MAJOR ARTICLE

Adequacy of Antimicrobial Treatment and Outcome of *Staphylococcus aureus* Bacteremia in 9 Western European Countries

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(See the editorial commentary by Moellering, on pages 1006–8.)

Background. Little is known about the incidence of inadequate treatment of severe *Staphylococcus aureus* infection in Europe. We aimed to evaluate the adequacy of antibiotic therapy for *S. aureus* bacteremia (SAB), to identify determinants of inadequate treatment, and to determine the effect of inadequate treatment on patient outcome in a representative selection of hospitals in 9 Western European countries.

Methods. In this retrospective cohort study, all adult patients with SAB (due to methicillin-susceptible *S. aureus* [MSSA] or methicillin-resistant *S. aureus* [MRSA]) who were admitted to 60 randomly selected hospitals from 1 November 2007 through 31 December 2007 were included. Adequate antimicrobial therapy was defined as intravenous administration of at least 1 antibiotic to which the isolate showed in vitro susceptibility that was initiated within 2 days after onset of SAB.

Results. A total of 334 SAB episodes (257 due to MSSA and 77 due to MRSA) were included. Ninety-four patients (28%) received inadequate empirical therapy (21% in the MSSA group and 52% in the MRSA group). Both length of stay before SAB onset and methicillin-resistant infection were associated with inadequate therapy, with adjusted odds ratios (ORs) of 1.01 (95% confidence interval [CI], 1.00–1.03) and 3.7 (95% CI, 2.2–6.4), respectively. Age (OR, 1.06; 95% CI, 1.03–1.10), Charlson comorbidity score (OR, 2.1; 95% CI, 1.2–3.6), severe sepsis or septic shock (OR, 2.7; 95% CI, 1.5–4.8), and intensive care unit stay at onset of SAB (OR, 2.9; 95% CI, 1.5–5.6) but not inadequate treatment (OR, 0.7; 95% CI, 0.4–1.3) were associated with increased 30-day mortality.

Conclusion. Inadequate empirical antimicrobial therapy for SAB is common in Western Europe and is strongly associated with infection caused by MRSA. In this study, inadequate treatment was not associated with increased 30-day mortality rates.

Staphylococcus aureus is responsible for 10%–18% of all community-acquired and ~20% of all nosocomial bacteremias [1, 2], thereby representing a significant burden on health care services [3]. Incidences of both community-acquired and nosocomial *S. aureus* bacteremia (SAB) have increased during recent decades, probably because of an increasing population at risk [4–6]. In addition, methicillin-resistant *S. aureus* (MRSA) has become endemic in the hospitals of most European countries, which may also add to the total burden of SAB [7]. Reported crude hospital mortality rates among adult patients with SAB have ranged from 18% to 46% [2, 8, 9]. Increased mortality rates have been associated with a respiratory source of SAB or unknown primary infection, presence of shock, older age, male sex, and severity of underlying disease [10–13]. Increasing incidences of MRSA infection confront physicians with

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Table 1. Complete List of Empirical Antibiotic Regimens Prescribed for 334 Patients with *Staphylococcus aureus* Bacteremia

This table is available in its entirety in the online version of *Clinical Infectious Diseases*

increasing difficulties in empirical treatment decisions [14]. The consequences of inadequate therapy include longer hospital stay, higher health care–associated costs, and even higher mortality rates [15–19], although this last association has not been found in some recent studies [20–22].

Little is known about the incidence of and outcomes associated with inadequate treatment of severe *S. aureus* infection in Western Europe. Our primary aim was, therefore, to determine the occurrence of inadequate empirical treatment among hospitalized patients with SAB in a representative sample of hospitals in 9 Western European countries. Secondary objectives were to determine associations between hospital-specific, patient-specific, and microorganism-specific characteristics and inadequate treatment of SAB and 30-day mortality rates.

MATERIALS AND METHODS

Study design, study setting, and study population. We performed a retrospective cohort study of patients with microbiologically confirmed SAB from 1 November 2007 through 31 December 2007 with in-hospital follow-up of 30 days. A randomized sample frame was created from a complete list of general and teaching hospitals in Denmark, France, Germany, Italy, the Netherlands, Spain, Sweden, Switzerland, and the United Kingdom. The hospitals were approached in consecutive order of the sample frame. Hospitals were deemed to be ineligible if they had had no SAB episodes during the surveillance period, were a pediatric or psychiatric hospital, or had <50 beds.

Eligible patients were those ⩾18 years of age who were hospitalized with SAB in any of the randomly selected hospitals (community-acquired SAB) or who acquired SAB during hospitalization (hospital-acquired SAB) during the study period. The following patients were excluded: those with SAB as part of a polymicrobial bacteremia, those in whom the antimicrobial susceptibility pattern (methicillin-susceptible *S. aureus* [MSSA] or MRSA) of *S. aureus* was unknown, those already receiving adequate antimicrobial therapy before the index blood culture was obtained, and those who died within 1 day after the index blood culture was obtained. Identification of *S. aureus* and determination of antibiotic susceptibilities were performed according to local guidelines and procedures.

Institutional review boards of participating hospitals were informed if deemed necessary by the local investigator. In most hospitals, a formal protocol review was not required, because the study did not influence standard care, and because data collection was completely anonymous. The Danish Data Protection Agency approved participation of Danish hospitals.

Data collection and variables of interest. Empirical therapy was defined as all antimicrobial agents administered between the time that the index blood culture was obtained and the receipt of the final blood culture result (ie, identification of *S. aureus* and its antimicrobial susceptibility pattern) (Table 1). Definitive therapy was defined as all antibiotic therapy administered subsequent to the receipt of final blood culture results [23]. To be categorized as adequate empirical treatment, antimicrobial therapy had to meet the following criteria: intravenous administration of at least 1 antibiotic to which the isolate expressed in vitro susceptibility that started within 2 days after the positive index blood culture had been obtained or within 1 day if the patient had severe sepsis or septic shock. On the basis of severity of illness and primary site of infection, in some cases oral therapy was also considered adequate empirical therapy. These cases were judged by 6 of the investigators (H.S., S.H., C.B.-B., A.T., J.K., and M.B.), and consensus was reached after discussion. To be categorized as adequate definitive treatment, antimicrobial therapy had to meet the following criteria: intravenous administration for at least 3 days (with few exceptions made by the investigators) of at least 1 antibiotic

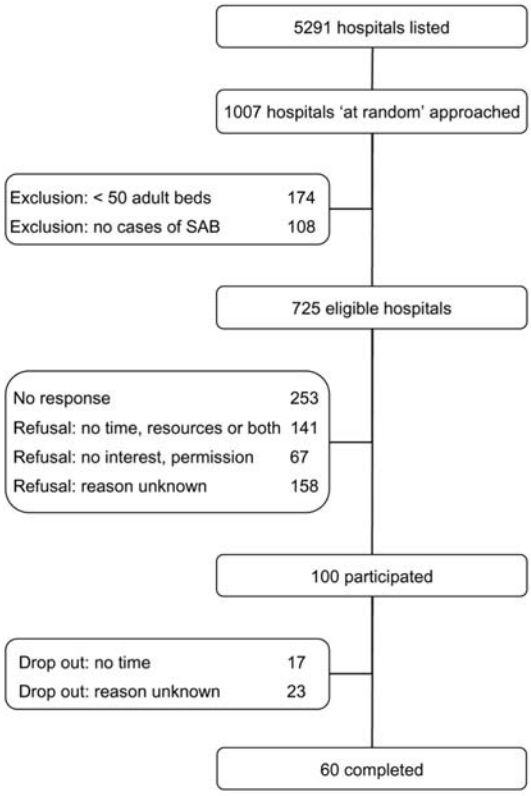

Figure 1. Results of hospital recruitment. SAB, *Staphylococcus aureus* bacteremia.

Table 2. Results of Hospital Recruitment per Country

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to which the isolate expressed in vitro susceptibility for a total duration of at least 14 days and, if empirical treatment was inadequate, adjustment of treatment on the day of the final blood culture result [23, 24]. No antibiotic therapy or monotherapy with aminoglycosides, trimethoprim, fusidic acid, or rifampicin was deemed inadequate.

For all patients in the cohort, the following covariates were considered: MRSA prevalence among SAB episodes in the country based on European surveillance data recorded in the European Antimicrobial Resistance Surveillance System (EARSS) network [7] dichotomized as high (>10%) versus low (≤10%), teaching or nonteaching hospital, age, sex, modified Charlson comorbidity score [25], immunodeficiency status (presence of human immunodeficiency virus or AIDS, splenectomy, immunosuppressive treatment, chemotherapy of <4 weeks duration for SAB, and solid organ or bone marrow transplantation), history of documented colonization or infection due to *S. aureus* within the previous 12 months, number of hospital days before the index blood culture was obtained (if a patient was transferred from another hospital, the date of admission to the first hospital was used), department at time that the index blood culture was obtained (dichotomized as intensive care unit [ICU] vs. non-ICU), methicillin susceptibility status of the *S. aureus* isolate, source of SAB (hospital or community acquired), primary site of infection (dichotomized as primary vs secondary SAB), and severity of sepsis (severe sepsis or septic shock vs sepsis [26]).

Mortality was defined as in-hospital death due to any cause within 30 days after the index blood culture was obtained. Whether an end-of-life decision had been made was also recorded.

To validate the quality of study data, we performed a validity check for the recorded data in a sample of 10% of case report forms (CRFs) in 2 randomly chosen participating hospitals per country. The validity check consisted of 2 quality indicators: first, we checked whether all consecutive eligible patients with SAB during the surveillance period were included. In a face-to-face interview, it was determined whether the number of complete CRFs agreed with a provided list of all patients with SAB and whether patients were correctly included or excluded. The inclusion percentage was derived from the number of included patients divided by the number of eligible patients. The second quality indicator was the accuracy of data reporting on treatment. To assess the accuracy of the collected CRFs compared with the "gold standard" medical record, we established the proportion of unknown or inappropriate data in the CRFs for the following selected variables: date of obtaining the index blood culture, date of definitive culture result, oxacillin susceptibility of *S. aureus,* starting date of first treatment, antibiotic(s) used as first treatment, administration of second treatment within 30 days after index blood culture (and if so, the starting date of second treatment and antibiotic(s) used as second treatment), and outcome 30 days after the index blood culture was obtained. We randomly selected 1, 2, or 3 CRFs per selected hospital. The percentage of correctly recorded answers was derived from the number of correctly recorded items divided by total number of checked items.

Statistical analysis. The primary goal of this study was independent of a specific statistical hypothesis and did not require a sample size calculation. However, to be able to answer the secondary research question (predictors of inadequate treatment), we aimed to include 400 SAB episodes, assuming 25% inadequate treatment and a final model containing 10 variables of significant importance.

Bivariate analyses were performed using Fisher's exact tests, and Mann-Whitney *U* tests were performed to compare continuous variables. To analyze adequate treatment and 30-day

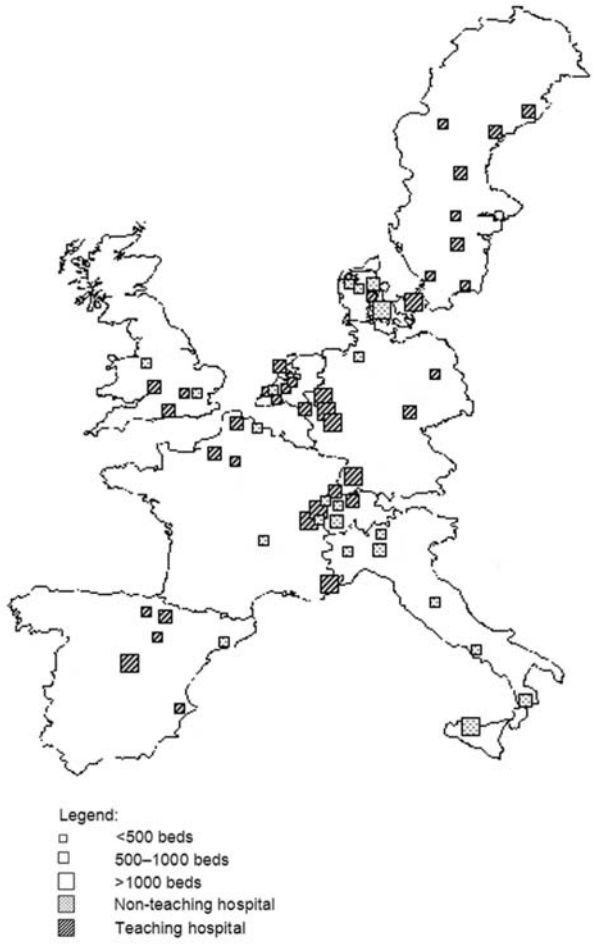

Figure 2. Hospitals from 9 Western European countries that participated in the study.

Table 3. Risk Factors for Inadequate Empirical Antimicrobial Therapy and Characteristics of Patients

Covariate	Adequate treatment (n = 240)	Inadequate treatment (n = 94)	OR (95% CI)[b]	P[a]
MRSA prevalence >10% (vs <10%)[c]	102 (42.7)	60 (63.8)	…	.001
Teaching (vs nonteaching) hospital	184 (76.7)	68 (72.3)	…	.40
Age, median years (IQR)	67 (52.5–78)	70 (59–81)	…	.08
Male (vs female)	155 (64.6)	69 (73.4)	…	.15
Modified Charlson comorbidity score, median value (IQR)	3.0 (1–5)	3.0 (1–5)	…	.13
Immunocompromised (vs nonimmunocompromised)	28 (11.7)	12 (12.8)	…	.85
Staphylococcus aureus history (vs no *S. aureus* history) within the last 12 months	38 (15.8)	22 (23.4)	…	.11
Length of stay before onset of SAB, median days (IQR)	1.0 (0.0–9.0)	3.0 (1.0–14.0)	1.01 (1.00–1.03)	.01
Hospital-acquired (vs community-acquired) bacteremia	106 (44.2)	52 (55.3)	…	.07
Secondary (vs primary) bacteremia	89 (37.1)	33 (35.1)	…	.80
Severe sepsis or septic shock (vs sepsis) at onset of SAB	88 (36.7)	38 (40.4)	…	.53
ICU hospitalization (vs non-ICU) at onset of SAB	55 (22.9)	18 (19.1)	…	.56
MRSA (vs MSSA)	37 (15.4)	40 (42.6)	3.73 (2.16–6.44)	<.001

NOTE. Data are presented as no. (%) of patients, unless otherwise indicated. CI, confidence interval; ICU, intensive care unit; IQR, interquartile range; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; OR, odds ratio; SAB, *Staphylococcus aureus* bacteremia.

[a] Results of bivariate analyses.

[b] Independent variables (adjusted ORs) associated with inadequate empirical antimicrobial therapy in a multivariate logistic regression model.

[c] MRSA prevalence in SAB episodes in the country [7] dichotomized as high (>10%) versus low (≤10%).

mortality rates and the different covariates contributing, we performed a multivariate logistic regression. Kaplan-Meier survival curves were plotted for patients with MSSA versus MRSA SAB and were compared by means of a signed log-rank test with time to adequate treatment as an outcome.

For sensitivity analysis, multilevel logistic regression analysis predicting adequate treatment and 30-day mortality rates was conducted to correct for cluster effects within hospitals and within countries. If results showed no cluster effects, we assumed patient independence and only present data of the multivariate logistic regression models. Moreover, a propensity score was added as an additional covariate to determine whether measured differences between the inadequate and adequate groups contributed to residual confounding. To calculate a propensity score for the probability of inadequate treatment, we used the multivariate logistic regression model with inadequate treatment as the dependent variable.

We used the Akaike information criterion to determine the model with the best fit of the data (ie, the model with the lowest Akaike information criterion value). Effect modification was examined by using clinically important interaction terms. Various covariates at the hospital and patient levels were screened for colinearity, and in some cases, decisions were made to exclude variables from the model.

Results are presented as odds ratios (ORs) with 95% confidence intervals (CIs). For interpretation of the final model results, tests of significance were 2-tailed, and $P \leqslant .05$ was considered to be statistically significant. The data were analyzed using SPSS statistical software, version 15.0 (SPSS), and R, version 2.8.0 (R Foundation for Statistical Computing).

RESULTS

Recruitment of hospitals. For each country, a randomly generated list of hospitals was created. In total, the 9 lists included 5291 hospitals, of which 1007 (19%) were contacted in consecutive order. Of these, 282 (28%) were deemed to be ineligible. Of the remaining 725 hospitals, 100 (14%) consented to participate, whereas 253 (35%) did not respond to the invitation, and 366 (50%) declined to participate (Figure 1; Table 2). Of the 100 hospitals that agreed to participate, 40 (40%) dropped out during the process of data collection.

The proportions of MRSA among SAB episodes per country in the final cohort of 60 hospitals accurately matched the EARSS data [7]; the only significant difference was found for Germany, which had an incidence of MRSA of 38% in our data versus 20% in the EARSS dataset. Furthermore, the balance between teaching and nonteaching hospitals in the complete list of hospitals and our final cohort of 60 hospitals was comparable for 6 countries. For Switzerland, Denmark, and France, teaching hospitals were overrepresented in our cohort compared with the hospital lists (50% vs 7%, 33% vs 2%, and 67% vs 4% for Switzerland, Denmark, and France, respectively). Figure 2 shows the location and characteristics of the participating hospitals.

Patient characteristics. The final cohort consisted of 334 episodes of SAB: 77 (23%) were caused by MRSA, 257 (77%) were caused by MSSA, 158 (47%) were hospital acquired (with

Table 4. Overview of Episodes of Inadequate Empirical Antimicrobial Therapy

Variable	No. of patients	
	MSSA (n = 257)	MRSA (n = 77)
Receipt of inadequate treatment	54[a]	40[a]
Receipt of antibiotic treatment to which the pathogen was not susceptible		
Overall	11	24
No treatment	5	2
Penicillin	5	2
Trimethoprim monotherapy	1	
Oxacillin, penicillin, and gentamicin	…	1
Other β-lactams	…	12[b]
Other β-lactam (piperacillin–tazobactam) and antibiotic resistance (ciprofloxacin)	…	2
Other β-lactam (piperacillin–tazobactam) and amikacin	…	1
Intermediate resistance to antibiotic	…	3[c]
Antibiotic resistance (ciprofloxacin)	…	1
Inadequate route of administration[d]	13	2
Antibiotic treatment started ⩾2 days (⩾1 day for patients with severe sepsis or septic shock) after index blood culture	34	19

NOTE. MRSA, methicillin-resistant *Staphylococcus aureus;* MSSA, methicillin-susceptible *S. aureus.*

[a] The total number of patients who received inadequate treatment is lower than the sum of the separate criteria, because some patients received inadequate treatment according to >1 criterion.

[b] Four patients received amoxicillin–clavulanic acid, 1 received cefazolin, 3 received ceftriaxone, 1 received cefuroxime, 1 received ertapenem, and 2 received piperacillin–tazobactam.

[c] Two patients received teicoplanin, and 1 received vancomycin.

[d] Oral prescription of empirical antibiotics was deemed to be inadequate (with few exceptions, depending on severity of illness and primary site of infection, on the basis of the opinion of the investigators).

a median length of stay before the index blood culture was obtained of 10 days; interquartile range [IQR], 5–25 days), and 175 (53%) were community acquired. A total of 212 patients (64%) had primary SAB (including unknown site and catheter-associated infections), and 122 patients (37%) had another site of infection as a source for SAB. The median patient age was 68 years (IQR, 55–79 years), and 224 patients were male (67%). Forty-nine index blood culture samples (15%) were obtained in the ICU, and 126 patients (38%) had severe sepsis or septic shock (Table 3).

The overall 30-day mortality rate was 24% (80 of 334 patients died), with an end-of-life decision being made for 31 patients (39%). The median time from onset of SAB to death was 6.0 days (IQR, 2–15 days).

Inadequate antimicrobial therapy. According to the definition, 94 episodes (28%) were considered to be inadequate empirical antimicrobial therapy. These proportions were 21% (54 of 257 cases) for MSSA and 52% (40 of 77 cases) for MRSA ($P < .001$) (Table 4). Oral therapy was considered to be adequate empirical therapy in 5 of 16 episodes.

According to our definitions, 114 episodes (34%) of SAB received inadequate definitive antimicrobial therapy (Table 5). These proportions were 30% (76 of 257) for MSSA and 49% (38 of 77) for MRSA ($P = .002$). The intravenous-to-oral switch of therapy within 14 days was considered to be adequate in 25 of 29 episodes. Five days after the index blood culture was obtained, 92% of the patients with MSSA received adequate therapy, compared with 83% of those with MRSA ($P < .001$) (Figure 3), although many did not receive appropriate antibiotics for the adequate duration: of those patients with a follow-up of ⩾14 days, 66% received antibiotics for at least 14 days.

Predictors of inadequate empirical antimicrobial therapy. The only 2 covariates significantly associated with inadequate empirical antimicrobial therapy were methicillin resistance (OR, 3.7; 95% CI, 2.2–6.4) and length of stay (in days) before SAB (OR, 1.01; 95% CI, 1.00–1.03) (Table 6). The only covariate that was significantly associated with inadequate definitive antimicrobial therapy was methicillin resistance (OR, 2.3; 95% CI, 1.4–3.9). After excluding methicillin resistance as a covariate (because it will be unknown at the time that the blood culture sample is obtained), high (>10%) MRSA prevalence in the country was independently associated with inadequate empirical antimicrobial therapy (OR, 2.2; 95% CI, 1.3–3.6) to-

Table 5. Overview of Episodes of Inadequate Definitive Antimicrobial Therapy

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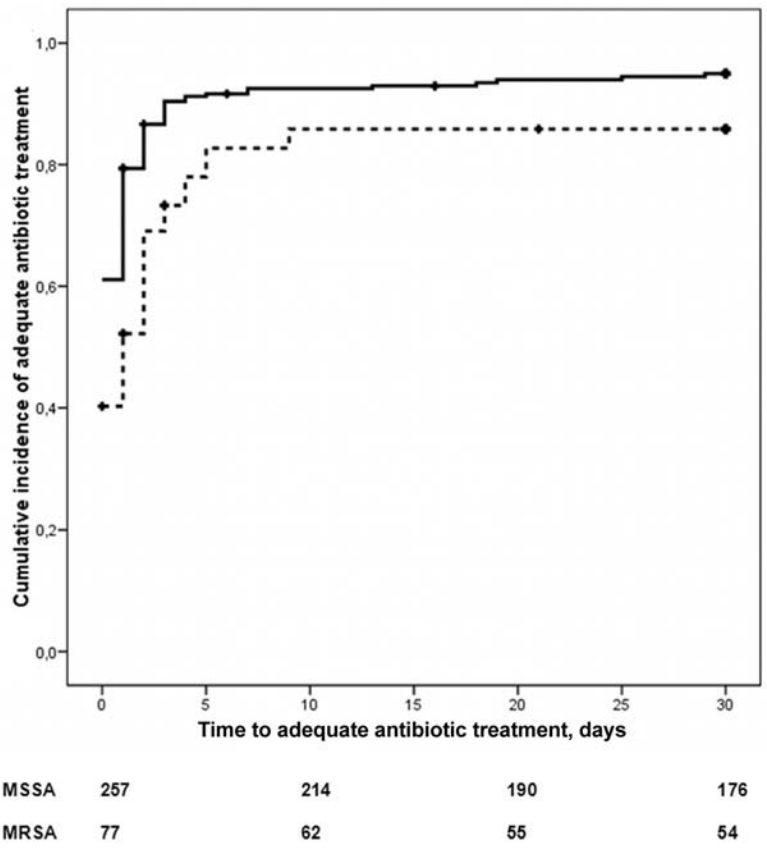

Figure 3. Kaplan-Meier curve with time to adequate antibiotic treatment in patients with *Staphylococcus aureus* bacteremia (SAB). *Dotted line,* methicillin-resistant *S. aureus* (MRSA) bacteremias; *solid line,* methicillin-susceptible *S. aureus* (MSSA) bacteremias; *plus sign,* censored cases (discharged from the hospital). The cumulative incidence of adequate antibiotic treatment over time was significantly lower among patients with MRSA-related SAB ($P < .001$).

gether with length of stay (in days) before SAB (OR, 1.02; 95% CI, 1.00–1.03).

Effect of inadequate empirical antimicrobial therapy on 30-day mortality rates. The 30-day mortality rate was 21.3% (20 of 94 patients died) for patients receiving inadequate and 25.0% (60 of 240 patients died) for those receiving adequate empirical therapy within the first 2 days after onset of bacteremia. In bivariate analysis, adequate empirical antimicrobial therapy was not significantly associated with 30-day mortality (OR, 0.69; 95% CI, 0.36–1.33) (Table 6). Covariates that were associated with 30-day mortality in multivariate logistic regression were age, modified Charlson comorbidity score, the severity of illness (defined by severe sepsis or septic shock), and ICU admission at time of onset of SAB. The interaction term between age and modified Charlson comorbidity score was significant and thus retained in the final model. Both inadequate empirical antimicrobial therapy and the presence of MRSA were not significantly associated with 30-day mortality. To adjust for clustering effects and residual confounding due to differences between the group that received adequate treatment and the group that received inadequate treatment, multilevel analysis and a propensity score were added to the final regression model, respectively. Both did not substantially change the effect estimates of the models (data not shown).

Validation of data quality. Eighteen (30%) of 60 participating hospitals were randomly assigned to the quality check of data. In these 18 hospitals, 118 of 122 eligible SAB episodes had been included (97%). Thirty-eight of the completed 334 CRFs were randomly selected to compare 9 items with the original patient records. In total, 282 (94%) of 300 items were in accordance with the patient records. No statistically significant differences were found in outcomes between the sampled cases and the total database.

DISCUSSION

In this study of 334 episodes of SAB in 9 Western European countries, 28% of patients initially received inadequate antimicrobial therapy, including 21% with MSSA bacteremia and 52% with MRSA bacteremia (even those with a severe clinical status). Five days after the index blood culture was obtained, 92% and 83% of patients received adequate treatment for MSSA

Table 6. Risk Factors for 30-Day Mortality and Characteristics of Patients

Covariate	Alive (n = 254)	Death (all cause) (n = 80)	OR (95% CI)[a]	P[b]
Teaching (vs nonteaching) hospital	197 (77.6)	55 (68.8)	…	.11
Age, median years (IQR)	66.0 (54–76.0)	74.5 (62.5–83)	1.06 (1.03–1.10)	<.001
Male (vs female)	170 (66.9)	54 (67.5)	…	.93
Modified Charlson comorbidity score, median value (IQR)	3.0 (0–5)	4.0 (2–6)	2.09 (1.21–3.63)	.001
Immunocompromised (vs nonimmunocompromised)	32 (12.6)	8 (10.0)	…	.53
Secondary (vs primary) bacteremia	94 (37.0)	28 (35.0)	…	.75
Length of stay before onset of SAB, median days (IQR)	2.0 (0–10)	2.0 (0–9.5)	…	.67
Hospital-acquired (vs community-acquired) bacteremia	119 (46.9)	39 (48.8)	…	.80
Severe sepsis or septic shock (vs sepsis) at onset of SAB	77 (30.3)	49 (61.3)	2.68 (1.52–4.75)	<.001
ICU hospitalization (vs non-ICU) at onset of SAB	44 (17.3)	29 (36.3)	2.89 (1.48–5.64)	<.001
Inadequate (vs adequate) empirical treatment	74 (29.1)	20 (25.0)	0.69 (0.36–1.32)	.57
MRSA (vs MSSA)	57 (22.4)	20 (25.0)	0.98 (0.50–1.94)	.64
Age × modified Charlson comorbidity score (interaction term)[c]	…	…	0.99 (0.98–0.999)	<.001

NOTE. Data are no. (%) of patients, unless otherwise indicated. CI, confidence interval; ICU, intensive care unit; IQR, interquartile range; MRSA, methicillin-resistant *Staphylococcus aureus;* MSSA, methicillin-susceptible *S. aureus;* OR, odds ratio; SAB, *S. aureus* bacteremia.

[a] Independent variables (adjusted ORs) associated with mortality in a multivariate logistic regression model.

[b] Results of bivariate analyses.

[c] Effect modification was examined by using clinically important interaction terms. The interaction term between age and modified Charlson comorbidity score was the only significant interaction and was retained in the final model.

and MRSA, respectively. Neither inadequate empirical treatment nor methicillin resistance was associated with 30-day mortality. These findings suggest that thousands of patients receive inadequate treatment for SAB in European countries and that, even with low estimated rates of attributable mortality due to inadequate empirical treatment, many patients may die as a result.

This study is unique in several ways. First, it is, to our knowledge, the first international study on SAB that involved the participation of hospitals from 9 European countries. Second, the hospitals in these countries were randomly approached for participation. Third, the quality of the data was validated, with 94% of the checked items found to be accurate and no evidence of selection bias of included patients. The representativeness of the participating hospitals is further supported by the consistency of MRSA prevalence in each country in our study with the data reported by EARSS. This suggests that the results and outcomes of this study adequately reflect the present situation in Western Europe regarding the adequacy of antibiotic treatment of patients with SAB.

Inadequate antimicrobial treatment was strongly associated with methicillin resistance. On a country level, high MRSA prevalence was associated with inadequate treatment. This seems surprising, because one would have expected that local guidelines had been adapted to MRSA endemicity.

In our study, inadequate antimicrobial therapy was not associated with increased mortality rates, which contradicts some [15–19] but not all studies [20–22]. These conflicting findings may result from differences in methods and populations, making generalizations difficult [23]. The obvious intuitive association between inadequate treatment and mortality may be obscured by several factors. First, evidence exists that certain β-lactam antibiotics, although assumed to be inadequate, have some effect in treating MRSA bacteremia [27]. This could explain why 7 (9%) of 77 patients with MRSA bacteremia continued to receive β-lactam antibiotics to which the isolate expressed in vitro resistance, even after recognition of MRSA in the blood culture results. Final results could have been overlooked; possibly, these patients had experienced clinical improvement while receiving so-called inadequate treatment, which is supported by the low 30-day mortality rate (11%) in this subset. Second, although glycopeptides are considered to be adequate for the treatment of MSSA bacteremia, there is evidence that vancomycin is inferior to β-lactam antibiotics for serious MSSA infections [28]. In our study, 13 of 257 MSSA bacteremia episodes were treated with glycopeptide monotherapy, but the 30-day mortality rate in this subset was 15%. Considering glycopeptide monotherapy as inadequate, therefore, would not have changed our interpretations. Third, we adjusted for multiple covariates by using multivariable regression and propensity scoring, but there is still a possibility that residual confounding by indication and confounding by other than antibiotic interventions (eg, foreign body removal and drainage of foci of infection) were insufficiently addressed. Finally, 50% of our patients had community-acquired SAB. Because the true onset of SAB is less obvious in this population, initial adequacy of antimicrobial therapy may have less impact on patient outcome. Restricting our analyses to hospital-acquired SAB episodes, though, did not change our findings.

Our study also has several limitations. First, we did not perform an external validation of the microbiology data: identifi-

cation of *S. aureus* and determination of antibiotic susceptibilities were performed according to local protocols. Second, 30-day mortality was assessed in the hospital setting only, and deaths occurring after hospital discharge (but still within 30 days after the index blood culture was obtained) were not included. Thus, informative censoring could have biased our effect estimates. However, all patients (except for 1 patient with an end-of-life decision) who were discharged from the hospital within 30 days were categorized as having resolved SAB (according to the physicians' opinion), and 31 of 36 patients with an end-of-life decision died during hospitalization. Of the remaining 5 patients (all of whom had unresolved SAB), only 1 was discharged within 30 days. This suggests that patients who were discharged before 30 days after the index blood culture had a good prognosis and that it is unlikely that incomplete follow-up strongly biased our findings. Third, although susceptibility test results, route and duration of administration, and time to adequate treatment were included in the definition of adequate treatment, appropriate dosing of antibiotic treatment, switching to narrow-spectrum antibiotics, and accordance with local antibiotic guidelines were not [23, 24]. With these criteria, rates of inadequate treatment would have been even higher.

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