination is debated. Some larger studies have demonstrated very high

frequencies of contamination.[6,26,41] We considered *S aureus* a contamination in only 6% of our cases based on the 1983 criteria by Weinstein et al.[26] Patients with *S aureus* contaminants had a much better outcome compared with other patients because they fully recovered without antibiotic treatment or after treatment with 1 dose of aminoglycoside alone. The patient record was based on observations of the attending physicians, ie, those participating in the daily care of the patient and not of the reviewer only. No differences were demonstrated between hospital-acquired and community-acquired cases according to phage type distribution and antibiotic resistance, indicating that no special hospital strains were present during the study period. Other studies from Denmark have similarly demonstrated that the phage type pattern and the antibiotic resistance are now almost identical among hospital- and community-acquired infections.[38,42,43]

Only 3 (1%) of the *S aureus* strains isolated were resistant to methicillin. These 3 methicillin-resistant strains were found in the same dermatology department at the same time and were a result of a clonal spread. The high frequency of penicillin-sensitive strains and particularly the low frequency of methicillin is similar to findings from previous studies in 1992 from the same area.[5,38] These findings are highly remarkable and exclusively found in the Scandinavian countries and may be because of the strict antibiotic policy and strict infection control policies enforced in the study area.

The median age for patients with community-acquired SAB was higher than for patients with hospital-acquired SAB (Table 1), while patients with underlying diseases more often had hospital-acquired SAB (Table 1), since these conditions necessitated hospital admission in themselves. Patients with an unknown focus most often had community-acquired SAB (Table 1), possibly because of a longer history of illness and less precise information for patients with community-acquired SAB prior to hospital admission.

Cases of SAB in which endocarditis and osteomyelitis developed were rarely hospital acquired (Table 1). Whether this is because of a longer duration of bloodstream infection without antibiotic therapy, which would have been instituted if patients had been in the hospital, is unknown. Of the 64 patients who underwent transthoracic echocardiography, 42 patients (66%) had no signs of endocarditis. However, the sensitivity of transthoracic echocardiography is only around 50%.[44,45] Patients with malignancies, patients treated with immunosuppressive therapy, and patients receiving hemodialysis more often had nosocomial SAB (Table 1). The high mortality of SAB associated with hospital-acquired respiratory tract infection has already been demonstrated[46,47] but may be explained by the high mortality of other conditions observed among these patients in the present study, such as sepsis, alcohol abuse, immunosuppressive therapy, and malignancy. Patients receiving hemodialysis had a low mortality rate similar to findings by Quarles et al,[48] probably because of the relatively good clinical conditions of patients with renal disease and good surgical and medical intervention that was available for these patients (eg, early initiation of antibiotic treatment and focus removal). The recurrence rate for patients with osteomyelitis was high (35%) compared with other patients and was even higher compared with that seen in our previous study (10%)[49]; however, rates varying from 3% to 40% have been seen in other studies[9,50-53] and is related to the duration of antibiotic treatment.[49] In contrast to what might be expected, patients with an identified focus did not have lower mortality and recurrence rates compared with other patients (Table 2). Instead, the mortality rate for patients with an eradicable focus was significantly lower compared with patients with an uneradicable focus (Table 2), and both the mortality and recurrence rates were significantly lower for patients in whom the focus was actually eradicated. Thus, the value of identifying and treating a focus is fully demonstrated in the present study (Table 3) and confirms results of other studies.[7,10,54] Our findings that patients in a septic shock and patients 60 years or older are at an increased mortality risk (Table 3) have already been demonstrated.[13,37,55,56] We could not differentiate between severe sepsis and septic shock. Neither could we establish more precise measures of predicting mortality, such as APACHE (Acute Physiology, Age, and Chronic Health Evaluation) II score because this scoring system only evaluates patients in intensive care treatment. The overall mortality rate was higher in patients with community-acquired SAB than in patients with hospital-acquired SAB; however, this difference was not significant (Table 1).

In the present study, multivariate analysis concerning SAB demonstrated that the total daily antibiotic dosage of dicloxacillin sodium is significantly associated with death (Table 3) and recurrence (Table 4). Both the $T_{>MIC}/T_{total}$ and the AUC/MIC percentages were correlated to outcome, but the statistical calculation did not allow the selection of either parameter as most important. The $T_{>MIC}$ value has been the most important pharmacokinetic parameter for β-lactam antibiotics,[14-18] which demonstrates that a dosage of dicloxacillin sodium of 1 g four times daily or 2 g three times daily is superior to 1 g three times daily. The dosage of 1 g three times daily theoretically provides a $T_{>MIC}$ for only 78% of the dosing interval in contrast to 100% for the former 2 doses. The fact that the importance of the $T_{>MIC}$ could not be discerned from the AUC/MIC percentage stems from the paucity of different dosing regimens used. If individual pharmacokinetic measurements had been devised (ie, by measuring serum dicloxacillin concentration in each patient) and related to outcome, this might have allowed a more exact estimate of the most important pharmacodynamic parameter. There was no difference in mortality between patients treated with intravenous therapy followed by oral therapy and patients treated with only oral therapy. Therefore, this aspect was not further evaluated. However, the results of this study lead to the conclusion that the dosing regimen of dicloxacillin sodium is important for outcome. A recent article retrospectively reported excellent outcomes in 20 patients treated with continuous flucloxacillin infusion for deep tissue infections.[57]

Decisions regarding dosage, interval, and duration of treatment were made by the attending physicians in

this study. Most patients were treated with dicloxacillin sodium (1 g three times daily) because this is the conventional, registered dosage in Denmark. The duration of antibiotic treatment was significantly related to outcome in the present study; however, proper evaluation of this factor is difficult in such an observational study because the patients in many cases are treated according to clinical response and not with fixed regimens. There was no significant relation between outcome and penicillin susceptibility (data not shown), and the outcome of patients with methicillin-resistant SAB could not be evaluated because there were very few patients with methicillin-resistant SAB in the study. The outcome of patients with penicillin-sensitive *S aureus* strains treated with penicillin was not significantly different from patients treated with dicloxacillin sodium (data not shown); however, there is a need for future case-control studies. Although this is not a controlled, randomized study and population-based pharmacokinetic calculations may be problematic, we find our results useful and relevant. However, for evaluation of different antibiotic treatment regimens, controlled, randomized studies are needed in the future.

In conclusion, SAB continues to be associated with high mortality and recurrence rates. The present study emphasizes that an uneradicated focus, septic shock, and older age are associated with SAB-related death, and the presence of a secondary focus is associated with the risk of recurrence. Furthermore, the present study indicates for the first time that dicloxacillin sodium taken 1 g four times daily or 2 g three times daily seems superior to 1 g three times daily in the treatment of SAB infection.

Accepted for publication April 30, 2001.

Dr Jensen was supported by research fellowship 12-1621 from the Danish Research Council, Copenhagen.

Corresponding author and reprints: Allan G. Jensen, MD, Bldg 45, Sector for Microbiology, Statens Serum Institut, Artillerivej 5, DK-2300 Copenhagen S, Denmark (e-mail: allan.garlik@dadlnet.dk).

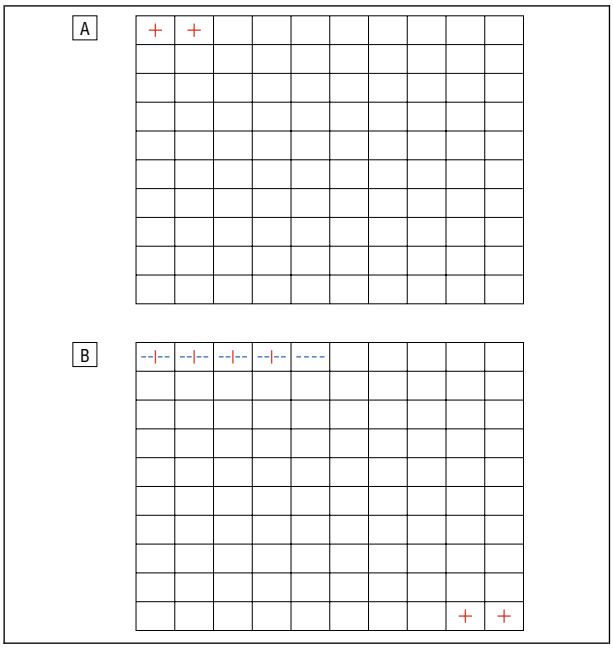
REFERENCES

1. Eykyn SJ, William R, Gransden WR. The causative organisms of septicaemia and their epidemiology. *J Antimicrob Chemother.* 1990;25(suppl C):41-58.
2. Duggan J, O'Connell D, Heller R, Ghosh H. Causes of hospital-acquired septicaemia—a case control study. *QJM.* 1993;86:479-483.
3. Geerdes HF, Ziegler D, Lode H, et al. Septicemia in 980 patients at a university hospital in Berlin: prospective studies during 4 selected years between 1979 and 1989. *Clin Infect Dis.* 1992;15:991-1002.
4. Schaberg DR, Culver DH, Gaynes RP. Major trends in the microbial etiology of nosocomial infection. *Am J Med.* 1991;91:72S-75S.
5. Jensen AG, Kirstein A, Jensen I, Scheibel J, Espersen F. A six-month prospective study of hospital-acquired bacteremia in Copenhagen County. *Scand J Infect Dis.* 1996;28:601-608.
6. Lautenschlager S, Herzog C, Zimmerli W. Course and outcome of bacteremia due to *Staphylococcus aureus*: evaluation of different clinical cases definitions. *Clin Infect Dis.* 1993;16:567-573.
7. Iannini PB, Crossley K. Therapy of *Staphylococcus aureus* bacteremia associated with a removable focus of infection. *Ann Intern Med.* 1976;84:558-560.
8. Mylotte JM, Beam TR Jr, Allen JC. *Staphylococcus aureus* bacteremia: a prospective study. *South Med J.* 1983;76:1131-1135.
9. Jensen AG, Espersen F, Skinhøj P, Rosdahl VT, Frimodt-Møller N. *Staphylococcus aureus* meningitis: a review of 104 nationwide, consecutive cases. *Arch Intern Med.* 1993;153:1902-1908.
10. Fowler VG Jr, Sanders LL, Sexton DJ, et al. Bacteremia according to compliance with recommendations of infectious diseases specialists: experience with 244 patients. *Clin Infect Dis.* 1998;27:478-486.
11. Romero-Vivas J, Rubio M, Fernandez C, Picazo JJ. Mortality associated with nosocomial bacteremia due to methicillin-resistant *Staphylococcus aureus*. *Clin Infect Dis.* 1995;21:1417-1423.
12. Harbarth S, Rutschmann O, Sudre P, Pittet D. Impact of methicillin resistance on the outcome of patients with bacteremia caused by *Staphylococcus aureus*. *Arch Intern Med.* 1998;158:182-189.
13. McClelland RS, Fowler VG Jr, Sander LL, et al. *Staphylococcus aureus* bacteremia among elderly vs younger adult patients: comparison of clinical features and mortality. *Arch Intern Med.* 1999;159:1244-1247.
14. Polk R. Optimal use of modern antibiotics: emerging trends. *Clin Infect Dis.* 1999; 29:264-274.
15. Craig W. Pharmacokinetic and experimental data on beta-lactam antibiotics in the treatment of patients. *Eur J Microbiol.* 1984;3:575-578.
16. Mattie H, Goslings RO, Noach EL. Cloxacillin and nafcillin: serum binding and its relationship to antibacterial effect in mice. *J Infect Dis.* 1973;128:170-177.
17. Merrikin D, Rolinson GN. Antibiotic levels in experimentally infected mice in relation to therapeutic effect and antibacterial activity in vitro. *J Antimicrob Chemother.* 1979;5:423-429.
18. Frimodt-Møller N. Correlation of in vitro activity and pharmacokinetic parameters with effect in vivo for antibiotics: observations from experimental pneumococcus infection. *Dan Med Bull.* 1988;35:422-437.
19. Raber S, Leggett J, Kohlhepp S, Dworkin R, Gilbert D. Continuous (CI) vs intermittent (II) infusion of oxacillin (OX) in patients with staphylococcal infections. Presented at: the 36th Interscience Conference on Antimicrobial Agents and Chemotherapy; September 15-18, 1996; New Orleans, La. Abstract No. A104.
20. Dessau RB, Steenberg P. Computerized surveillance in clinical microbiology with time series analysis. *J Clin Microbiol.* 1993;31:857-860.
21. Prag J, Jensen J, Lebech K. Darkening of haemoglobin in simulated, continuously agitated aerobic blood cultures: an early indicator of bacterial growth. *APMIS.* 1991;99:1083-1088.
22. Prag J, Jensen J, Lebech K. Colorbact, a visually read blood culture system using darkening of haemoglobin in aerobic blood cultures as an early growth indicator, compared with Bactec 6A and 7A. *APMIS.* 1991;99:1089-1095.
23. Blair JE, Williams REO. Phage typing of staphylococci. *Bull World Health Organ.* 1961;24:771-784.
24. Parker MT. Phage-typing and the epidemiology of *Staphylococcus aureus* infection. *J Appl Bacteriol.* 1962;25:389.
25. Thomsen VF. Correlation of the plate-dilution method to the agar diffusion method (disc- and tablet methods) with a special view to the importance of pre-diffusion. *APMIS.* 1962;54:107-120.
26. Weinstein MP, Reller LB, Murphy JR, Lichtenstein KA. The clinical significance of positive blood cultures: a comprehensive analysis of 500 episodes of bacteremia and fungemia in adults, I: laboratory and epidemiologic observations. *Rev Infect Dis.* 1983;5:35-53.
27. Muchardt DJ, Bhagwanjee S. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference definitions of the systemic inflammatory response syndrome and allied disorders in relation to critically injured patients. *Crit Care Med.* 1997;25:1789-1795.
28. Löfgren S, Bucht G, Hermansson B, Holm SE, Winblad B, Norrby R. Single-dose pharmacokinetics of dicloxacillin in healthy subjects of young and old age. *Scand J Infect Dis.* 1986;18:365-369.
29. Libman H, Arbeit RD. Complications associated with *Staphylococcus aureus* bacteremia. *Arch Intern Med.* 1984;144:541-545.
30. Mylotte JM, McDermott C. *Staphylococcus aureus* bacteremia caused by infected intravenous catheters. *Am J Infect Control.* 1987;15:1-6.
31. Mirimanoff RO, Glauser MP. Endocarditis during *Staphylococcus aureus* septicemia in a population of non-drug addicts. *Arch Intern Med.* 1982;142:1311-1313.
32. Bryan CS, Kirkhart B, Brenner ER. Staphylococcal bacteremia: current patterns in nonuniversity hospitals. *South Med J.* 1984;77:693-696.
33. Finkelstein R, Sobel JD, Nagler A, Merzbach D. *Staphylococcus aureus* bacteremia and endocarditis: comparison of nosocomial and community-acquired infection. *J Med.* 1984;15:193-211.
34. Julander I. Unfavourable prognostic factors in *Staphylococcus aureus* septicemia and endocarditis. *Scand J Infect Dis.* 1985;17:179-187.
35. Leibovici L, Gransden WR, Eykyn SJ, et al. Clinical index to predict bacteraemia caused by staphylococci. *J Intern Med.* 1993;234:83-89.
36. Hedström SA, Christensson B. *Staphylococcus aureus* septicaemia and endocarditis at the University Hospital in Lund 1976-1980. *Scand J Infect Dis.* 1983; 41(suppl):38-48.
37. Gransden WR, Eykyn SJ, Phillips I. *Staphylococcus aureus* bacteraemia: 400 episodes in St Thomas's Hospital. *BMJ.* 1984;288:300-303.

38. Espersen F, Rosdahl VT, Frimodt-Møller N, Skinhøj P. Epidemiology of *Staphylococcus aureus* in Denmark. *J Chemother*. 1994;6:219-225.
39. Roberts FJ, Geere IW, Coldman A. A three-year study of positive blood cultures, with emphasis on prognosis. *Rev Infect Dis*. 1991;13:34-46.
40. Jensen AG, Wachmann CH, Poulsen KB, et al. Risk factors for hospital-acquired *Staphylococcus aureus* bacteremia. *Arch Intern Med*. 1999;159:1437-1444.
41. Nolan CM, Beaty HN. *Staphylococcus aureus* bacteremia: current clinical patterns. *Am J Med*. 1976;60:495-500.
42. Espersen F, Frimodt-Møller N, Rosdahl VT, Skinhøj P, Bentzon MW. Changing pattern of bone and joint infections due to *Staphylococcus aureus*: study of cases of bacteremia in Denmark, 1959-1988. *Rev Infect Dis*. 1991;13:347-358.
43. Faber M, Rosdahl VT. Changing pattern of phage group II *Staphylococcus aureus* infections: from community to hospital. *Scand J Infect Dis*. 1993;25:647-653.
44. Espersen F, Frimodt-Moller N. *Staphylococcus aureus* endocarditis: a review of 119 cases. *Arch Intern Med*. 1986;146:1118-1121.
45. Roder BL, Wandall DA, Frimodt-Moller N, Espersen F, Skinhoj P, Rosdahl VT. Clinical features of *Staphylococcus aureus* endocarditis: a 10-year experience in Denmark. *Arch Intern Med*. 1999;159:462-469.
46. Watanakunakorn C. Bacteremic *Staphylococcus aureus* pneumonia. *Scand J Infect Dis*. 1987;19:623-627.
47. Gonzalez C, Rubio M, Romero-Vivas, J, Gonzalez M, Picazo JJ. Bacteremic pneumonia due to *Staphylococcus aureus*: a comparison of disease caused by methicillin-resistant and methicillin-susceptible organisms. *Clin Infect Dis*. 1999;29:1171-1177.
48. Quarles LD, Rutsky EA, Rostand SG. *Staphylococcus aureus* bacteremia in patients on chronic hemodialysis. *Am J Kidney Dis*. 1985;6:412-419.
49. Jensen AG, Espersen F, Skinhøj P, Rosdahl VT, Frimodt-Møller N. Increasing frequency of vertebral osteomyelitis following *Staphylococcus aureus* bacteremia in Denmark 1980-1990. *J Infect*. 1997;34:113-118.
50. Collert S. Osteomyelitis of the spine. *Acta Orthop Scand*. 1977;48:283-290.
51. Griffiths HE, Jones DM. Pyogenic infection of the spine: a review of twenty-eight cases. *J Bone Joint Surg Br*. 1971;53:383-391.
52. Torda AJ, Gottlieb T, Bradbury R. Pyogenic vertebral osteomyelitis: analysis of 20 cases and review. *Clin Infect Dis*. 1995;20:320-328.
53. Osenbach RK, Hitchon PW, Menezes AH. Diagnosis and management of pyogenic vertebral osteomyelitis in adults. *Surg Neurol*. 1990;33:266-275.
54. 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.
55. Conterno LO, Wey SB, Castelo A. Risk factors for mortality in *Staphylococcus aureus* bacteremia. *Infect Control Hosp Epidemiol*. 1998;19:32-37.
56. Willcox PA, Rayner BL, Whitelaw DA. Community-acquired *Staphylococcus aureus* bacteraemia in patients who do not abuse intravenous drugs. *QJM*. 1998;91:41-47.
57. Leder K, Turnidge JD, Korman TM, Grayson ML. The clinical efficacy of continuous-infusion flucloxacillin in serious staphylococcal sepsis. *J Antimicrob Chemother*. 1999;43:113-118.

Correction

Error in Figure. In the Special Article by Lloyd et al titled "Accuracy and Ambiguity in Counseling Patients About Genetic Risk," published in the November 12, 2001, issue of the ARCHIVES (2001;161:2411-2413), the color did not appear in the **Figure**. The Figure is reprinted correctly here.



Sensitivities, specificities, and positive and negative predictive values of genetic testing in 2 groups of patients with hemochromatosis. A, Patients with elevated transferrin iron saturation only. B, Patients with diabetes mellitus and elevated transferrin iron saturation. Blue and red marks indicate true positives; blue marks alone, false negatives; red marks alone, false positives; and no marks, true negatives. The pretest probability for patients with and without diabetes mellitus and elevated transferrin iron saturation is assumed to be 5% and less than 1%, respectively.