JOURNAL OF CLINICAL MICROBIOLOGY, Apr. 2006, p. 1342–1346 Vol. 44, No. 4
0095-1137/06/$08.00+0 doi:10.1128/JCM.44.4.1342–1346.2006


# Time to Blood Culture Positivity as a Predictor of Clinical Outcome of *Staphylococcus aureus* Bloodstream Infection

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Received 13 December 2005/Returned for modification 23 January 2006/Accepted 25 January 2006

**Few studies have assessed the time to blood culture positivity as a predictor of clinical outcome in bloodstream infections (BSIs). The purpose of this study was to evaluate the time to positivity (TTP) of blood cultures in patients with *Staphylococcus aureus* BSIs and to assess its impact on clinical outcome. We performed a historical cohort study with 91 adult patients with *S. aureus* BSIs. TTP was defined as the time between the start of incubation and the time that the automated alert signal indicating growth in the culture bottle sounded. Patients with BSIs and TTPs of culture of ≤12 h ($n = 44$) and >12 h ($n = 47$) were compared. Septic shock occurred in 13.6% of patients with TTPs of ≤12 h and in 8.5% of patients with TTP of >12 h ($P = 0.51$). A central venous catheter source was more common with a BSI TTP of ≤12 h ($P = 0.010$). Univariate analysis revealed that a Charlson score of ≥3, the failure of at least one organ (respiratory, cardiovascular, renal, hematologic, or hepatic), infection with methicillin-resistant *S. aureus*, and TTPs of ≤12 h were associated with death. Age, gender, an APACHE II score of ≥20 at BSI onset, inadequate empirical antibiotic therapy, hospital-acquired bacteremia, and endocarditis were not associated with mortality. Multivariate analysis revealed that independent predictors of hospital mortality were a Charlson score of ≥3 (odds ratio [OR], 14.4; 95% confidence interval [CI], 2.24 to 92.55), infection with methicillin-resistant *S. aureus* (OR, 9.3; 95% CI, 1.45 to 59.23), and TTPs of ≤12 h (OR, 6.9; 95% CI, 1.07 to 44.66). In this historical cohort study of BSIs due to *S. aureus*, a TTP of ≤12 h was a predictor of the clinical outcome.**

The evaluation for bloodstream infection (BSI) is an important step in the workup of febrile patients (24). The majority of positive blood cultures are associated with true bloodstream infections (10), and a positive blood culture is frequently the trigger for the initiation of antimicrobial therapy (24).

*Staphylococcus aureus* is a highly common cause of BSIs (27). Moreover, mortality increases when inadequate empirical antibiotic therapy is given to patients with BSIs due to *S. aureus* (12). The rapid detection of a BSI has an impact on the length of hospitalization (2) and the mortality of bacteremic patients (4).

Physicians often make clinical predictions about individual patients (13). However, few studies have formally assessed the bacterial load (9), as indirectly measured as the time to positivity (TTP) of blood cultures, as a predictor of clinical outcome (14, 23).

The purpose of this study was to evaluate the association between the time to positivity of blood cultures in patients with *S. aureus* BSIs and the clinical outcome.

## MATERIALS AND METHODS

**Setting.** The Virginia Commonwealth University Medical Center (VCUMC) is an 820-bed tertiary-care facility in Richmond, Virginia. The hospital houses nine intensive care units (ICUs), including pediatric ICUs and a burn unit. Approximately 30,000 patients are admitted annually.

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**Study design.** Patients with BSIs at VCUMC from 15 December 2003 through 31 December 2004 were identified retrospectively by use of the electronic medical microbiology record. For each case, the time to blood culture positivity was retrieved from the hospital's automated blood culture instrument. The medical microbiology record identified the patient by medical record number so that a retrospective chart review could be conducted. Patients were considered to have had a BSI due to *S. aureus* if one or more blood cultures were positive for this organism. Each patient was included only once, at the time of the first BSI. Patients less than 18 years old, those with polymicrobial infections, and those receiving antimicrobial therapy at the time of the BSI were excluded from the analysis.

Data collected included age; gender; location of the patient (ward versus ICU); the duration of hospitalization prior to the onset of the BSI; the presence of predisposing clinical factors, including neutropenia (defined as an absolute neutrophil count of <500/μl); the use of peritoneal dialysis or hemodialysis; and the presence of central venous catheters. The sources of secondary BSIs were identified by cultures of samples obtained from the primary site of infection that yielded the same pathogen. Adverse outcomes (organ failure and in-hospital mortality) occurring during the course of hospitalization were recorded.

The severity of the underlying disease preceding the positive blood culture was classified by use of the Charlson weighted comorbidity index (6) and the McCabe classification (19). The patient's physiological condition on the day of the BSI was assessed by using the APACHE II score (15). At the onset of the BSI, the clinical condition of each patient was classified as systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, or septic shock by using criteria previously published by the American College of Chest Physicians/Society of Critical Care Medicine (1). SIRS was defined as two or more of the following: (i) a temperature of >38°C or <36°C, (ii) a heart rate of >90 beats per minute, (iii) a respiratory rate of >20 breaths per minute or a partial arterial $CO_2$ pressure of <32 mm Hg, or (iv) a white blood cell count of $>12 \times 10^9$/liter or $<4 \times 10^9$/liter or the presence of more than 10% immature neutrophils.

Severe sepsis was defined as organ dysfunction, hypotension, or systemic manifestations of hypoperfusion. Septic shock was defined as sepsis associated with hypotension unresponsive to intravenous fluid challenge or the need for treatment with a vasopressor agent. The maximal inflammatory response was defined as severe sepsis, septic shock, or death. The presence of organ system

failure at the time of the BSI and during the clinical course was assessed by using the criteria described by Fagon et al. (7). Nosocomial infection was defined as an infection that occurred >48 h after hospital admission, an infection that occurred <48 h after admission to the hospital for patients who had been hospitalized in the 3 weeks prior to the admission, or an infection that occurred <48 h after admission to the hospital for patients who had been transferred from another hospital or nursing home (8). The sources of infection were also defined according to Centers for Disease Control and Prevention criteria (8). Endocarditis was diagnosed by means of the modified Duke criteria (18). Time to positivity was defined as the time between the start of incubation and the time to sounding of the alert signal on the automated blood culture instrument. Adequate empirical antimicrobial treatment was defined as therapy that was administered within 24 h after samples for blood culture were obtained and that included any antimicrobial agent to which the *S. aureus* isolate was susceptible.

**Microbiological methods.** Blood cultures were processed by the institution's clinical laboratory using the BacT/ALERT blood culture instrument (bioMérieux, Durham, NC). Each blood culture set consisted of an FA aerobic bottle and an SN anaerobic bottle. All the samples of blood cultures were collected and submitted in a timely manner to the microbiology laboratory. All the bottles were loaded into the instrument at any time of the day (24 h a day, 7 days a week) without delay. The time to positivity of the first bottle in a set to be flagged as positive was used to determine the time to positivity and was obtained by using the system's software.

**Statistical analysis.** Continuous variables were compared by using the Student *t* test for normally distributed variables and the Mann-Whitney U test for nonnormally distributed variables. Differences in proportions were compared by a chi-square test or Fisher's exact test, when appropriate. Mean values ±1 standard deviation were reported. Alpha was set equal to 0.05, and all tests of significance were two tailed. When collinearity was identified between two variables in a correlation matrix, the one with the greatest clinical relevance associated with mortality was included in the multivariate analysis. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for all variables. Variables found to be significant by univariate analysis were then entered into a multivariate model. All statistical analyses were done by using the Statistical Package for the Social Sciences software (SPSS, Inc., Chicago, IL).

## RESULTS

**Study population and patient characteristics.** A total of 373 patients with clinically significant episodes of BSIs were identified at VCUMC during the 1-year study period. Of these, 294 patients (78.8%) had bacterial BSIs and 79 (21.2%) had fungal BSIs. A total of 113 patients (30.3%) with *S. aureus* BSIs were identified. Of these 113 patients, 18 patients were excluded because they were on antimicrobial therapy when blood samples for culture were obtained and 4 patients were excluded because they had polymicrobial BSIs. Only the remaining 91 patients were analyzed.

The mean age was 50 ± 15 years (range, 20 to 86 years). Twenty-four patients (26.4%) were over 60 years of age. The most frequent diagnoses responsible for hospitalization were infection (cellulitis, septic arthritis, and endocarditis) (31.9%), renal failure (19.8%), gastrointestinal diseases (15.4%), and solid and hematologic malignancies (13.2%). The most frequent sources of BSIs were central venous catheters (26.4%) and skin and soft tissues (13.2%). The average duration of hospitalization was 18 ± 14.8 days (range, 3 to 78 days). Most BSIs (63.7%) occurred during the first 48 h of hospitalization. Thirteen cases had been hospitalized less than 3 weeks previously (Table 1).

**Time to positivity.** The median time to positivity was 12.2 h. Because previous studies reported that the growth of *S. aureus* from endovascular sources within 14 h correlated with complications, we divided our study into two groups: patients with an early time to positivity (TTP of ≤12 h) and patients with a late time to positivity (TTP of >12 h). Associated risk factors and outcomes of the two TTP groups are summarized in Table 2. There were significant differences in age ($P = 0.027$) but not gender ($P = 0.078$) between the two groups. No statistically significant differences in the proportion of patients with end-stage renal disease, diabetes mellitus, or underlying malignancy were observed between the two TTP groups ($P > 0.05$). Endocarditis was more commonly associated with a BSI TTP of ≤12 h than with a BSI TTP of >12 h (25.0% and 8.5%, respectively; $P = 0.048$). Patients with early positive cultures were more likely to have more severe underlying disease (52.3% of patients with early positive cultures had a Charlson score of ≥3, whereas 29.8% of patients with late positive cultures had a Charlson score of ≥3; $P = 0.029$). All neutropenic patients (five cases) had TTPs <12 h (100.0%). Central venous catheters were also more commonly associated with a BSI TTP of ≤12 h than with a BSI TTP of >12 h (38.6% and 14.9%, respectively; $P = 0.010$). There were no differences in the nonintravascular catheter sources of BSIs between the two groups ($P > 0.05$). No statistically significant differences in the proportion of methicillin resistance in the *S. aureus* isolates between the two groups were observed (50.0% in the group with a TTP of ≤12 h and 42.6% in the group with a TTP of >12 h; $P = 0.48$).

TABLE 1. Demographic characteristics of 91 adult patients with monomicrobial *S. aureus* BSIs

| Variable | No. of patients | % of patients |
|---|---|---|
| Gender | | |
| Male | 50 | 54.9 |
| Female | 41 | 45.1 |
| Age (yr) | | |
| ≤60 | 67 | 73.6 |
| >60 | 24 | 26.4 |
| Diagnosis on admission | | |
| Infection (cellulitis, septic arthritis, endocarditis) | 29 | 31.9 |
| Renal failure | 18 | 19.8 |
| Gastrointestinal disease | 14 | 15.4 |
| Neoplasm | 12 | 14.2 |
| Trauma | 7 | 7.7 |
| Cardiovascular disease | 5 | 5.5 |
| Respiratory disease | 3 | 3.3 |
| Neurologic disease | 3 | 3.3 |
| Site of infection | | |
| Intravascular catheter | 24 | 26.4 |
| Skin and soft tissue | 12 | 13.2 |
| Bone and joint | 7 | 7.7 |
| Respiratory | 6 | 6.6 |
| Wound | 5 | 5.5 |
| Abdominal | 3 | 3.3 |
| Urinary tract | 2 | 2.2 |
| Other | 9 | 9.9 |
| Unknown | 23 | 25.3 |
| Hospital stay (days) prior to BSI | | |
| ≤2[a] | 66 | 72.5 |
| 3–7 | 17 | 18.7 |
| 8–14 | 7 | 7.7 |
| >15 | 1 | 1.1 |

[a] Eight cases were considered hospital acquired (includes patients with hospitalization in the previous 3 weeks).

TABLE 2. Risk factors for and outcomes associated with time to positivity (≤12 or >12 h) in *S. aureus* BSIs

| Variable | Time to positivity ≤12 h ($n$ = 44) | | Time to positivity >12 h ($n$ = 47) | | $P$ |
|---|---|---|---|---|---|
| | No. of patients | % of patients | No. of patients | % of patients | |
| Demographic characteristics[a] | | | | | 0.027 |
| Female | 24 | 54.5 | 30 | 63.8 | 0.078 |
| ICU stay | 4 | 9.1 | 7 | 14.9 | 0.52 |
| Underlying conditions | | | | | |
| Charlson score ≥3 | 23 | 52.3 | 14 | 29.8 | 0.029 |
| Rapidly fatal disease (MacCabe classification) | 8 | 18.2 | 3 | 6.4 | 0.11 |
| End-stage renal disease | 9 | 20.5 | 7 | 14.9 | 0.59 |
| Diabetes | 16 | 36.4 | 14 | 29.8 | 0.50 |
| Neoplasia | 7 | 15.9 | 3 | 6.4 | 0.19 |
| Neutropenia | 5 | 11.4 | 0 | | 0.023 |
| Endocarditis | 11 | 25.0 | 4 | 8.5 | 0.048 |
| Conditions related to the clinical course | | | | | |
| Maximal inflammatory response | 9 | 20.5 | 7 | 14.9 | 0.59 |
| APACHE II score ≥20 at BSI onset | 15 | 34.1 | 5 | 10.6 | 0.010 |
| Hospital-acquired bacteremia | 14 | 31.8 | 19 | 40.4 | 0.39 |
| Methicillin-resistant *S. aureus* | 22 | 50.0 | 20 | 42.6 | 0.48 |
| Adequate antibiotic therapy | 35 | 79.5 | 29 | 61.7 | 0.063 |
| Source of infection | | | | | |
| Intravascular catheter | 17 | 38.6 | 7 | 14.9 | 0.010 |
| Respiratory tract | 1 | 2.3 | 5 | 10.6 | 0.20 |
| Urinary tract | 0 | 0.0 | 2 | 4.3 | 0.49 |
| Skin and soft tissue | 5 | 11.4 | 7 | 14.9 | 0.76 |
| Bone and joint | 4 | 9.1 | 3 | 6.4 | 0.71 |
| Gastrointestinal | 0 | 0.0 | 3 | 6.4 | 0.24 |
| Wound | 2 | 4.5 | 3 | 6.4 | 1.0 |
| Other | 5 | 11.4 | 5 | 10.6 | 1.0 |
| Unknown | 10 | 22.7 | 13 | 27.7 | 0.59 |
| Outcomes | | | | | |
| Organ failure | 16 | 36.4 | 15 | 31.9 | 0.66 |
| Septic shock | 6 | 13.6 | 4 | 8.5 | 0.51 |
| Respiratory failure | 7 | 15.9 | 10 | 21.3 | 0.60 |
| Renal failure | 3 | 6.8 | 6 | 12.8 | 0.49 |
| Hematologic failure | 7 | 15.9 | 1 | 2.1 | 0.027 |
| Hepatic failure | 3 | 6.8 | 5 | 10.6 | 0.72 |
| In-hospital mortality | 11 | 25.0 | 2 | 4.3 | 0.006 |

[a] The mean ages of the patients in the groups with TTPs of ≤12 h and >12 h were 53.5 ± 14.9 and 46.3 ± 15.5 years, respectively.

**Clinical course.** Septic shock occurred in 13.6% of the group with a TTP of ≤12 h and in 8.5% of the group with a TTP of >12 h ($P$ = 0.22). No statistically significant differences were observed in maximal SIRS (severe sepsis, septic shock, or death) between the two groups (20.5% in the group with a TTP of ≤12 h and 14.9% in the group with a TTP of >12 h; $P$ = 0.59). Patients with a TTP of ≤12 h were significantly more likely to have an APACHE II score of ≥20 at BSI onset (39% versus 10.6% for the group with a TTP of >12 h; $P$ = 0.010). No difference in hospital-acquired bacteremia was observed between the two groups (31.8% for the group with a TTP of ≤12 h versus 40.4% for the group with a TTP of >12 h; $P$ = 0.39). Appropriate empirical antimicrobial use was documented in greater than 79.5% of the group with a TTP of ≤12 h; however, this was not statistically significant (79.5% in the group with a TTP of ≤12 h versus 61.7% in the group with a TTP of >12 h; $P$ = 0.063). Patients with BSIs caused by methicillin-resistant *S. aureus* (MRSA) strains were more likely to have received inadequate empirical antimicrobial therapy (70.4% in MRSA-infected patients versus 29.6% in non-MRSA-infected patients; $P$ = 0.003).

Hematologic failure was more commonly seen in the group with a TTP of ≤12 h (15.9% versus 2.1% for the group with a TTP of >12 h; $P$ = 0.027). No significant differences in the incidence of respiratory, renal, and hepatic failures were noted between the two groups. The overall crude mortality was 14.3% (13 of 91 patients). In-hospital mortality was greater in the group with a TTP of ≤12 h than in the group with a TTP of >12 h TTP (25.0% and 4.3%, respectively; $P$ = 0.006).

Univariate analysis revealed that a Charlson score of ≥3, the development of at least one organ system failure (respiratory, cardiovascular, renal, hematologic, or hepatic), infection with methicillin-resistant *S. aureus*, and time to positivity of ≤12 h were associated with death (Table 3). Age, gender, an APACHE II score ≥20 at BSI onset, inadequate empirical antibiotic therapy, hospital-acquired bacteremia, and endocarditis were not significant predictors of mortality on univariate analysis. By using logistic regression analysis,

TABLE 3. Risk factors for hospital mortality in patients with *S. aureus* BSIs

| Variable | Death ($n$ = 13) | | Recovery ($n$ = 78) | | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|---|---|---|---|
| | No. of patients | % of patients | No. of patients | % of patients | OR | 95% CI | OR | 95% CI |
| Age >60 yr | 5 | 38.5 | 19 | 24.4 | 1.9 | 0.57–6.65 | | |
| Female gender | 9 | 69.2 | 32 | 41.0 | 3.2 | 0.92–11.42 | | |
| APACHE II score ≥20 at BSI onset | 5 | 38.5 | 15 | 19.3 | 2.6 | 0.75–9.17 | | |
| Organ failure (at least one) | 9 | 69.2 | 22 | 28.2 | 5.7 | 1.60–20.53 | 4.0 | 0.80–20.31 |
| Respiratory failure | 5 | 38.5 | 12 | 15.4 | 3.4 | 0.96–12.31 | | |
| Cardiovascular failure | 4 | 30.8 | 6 | 7.7 | 5.3 | 1.26–22.57 | | |
| Renal failure | 2 | 15.4 | 7 | 9.0 | 1.8 | 0.34–10.04 | | |
| Hematologic failure | 5 | 38.5 | 3 | 3.8 | 15.6 | 3.13–77.88 | | |
| Hepatic failure | 2 | 15.4 | 6 | 7.7 | 2.2 | 0.39–12.20 | | |
| Inadequate antibiotic therapy | 6 | 46.2 | 21 | 26.9 | 2.3 | 0.70–7.75 | | |
| Charlson score ≥3 | 11 | 84.6 | 26 | 33.3 | 11.0 | 2.27–53.3 | 14.4 | 2.24–92.55 |
| Hospital-acquired bacteremia | 6 | 46.2 | 27 | 34.6 | 1.6 | 0.49–5.30 | | |
| Endocarditis | 2 | 15.4 | 13 | 16.7 | 0.9 | 0.18–4.59 | | |
| Methicillin-resistant *S. aureus* | 11 | 84.6 | 31 | 39.7 | 8.3 | 1.73–40.22 | 9.3 | 1.45–59.23 |
| Time to positivity ≤12 h | 11 | 84.6 | 33 | 42.3 | 7.5 | 1.56–36.13 | 6.9 | 1.07–44.66 |

the following variables were found to be independent predictors of death (Table 3): Charlson score of ≥3 (OR, 14.4; 95% CI, 2.24 to 92.55), infection with methicillin-resistant *S. aureus* (OR, 9.3; 95% CI, 1.45 to 59.23), and a TTP of ≤12 h (OR, 6.9; 95% CI, 1.07 to 44.66).

## DISCUSSION

We studied the association of clinical outcome and time to positivity of blood cultures for *S. aureus* BSIs. Unlike prior studies, we did not investigate the utility of blood culture TTP as a diagnostic tool for catheter-related or endovascular *S. aureus* BSIs (5, 26).

During the study period, nearly half of the patients with *S. aureus* BSIs exhibited an early TTP of the blood culture (TTP < 12 h). These cases were associated with a sevenfold higher rate of mortality than those with TTPs later than 12 h. Prior studies have shown that the growth of *S. aureus* from endovascular sources within 14 h can predict complications and can possibly predict mortality (14). We found similar results; however, our investigation also controlled for other variables that could explain the rapid bacterial growth, such as underlying conditions (diabetes mellitus, neoplasia, end-stage renal disease), source of infection (intravascular catheter), and the severity of the patients' conditions related to the clinical course (APACHE II score and maximal inflammatory response).

Of interest, no differences in the inflammatory responses were observed between the two TTP groups. Additionally, no differences in blood culture TTP were observed in patients with diabetes mellitus, neoplasia, or end-stage renal disease. Prompt adequate antimicrobial therapy in the group with a TTP of ≤12 h may have favorably altered the outcomes in these patients (12).

A statistically significant difference in APACHE II scores was noted between the two TTP comparison groups at the onset of the *S. aureus* BSIs. A previous study by Khatib et al. showed that patients with early times to positivity were more acutely ill and subsequently developed greater clinical complications (14). However, that study did not control for the severity of the underlying illnesses. In our study, the Charlson weighted comorbidity index and serial APACHE II scores were used to assess the severities of the patients' illnesses. The impact of underlying disease, as measured by the Charlson weighted comorbidity index, in patients with BSIs due to *S. aureus* was reported previously (16). Although in our study the APACHE II score was not a predictor of mortality in patients with *S. aureus* BSIs, other authors have had different results (22, 28). Thus, after controlling for the severity of illness, an early time to positivity of the blood culture was associated with increased mortality.

By multivariate analysis we could demonstrate that patients who acquired a strain of methicillin-resistant *S. aureus* had a high mortality rate related to the BSI. Although previous studies (11, 17, 28) have reported no increase in the mortality rate from infections caused by resistant microorganisms, other studies have shown the opposite (20, 21, 25). Although our observations show that infection with methicillin-resistant *S. aureus* is a predictor for mortality in patients with BSIs, the importance of virulence factors and pathogenesis remains unclear. As well, the restricted therapeutic options available for the treatment of MRSA BSIs could explain the differences in mortality between patients with methicillin-susceptible and -resistant *S. aureus* bacteremia (3, 20). Patients with MRSA BSIs were more likely to have received inadequate empirical antimicrobial therapy (70.4% in MRSA-infected patients versus 29.6% in non-MRSA-infected patients; $P = 0.003$).

Our study is limited by the retrospective nature of our analysis. In addition, because of the relatively small sample size of our study ($n = 91$), a type II error could have occurred, which would limit the ability to detect a statistically significant difference in SIRS or organ failure as predictors of mortality.

In conclusion, among adult patients with monomicrobial *S. aureus* BSIs, almost one-half of the cases had a time to blood culture positivity of ≤12 h. An early TTP is associated with a significantly greater risk for mortality. TTP data are easily obtainable in hospitals where microbiology laboratories use automated blood culture detection methods. These data can assist clinicians with choosing the appropriate antimicrobial therapy as soon as possible and provide prognostic information for patients with *S. aureus* BSIs.

## ACKNOWLEDGMENT

This work was supported by CAPES (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior, Brasilia, Brazil).

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