Systemic Inflammatory Response Syndrome in Adult Patients with Nosocomial Bloodstream Infection Due to *Staphylococcus aureus*

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To determine the impact of methicillin resistance on clinical course and outcome, we evaluated nosocomial bloodstream infections (BSIs) due to *Staphylococcus aureus* that were diagnosed in 82 adult patients at the Medical College of Virginia Hospitals from December 1995 through May 1997. Patients with BSI due to methicillin-resistant *S. aureus* were compared with patients with BSI due to methicillin-susceptible *S. aureus;* the groups did not differ with regard to inflammatory response or outcome. Mortality was predicted by systemic inflammatory response and Acute Physiology and Chronic Health Evaluation II score but did not correlate with bacterial resistance to methicillin.

In the 1980s, gram-positive organisms, including *Staphylococcus aureus,* reemerged as the leading pathogenic causes of nosocomial bloodstream infections (BSIs). Strains of methicillin-resistant *S. aureus* (MRSA) have also contributed to the increase in *S. aureus* infections. In hospitals in the United States, the proportion of isolates of *S. aureus* that are resistant to methicillin increased from 2.4% in 1975 to up to 55% in recent years [1]. Whether resistance to methicillin is related to transmission or virulence is controversial. Several clinical studies could not identify significant differences in the mortality rate for patients with infections due to methicillin-resistant strains and that for patients with methicillin-susceptible *S. aureus* (MSSA) strains, after correcting for various confounding variables [2–5]. In contrast, other studies have suggested that methicillin resistance is an independent predictor of adverse outcome of patients with *S. aureus* infections [6–9]. To evaluate relationships between the inflammatory response, clinical course, and outcome of BSI due to MRSA and MSSA, we conducted a historical cohort study during an 18-month period from 1 December 1995 through 31 May 1997.

Methods. The Medical College of Virginia Hospitals (MCVH) is a 750-bed tertiary care facility affiliated with Virginia Commonwealth University, Richmond, Virginia. The hospital houses 9 intensive care units (ICUs), including pediatric ICUs and a burn unit. Approximately 30,000 patients are admitted annually.

Using the Surveillance and Control of Pathogens of Epidemiological Importance (SCOPE) database [10], we identified all patients who received a diagnosis of BSI due to *S. aureus* at MCVH from 1 December 1995 through 31 May 1997. Second episodes were excluded. Patients who had nosocomial BSI due to MRSA were then compared with patients who had nosocomial BSI due to MSSA. The variables that were compared included patient age and sex, underlying diseases, duration of hospitalization prior to onset of BSI, and putative risk factors, such as intravascular devices, mechanical ventilation, urinary catheters, total parenteral nutrition, dialysis, and ICU care. Adverse outcomes that occurred during the hospital stay were recorded.

Episodes of bacteremia were considered clinically significant if patients met the Centers for Disease Control and Prevention definition for nosocomial BSI [11]. Patients were considered to have had *S. aureus* BSI if $\geq$1 blood cultures were positive for this organism. The clinical condition of each patient was classified according to systemic inflammatory response syndrome criteria, as described elsewhere [12].

Identification to species level and susceptibility testing were done using the standard methodology of the MCVH microbiology laboratory. Antimicrobial susceptibility testing was performed by use of the disk-diffusion method. Methicillin susceptibility was determined by use of the agar dilution method according to the standards of the National Committee for Clinical Laboratory Standards.

Values are reported as means $\pm$ SD. Mean values were compared by use of 2 sample *t* tests, for independent samples, and a χ^2 test or Fisher's exact test, when appropriate. All tests of significance were 2-tailed, and α was set at 0.05. Independent

Received 3 October 2000; revised 24 January 2001; electronically published 6 August 2001.

Presented in part: 99th Annual Meeting of the American Society of Microbiology, Chicago, 30 May–3 June 1999 (abstract L-2).

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Clinical Infectious Diseases 2001;33:733–6

1058-4838/2001/3305-0022$03.00

Table 1. Results of initial cultures for *Staphylococcus aureus* in patients with bloodstream infection due to methicillin-resistant *S. aureus* (MRSA) and methicillin-susceptible *S. aureus* (MSSA).

Variable	No. (%) of patients with MSSA (n = 42)	No. (%) of patients with MRSA (n = 40)	P	OR (95% CI)
Intravascular devices	11 (26)	8 (20)	.60	1.4 (0.5–4.5)
Respiratory tract infection	3 (7)	2 (5)	.99	1.5 (0.2–9.3)
Urinary tract infection	2 (5)	3 (8)	.67	0.6 (0.1–4.9)
Wound infections	2 (5)	2 (5)	.99	0.9 (0.1–7.2)
Other	5 (12)	3 (8)	—	—
Unknown	19 (45)	22 (55)	—	—

predictors of outcome of BSI were identified by means of stepwise logistic regression analysis, with a limit for entering and removing variables at 0.05.

Results. From December 1995 through May 1997, 958 cases of nosocomial BSI were identified at MCVH. Among them, 127 clinically significant episodes of bacteremia due to *S. aureus* were identified in 96 adult patients and 31 pediatric patients, which accounted for 13% of all cases of BSI (2.7 cases per 1000 hospital admissions). Eight cases were classified as second episodes, and charts could not be obtained for 6 patients; these cases were excluded from further analysis. Among the 82 remaining adult patients, a total of 40 patients (49%) had BSI that was caused by methicillin-resistant strains. Duration of stay prior to BSI averaged 21 days (33 days for patients with MRSA vs. 11 days for patients with MSSA; $P = .0004$). Patients in both groups were predominantly male (60%), and the mean age was 50 years.

On admission, 20 patients (24%) had underlying diseases that were classified as ultimately fatal, and 5 (6%) had underlying diseases that were classified as rapidly fatal. An examination of underlying conditions and predisposing factors indicated that 26 patients (32%) required intensive care prior to BSI (18 patients [45%] with MRSA and 8 patients [19%] with MSSA; OR, 3.7; 95% CI, 1.2–11.2; $P = .01$). Potentially predisposing factors included presence of intravascular devices (i.e., central venous catheters in 28 patients [70%] with MRSA and 21 patients [50%] with MSSA [$P = .08$] and peripheral iv devices in 9 patients [27%] with MRSA and 27 patients [63%] with MSSA; OR, 5.8; 95% CI, 2–17; $P = .0003$). Other potential risk factors were presence of urinary catheters (24 patients [60%] with MRSA and 19 patients [44%] with MSSA) and administration of total parenteral nutrition (18 patients [45%] with MRSA and 8 patients [19%] with MSSA), and blood products (27 patients [68%] with MRSA vs. 16 patients [37%] with MSSA). The groups did not differ with regard to sources of BSI (table 1)

Duration of hospital stay prior to onset of BSI was significantly longer for patients who subsequently developed MRSA BSI than it was for patients who developed MSSA BSI (11 days vs. 33 days; $P = .001$). Overall, severe sepsis was found in 5 patients (17%) with MRSA (vs. 9 patients [21%] with MSSA; $P = .38$), and septic shock was identified in 6 patients (11%) with MRSA (vs. 3 patients [7%] with MSSA; $P = .31$). There were no significant differences between the 2 groups with regard to initial and most severe inflammatory response during the course of BSI (figure 1). End-organ dysfunctions or hypoperfusion abnormalities were seen in 15 patients (18%), the most common of which were acute renal failure (7 patients [18%] with MRSA and 5 patients [12%] with MSSA; $P = .54$) or altered mental status (7 patients [18%] with MRSA and 4 patients [9%] with MSSA; $P = .34$). Severe sepsis correlated with a high mortality rate (57% of the patients died; OR, 39; 95% CI, 6–151; $P < .0001$), as did progression to septic shock (100% of the patients died; OR, 22; 95% CI, 8–134; $P = .0001$). An Acute Physiology and Chronic Health Evaluation (APACHE) II score of >20 at the onset of BSI was associated with development of severe sepsis or septic shock (OR, 26; 95% CI, 4–96; $P = .001$), end-organ dysfunction (OR, 6; 95% CI, 1–25; $P = .026$), and hypoperfusion abnormalities (OR, 33; 95% CI, 5–118; $P = .0001$), as was an increase in APACHE II score of >5 points within the 48 h prior to onset of BSI (all $P < .0001$).

Among patients with MRSA BSI, 16 patients (40%) initially received vancomycin, compared with 18 patients (44%) with MSSA BSI. Administration of empiric antibiotic therapy within the first 24 h of bacteremia was judged to be appropriate in 91% of patients with MSSA BSI and in 50% of patients with MRSA BSI. Patients with bacteremia due to MRSA did not differ from patients with MSSA BSI with regard to mortality rates (24% vs. 23% died; $P = .99$; figure 2). Patients for whom empiric antimicrobial therapy within the first 48 h was judged

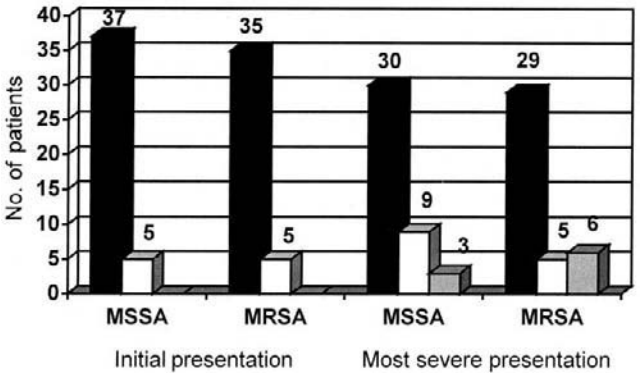

Figure 1. Initial and most severe inflammatory responses during the course of bloodstream infection. MRSA, methicillin-resistant *Staphylococcus aureus;* MSSA, methicillin-susceptible *S. aureus. Black bars,* systemic inflammatory response syndrome or sepsis; *gray bars,* septic shock; *white bars,* severe sepsis.

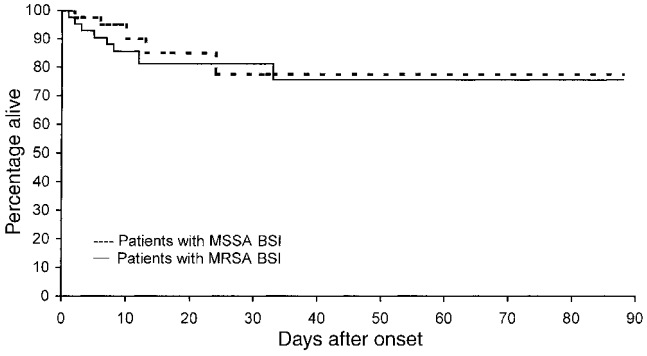

Figure 2. Mortality in patients with methicillin-resistant *Staphylococcus aureus* (MRSA) bloodstream infection (BSI) and methicillin-susceptible *S. aureus* (MSSA) BSI after the onset of BSI (Kaplan-Meier survival curve).

to be appropriate did not significantly differ from those for whom it was not judged to be appropriate with regard to outcome (24% vs. 23% died; $P = .99$). When stratified by markers of severity of illness at the onset of BSI, however, patients with high APACHE II scores were at higher risk for adverse outcome.

Multivariate analysis showed that outcome was predicted by APACHE II scores at the onset of BSI (OR, 1.2; 95% CI, 1.12–1.39; $P = .033$). Other variables tested, including MRSA versus MSSA, appropriate versus inappropriate antimicrobial therapy within the first 24 h, and all significant univariate risk factors, did not have any influence on outcome; however, severe sepsis and septic shock were also found to predict mortality independently (OR, 35; 95% CI, 6–82; $P = .01$; table 2).

Discussion. During the past 2 decades, several studies have evaluated the clinical, microbiological, and epidemiological features of MRSA infections, and these studies have also compared mortality associated with MRSA BSI with that associated with MSSA BSI [2, 5, 6, 13]. Few studies, however, have provided detailed descriptions of the clinical course of patients with MRSA BSI. To our knowledge, our study is the first to have monitored the inflammatory response among patients with *S. aureus* BSI and to assess the difference in clinical course and outcome for patients with BSI caused by methicillin-susceptible versus those for patients with BSI caused by methicillin-resistant isolates.

Table 2. Multivariate logistic regression analyses of factors associated with the outcome of patients with methicillin-resistant *Staphylococcus aureus* bloodstream infection (BSI) versus that of patients with methicillin-susceptible *S. aureus* BSI.

Factor	Coefficient	SE	*P*	OR (95% CI)
APACHE II on day of onset of BSI	.1712	.0804	.03	1.2 (1.1–1.4)
Severe sepsis/ septic shock	3.5633	.9056	.01	35.3 (6.0–82.1)

NOTE. APACHE, Acute Physiology and Chronic Health Evaluation; SE, standard error of the coefficient.

Most clinical studies have concluded that the clinical features of infections due to MRSA and MSSA, as measured by the duration of fever, infectious complications, duration of hospital stay, and mortality, appear to be similar. Several other studies also failed to identify any significant differences between MRSA BSI and MSSA BSI with regard to outcome [2–5], and it has been argued that the adjustment for confounding variables in previous studies might have not been complete [2]. In a large prospective study, Romero-Vivas et al. [6] found a 3-fold increase in risk of mortality in patients with bacteremia due to MRSA, even when they analyzed only patients who received adequate antibiotic treatment. Others have made similar observations [7–9]. Because many of these studies included only a small number of patients, and because most studies with a larger number of patients focus on outbreak situations, the statistical value of the results remains unclear [6]. Most recently, Soriano et al. [14] found that methicillin resistance was not an independent predictor for mortality, after correction for such confounding variables as shock, source of bacteremia, presence of an ultimately or rapidly fatal disease, acquisition of the infection in an ICU, receipt of inappropriate empirical therapy, age, and female sex; however, they found that methicillin resistance independently predicted shock.

The findings of our study support the idea that the outcome of *S. aureus* BSI is more closely related to the underlying physiological response to sepsis than it is to the methicillin susceptibility of the causative strain. Predisposing factors that have been previously identified for MRSA bacteremia include an APACHE II score of >15, duration of stay in the hospital, previous surgery, previous ICU stay, previous exposure to antimicrobial agents, intravascular catheters, total parenteral nutrition, and endotracheal intubation [2, 3, 5–9]. Among these factors, only duration of stay prior to onset of BSI and ICU stay were statistically significant in our study. This is further supported by the lack of statistical difference in outcome between patients for whom the initial antibiotic therapy was appropriate and those for whom it was not. Romero-Vivas et al. [6] also did not find any significant differences between the 2 groups with regard to severity of underlying diseases. In our analysis of the clinical course, the progression to severe sepsis and septic shock correlated with the severity of the underlying disease (as measured by the APACHE II) but showed no association with the methicillin susceptibility of the causative agent. Also, the groups did not differ with regard to the initial presentation or the most severe presentation of inflammatory response within 14 days of detection. In addition, no difference in outcome was observed between patients with MRSA BSI and those with MSSA BSI. The population that we investigated in this study was relatively small. Therefore, minor differences that

might be attributable to methicillin resistance may not have reached statistical significance. Insignificant variables were distributed almost equally, however, and no trend could be seen for any of the investigated variables that were not significant. Larger prospective studies will be necessary to confirm our results.

In summary, as with outcome, the clinical course in patients with BSI due to MRSA appears to be very similar to that of patients with BSI due to MSSA, and it is more closely related to the underlying condition of the patients than it is to the methicillin susceptibility of the causative pathogen. Adverse outcome in our study was independently predicted by a high APACHE II score at the onset of BSI and development of severe sepsis or septic shock.

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