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# Bloodstream infections caused by *Staphylococcus aureus* in a university hospital in Turkey: clinical and molecular epidemiology of methicillin-resistant *Staphylococcus aureus*

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## ABSTRACT

In total, 177 patients with bloodstream infections caused by *Staphylococcus aureus* (BSISA) were investigated prospectively between June 1999 and June 2001. Of these, 19.8% had community-acquired BSISA, while 80.2% had nosocomial BSISA. Surgical intervention, foreign body, mechanical ventilation, total parenteral nutrition, and previous antibiotic treatment were found to be important risk factors for the nosocomial BSISA group. Secondary BSISA formed a greater proportion (62.9%) of community-acquired infections than of nosocomial infections (26.8%; p 0.0001). Catheter-related nosocomial BSISA was observed in 72.1% of patients. The suppurative complication rate was significantly higher among community-acquired infections (22.9%) than among nosocomial infections (6.3%; p 0.008). Of the nosocomial BSISA, 65.5% were methicillin-resistant. Analysis of 80 methicillin-resistant *S. aureus* isolates by pulsed-field gel electrophoresis identified ten main clones (A–J), but 61 (76.3%) of the 80 isolates belonged to clone A.

**Keywords** Bloodstream infections, methicillin-resistance, MRSA, PFGE, *Staphylococcus aureus*

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## INTRODUCTION

Staphylococci are among the most important causes of both hospital- and community-acquired infections worldwide [1–3]. *Staphylococcus aureus* causes superficial and deep skin and soft tissue infections, bacteraemia with metastatic abscess formation, and a variety of toxin-mediated infections, including gastroenteritis, staphylococcal scalded skin syndrome and toxic shock syndrome [2,4–7]. In the early 1980s, a change in the spectrum of nosocomial pathogens became apparent, as Gram-positive cocci began to re-emerge as predominant nosocomial pathogens [8]. The two most common causes of nosocomial bloodstream infections were identified as coagulase-negative staphylococci and *S. aureus* [8,9]. Methicillin-resistant *S. aureus* (MRSA) is now recognised worldwide as one of the most important nosocomial pathogens [9–13], including in Turkey [14–16]. The treatment of severe infections caused by some epidemic strains of MRSA is often difficult [17].

The aim of this study was to investigate the epidemiological characteristics and clinical outcome of bloodstream infections caused by *S. aureus* (BSISA). In addition, the clonal relationship among MRSA isolates was analysed by pulsed-field gel electrophoresis (PFGE).

## PATIENTS AND METHODS

### Setting

This prospective study was carried out between June 1999 and June 2001 at Erciyes University Hospital. This hospital is a tertiary care hospital with 1000 adult beds, including four intensive care units (ICUs). The study was approved by the Ethics Committee of the Faculty of Medicine at Erciyes University.

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### Patients

Patients aged >16 years and diagnosed with BSISA were enrolled in the study. Patients with signs of infection and/or positive blood cultures for *S. aureus* were evaluated for BSISA by the same infectious diseases team. Routine laboratory tests, with radiological investigation if required, and blood and other sample cultures were performed for all patients. At least two blood cultures were obtained from each patient. Data recorded were: age, sex, underlying conditions, all surgical procedures, foreign body, mechanical ventilation, total parenteral nutrition, previous antibiotic therapy. The severity of infection was classified as bacteraemia, sepsis, severe sepsis, or septic shock according to published recommendations [18]. The patients were followed until discharged from the hospital. The duration of hospital stay for patients with BSISA, as well as suppurative complications and mortality, were also recorded.

### Definitions

The Centers for Diseases Control criteria for blood stream infection (BSI) were modified for the diagnosis of BSISA [19]. Positive blood cultures for *S. aureus* in a patient were evaluated as follows:

*Primary BSISA*

**1** One or more positive blood culture(s) for *S. aureus*, unrelated to infection at another site;
**2** A positive blood culture for *S. aureus* from a patient's intravascular access device, with antimicrobial therapy initiated by the physician;
**3** Intravascular catheter-related infections caused by *S. aureus*.

*Secondary BSISA*

When *S. aureus* isolated from blood culture was compatible with a related infection at another site, the BSI was classified as a secondary BSISA. The source of secondary BSISA was defined as the site of infection that was evident clinically at the onset of symptoms and signs associated with the initial positive blood cultures.

*Catheter-related BSISA*

When the same *S. aureus* strain was isolated in blood cultures and in the semi-quantitative culture of a catheter segment (yield of ≥15 colonies), and if localised signs of infection were present at the access site, and if no primary site other than the intravascular catheter could be identified [20].

*Nosocomial BSISA*

When the positive blood cultures were taken at least 72 h after admission to the hospital, or within 10 days of discharge.

*Community-acquired BSISA*

When the positive blood cultures were taken within the first 72 h following admission to the hospital.

*Suppurative complication*

When a diagnosis of a suppurative complication was made on the basis of physical examination, pertinent diagnostic evaluation, and a positive culture for *S. aureus* from the site involved [21].

### Microbiological studies

BACTEC 9240 blood culture systems (Becton Dickinson, Franklin Lakes, NJ, USA) were used during the study period. *S. aureus* isolates were identified by standard microbiological methods at the Clinical Microbiology Laboratory in Erciyes University Hospital. Catheter tips were cultured by the method of Maki *et al*. [22]. Oxacillin resistance was determined after incubation for 24 h at 35 °C with a 1-μg oxacillin disc, according to National Committee for Clinical Laboratory Standards (NCCLS) guidelines [23]. Resistance was reported if there was growth within a 10-mm zone of inhibition. MRSA isolates were collected and stored in microbanks at −70 °C until analysed. Confirmation of methicillin resistance was carried out with the oxacillin agar screening technique, according to NCCLS guidelines [24].

### PFGE analysis

PFGE analysis of 80 MRSA isolates was performed at the Infectious Diseases Unit, Faculty of Medicine, Hacettepe University, Ankara, Turkey. Genomic DNA from *S. aureus* was prepared as described by de Lencastre *et al*. [10] and digested with *Sma*I (Promega, Madison, WI, USA). The DNA macrorestriction fragments were separated in agarose (Genaxis, Spechbach, Germany) 1.1% w/v gels by PFGE (General Navigator system; Pharmacia, Uppsala, Sweden). A λ-ladder (Sigma, Deisenhofen, Germany) was used for molecular size markers. Strains showing changes in more than three fragments were assumed to represent different major patterns (assignment of capital letters), while changes in between one and three fragments were considered to represent subtypes (capital letters with numerical subcode) [25].

### Statistical analysis

The $\chi^2$ test, Fisher's exact $\chi^2$test, and Student *t*-tests were used for statistical analyses; p values < 0.05 were considered to be statistically significant.

## RESULTS

This study included 177 patients, of whom 35 (19.8%) had community-acquired BSISA and 142 (80.2%) had nosocomial BSISA. The incidence of nosocomial BSISA was 2.34/1000 in the study period. Characteristics of the patients with BSISA are summarised in Table 1. No significant difference was found between the groups in terms of age and underlying diseases. In the community-acquired BSISA group, diabetes mellitus was present in 13 (37.1%) patients, cardiovascular disease in six (17.1%), chronic renal failure in four (11.4%), cerebrovascular disease in two (5.7%), and lymphoma, leukaemia and another disease in one (2.9%) patient each. Five patients each had two underlying diseases in the community-acquired BSISA group. In the nosocomial BSISA group, chronic renal failure was present in 43 (30.3%) patients, cardiovascular disease in 33 (23.2%), diabetes mellitus in 14 (9.9%), chronic obstructive pulmonary disease in ten (7.0%),

**Table 1.** Characteristics of patients with bloodstream infections caused by *Staphylococcus aureus*

| Characteristics | Community-acquired BSISA ($n$ = 35) $n$ (%) | Nosocomial BSISA ($n$ = 142) $n$ (%) | Total | $\chi^2$ | p |
|---|---|---|---|---|---|
| Female | 15 (42.9) | 68 (47.9) | 83 | 0.119 | 0.730 |
| Male | 20 (57.1) | 74 (52.1) | 94 | | |
| Total | 35 (19.8) | 142 (80.2) | 177 | | |
| Age (years) (mean ± SD)[a] | 48.5 ± 20.1 | 52.1 ± 30.8 | | | 0.512 |
| Underlying disease | 23 (65.7) | 107 (75.4) | 130 | 0.889 | 0.346 |
| Surgical intervention | – | 70 (49.3) | 70 | | |
| Foreign body | – | 128 (90.1) | 128 | | |
| Mechanical ventilation | – | 28 (19.7) | 28 | | |
| Total parenteral nutrition | – | 43 (30.3) | 43 | | |
| Previous antibiotic treatment | 4 (11.4) | 74 (52.1) | 78 | 17.272 | < 0.0001 |
| Primary BSI | 13 (37.1) | 104 (73.2) | 117 | 14.756 | 0.0001 |
| Secondary BSI | 22 (62.9) | 38 (26.8) | 60 | | |
| Primary BSI | | | | | |
| Use of catheter | 3 (23.1) | 75 (72.1) | 78 | 10.395 | 0.0009 |
| Peritoneal | 2 | 0 | | | |
| Intravascular | 1[b] | 75 | | | |
| Secondary BSI | | | | | |
| Skin and soft tissue | 16 (72.7) | 8 (21.1) | 24 | | |
| Musculoskeletal system | 5 (22.7) | 1 (2.6) | 6 | | |
| Lung | 1 (4.5) | 13 (34.2) | 14 | | |
| Urinary system | – | 1 (2.6) | 1 | | |
| Surgical site | – | 15 (39.5) | 15 | | |

BSISA, bloodstream infection caused by *S. aureus*; [a]Student *t*-test; [b]Hickman–Broviac catheter for haemodialysis.

lymphoma in six (4.2%), cerebrovascular disease in five (3.5%), leukaemia in four (2.8%), cirrhosis in two (1.4%), and other rare underlying diseases in 25 (17.6%) patients. Twenty-three patients had two underlying conditions, four patients had three underlying diseases, and one patient had five underlying diseases.

Surgical intervention, foreign body, mechanical ventilation and total parenteral nutrition, were found to be important risk factors for the nosocomial BSISA group. The rate of previous antibiotic administration in patients with nosocomial BSISA (52.1%) was also higher than in patients with community-acquired BSISA (11.4%; p < 0.0001). Primary BSISA were found in 37.1% of the community-acquired BSISA group, and in 73.2% of the nosocomial BSISA group (p 0.0001).

The site of infection could not be determined for ten (76.9%) of the community-acquired primary BSISA group, and for 29 (27.9%) of the nosocomial primary BSISA group. Catheter-related BSISA was significantly higher in the nosocomial primary BSISA group (72.1%) than in the community-acquired primary BSISA group (23.1%; p 0.0009). While the most frequent source of infection was the skin and/or soft tissue (72.7%) in patients with community-acquired secondary BSISA, a surgical site (39.5%) was the most frequent source of infection in the patients with nosocomial secondary BSISA. When the patients included in the study were classified according to severity of infection (Table 2), the bacteraemia rate for patients with nosocomial primary BSISA (61.5%) was significantly higher than for patients with community-acquired primary BSISA (30.8%; p 0.041).

Two (5.7%) of 35 patients with community-acquired BSISA were hospitalised in ICUs, with 16 (45.7%) patients in the infectious diseases clinic, and the remainder in other wards. Acquisition of nosocomial BSISA occurred in ICUs for 71 (50%) of 142 patients, in the nephrology clinic for 33 (23.2%) patients, and in other wards for the remaining 38 (26.8%) patients.

The mean length of hospital stay associated with community-acquired BSISA was 19.7 ± 10.8 days. The mean extra hospital stay associated with nosocomial BSISA was 11.8 ± 7.3 days. Of 177 patients, 47 (26.6%) died. Five (14.3%) patients with community-acquired BSISA, and 20 (14.3%) with nosocomial BSISA, died because of infection. Various suppurative complications developed in 17 (9.6%) of 177 patients. The complication rate was significantly higher for community-acquired infections (22.9%) than for nosocomial infections (6.3%; p 0.008). In the community-acquired BSISA group, skin and/or soft tissue abscess and pneumonia were seen in two patients, while cerebral emboli, septic arthritis, endocarditis, vertebral osteomyelitis, cerebral emboli plus soft tissue abscess, splenic abscess plus arthritis, and pneumonia plus pleural empyema were each seen in one patient. In the nosocomial BSISA group, endocarditis was seen in four patients, pneumonia in two patients, and skin

**Table 2.** Distribution of BSISA according to severity of infection

| Severity of infection | Community-acquired BSISA ($n$ = 35) $n$ (%) | Nosocomial BSISA ($n$ = 142) $n$ (%) | Total | $\chi^2$ | p |
|---|---|---|---|---|---|
| Primary BSI | | | | | |
| Bacteraemia | 4 (30.8) | 64 (61.5) | 68 | 3.319 | 0.041 |
| Sepsis | 5 (38.5) | 33 (31.7) | 38 | 0.03 | 0.755 |
| Severe sepsis | 3 (23.1) | 6 (5.8) | 9 | 2.742 | 0.061 |
| Septic shock | 1 (7.7) | 1 (1) | 2 | 0.397 | 0.211 |
| Total | 13 (100) | 104 (100) | 117 | | |
| Secondary BSI | | | | | |
| Bacteraemia | 8 (36.4) | 15 (39.5) | 23 | 0.057 | 0.811 |
| Sepsis | 13 (59.1) | 22 (57.9) | 35 | 0.008 | 0.928 |
| Severe sepsis | 1 (4.5) | 1 (2.6) | 2 | 0.158 | 1.000 |
| Septic shock | – | – | – | – | – |
| Total | 22 (100) | 38 (100) | 60 | | |

BSISA, bloodstream infection caused by *S. aureus*.

and/or soft tissue abscess, cerebral emboli, and septic arthritis each in one patient. All *S. aureus* isolates from the community-acquired BSISA group were susceptible to methicillin, but 93 (65.5%) of 142 *S. aureus* isolates from the nosocomial BSISA group were resistant to methicillin.

When 80 MRSA isolates were analysed by PFGE, ten main clones (A–J) were detected, with 61 (76.3%) of the 80 isolates belonging to clone A, which contained five different subtypes. Most ICU isolates (44 of 55) belonged to clone A. Five clinical isolates belonged to clone B, four to clone C, three to clone D, two to clone E, and one each to clones F, G, H, I and J.

## DISCUSSION

Staphylococci are frequently isolated as aetiological agents of infectious processes, with *S. aureus* being the most important human pathogen [6]. In the 1980s, Gram-positive organisms, including *S. aureus* and coagulase-negative staphylococci, re-emerged as the leading causes of nosocomial bacteraemia [10,26,27]. Edmond *et al.* [28] reported that staphylococci accounted for 47.6% of 10 617 nosocomial episodes of bacteraemia. As reported by Pittet and colleagues [29], 55% of 1745 nosocomial BSI were caused by Gram-positive cocci. In the present study, community-acquired BSISA accounted for 19.8% of patients, and nosocomial BSISA for the remaining 80.2%. This compares with a range of 50.9–86% reported in other studies [30–32].

The patients most susceptible to staphylococcal bacteraemia are those with an underlying condition such as cirrhosis, diabetes mellitus, chronic obstructive pulmonary disease, congestive heart failure or renal failure requiring dialysis [33]. In the present study, 73.4% of BSISA were accompanied by one or more underlying diseases, of which the most frequent were diabetes mellitus, chronic renal failure and cardiovascular disease. Severe underlying disease, confinement to bed, a poor clinical prognosis, prolonged hospital stay, previous antibiotic therapy, and severe burns have all been described as risk factors for MRSA bacteraemia [34].

Staphylococci are the most frequent cause of foreign device infections. Most nosocomial staphylococcal bacteraemia is related to intravascular catheter usage [29,35,36], and catheter-related infection was observed in 72.1% of patients with nosocomial primary BSISA. Pittet *et al.* [29] demonstrated that most nosocomial staphylococcal BSIs are primary infections, and Mylotte *et al.* [37] noted that nosocomial *S. aureus* bacteraemias are seen more frequently as primary infections, while community-acquired bacteraemias are mostly secondary. These findings correlate with those of the present study, and are possibly associated with the use of foreign materials, e.g., intravascular catheters. Secondary *S. aureus* bacteraemias are commonly a complication of skin and soft tissue or respiratory tract infections [34], and the most frequent source of infection in the present study was skin and soft tissue for community-acquired secondary BSISA, and a surgical site for nosocomial secondary BSISA. Similar results have been reported by Cunney *et al.* [27] and Mylotte *et al.* [36]. In the present study, sepsis was the clinical condition defined most frequently for both primary and secondary community-acquired BSISA. In contrast to Conterno *et al.* [30], who reported a rate of 22%, septic shock was observed in only one patient from each group.

Distant infectious metastasis is a major concern with BSISA. The vertebral column constitutes the most common site of septic metastasis complicating *S. aureus* bacteraemia, with an endocarditis rate of 1.7–18% [34]. The suppurative complication rate was 22.9% for patients with community-acquired infections in the present study, possibly because of delayed diagnosis and antimicrobial treatment. Cunney *et al.* [27] reported complication rates of 53% and 6%, respectively, for community-acquired and nosocomial episodes of *S. aureus* bacteraemia, with infective endocarditis being the most frequent complication. Similar high complication rates were reported by Raad *et al.* [38] and Libman *et al.* [21].

The mortality rate is generally low for BSIs associated with most Gram-positive bacteria, but the mortality rate for *S. aureus* bacteraemia is 21–43% [27,31]. Mortality rates for community-acquired BSISA and nosocomial BSISA were 14.3% and 14.1%, respectively, in the present study. Other studies of nosocomial *S. aureus* bacteraemia have reported mortality rates of 11.9% [39] and 25% [28].

Studies conducted since the late 1970s have recorded an increasing frequency of methicillin resistance among strains recovered from hospitalised patients. The percentage of MRSA among all hospitals in the NNIS system rose from 2.1% in 1975, to 29% in 1991, and to 35% in 1996 [40]. The present study observed a high rate of methicillin resistance (65%) in nosocomial BSISA, but all community-acquired BSISA isolates were susceptible. van Belkum *et al.* [16] reported that a major MRSA clone had spread through a large part of Turkey. The present study identified ten different clones among 80 isolates typed by PFGE. Of these isolates, 76.3% belonged to clone A, and most of these originated from surgical ICUs. This indicated that general infection control procedures, such as hand-washing and wound care, require more emphasis. Epidemiological studies have revealed that the main reservoir of MRSA is the patient, including previously colonised or infected patients who are readmitted to the hospital [34]. The main transmission route of MRSA is from person to person [41]. Although most MRSA isolates belonged to clone A, the other nine clones identified might eventually spread if infection control procedures are not enforced properly.

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