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Predisposing factors, disease progression and outcome in 430 prospectively followed patients of healthcare- and community-associated *Staphylococcus aureus* bacteraemia

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SUMMARY

Staphylococcus aureus bacteraemia (SAB) episodes identified in a prospective multicentre study during 1999–2002 (not including MRSA) were followed up by an infectious disease specialist. The aim of this study was to compare predisposing factors, disease progression and outcome of healthcare (HA)- and community (CA)-associated SAB. Of 430 SAB episodes, 232 (54%) were HA. The HA-SAB patients were significantly older and more chronically ill compared to CA-SAB. Deep infection foci prevalence within three days of onset of SAB for HA versus CA were deep-seated abscesses (26% vs 37%, $P < 0.05$), pneumonia [25% vs 31%, non-significant (NS)], osteomyelitis (24% vs 36%, $P < 0.01$), permanent foreign body (24% vs 9%, $P < 0.001$), endocarditis (11% vs 15%, NS), septic arthritis (9% vs 13%, NS) and no infection focus (3% vs 6%, NS). The case fatality rates for HA-SAB versus CA-SAB at 28 days were 14% vs 11% (NS). Independent risk factors according to multivariate analysis for a fatal outcome were age, chronic alcoholism, immunosuppressive treatment, ultimately or rapidly fatal underlying diseases, severe sepsis on the onset of SAB, *S. aureus* pneumonia and endocarditis. As a result of a prospective study design, meticulous infection foci search and infectious disease specialist follow-up of each SAB episode, the case fatality remained low and 97% of the HA-SAB episodes presented infection foci within three days of onset of bacteraemia.

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Introduction

Staphylococcus aureus represents an important bloodstream pathogen and a leading cause for both healthcare (HA)- and community-associated (CA) bacteraemias.[1,2] Despite anti-staphylococcal antibiotics, the case fatality (CF) associated with *S. aureus* bacteraemia (SAB) remains high, ranging from 7% to 39%.[3–5] The prognosis of SAB is dictated by complications such as deep infection foci due to metastatic spread, thromboembolic events and recurrence of bacteraemia.[3,6] Generally, HA-SAB patients are older and the source of bacteraemia is known[7,8] whereas CA-SAB patients are younger and without an identifiable infection focus.[7–9] Furthermore, secondary or metastatic foci and endocarditis are regarded as frequent complications in SAB and are found considerably more often among patients with unknown infection focus or CA-SAB.[7–10]

Some studies connect HA-SAB to higher CF whereas others do not.[3,8,10–12] In many studies meticillin-resistant *S. aureus* (MRSA) has been one additional variable affecting the differences reported between HA- and CA-SAB. Prevalence of MRSA among invasive infections in Finland has generally been less than 1%. An increase in the incidence of MRSA bacteraemia was observed in 2004[13] with the prevalence remaining still under 3%. Furthermore, Panton–Valentine leucocidin (PVL)-positive strains have been rare in Finland. Only 2% of meticillin-susceptible *S. aureus* (MSSA) strains and 12% of CA-MRSA strains have been PVL positive.[14,15] Hence, the possible contribution to morbidity and mortality provided by MRSA seen in several other countries, e.g. USA and UK, is minimal in the Finnish healthcare system. In this study it was therefore decided to exclude all MRSA cases by focusing explicitly on MSSA to study the predisposing factors,

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disease progression and outcome of HA-SAB compared with CA-SAB. Infectious disease specialists prospectively followed up each SAB episode and infection foci were searched for meticulously.

Methods

Settings and study population

A multicentre study was conducted at all five university and seven central hospitals in Finland during January 1999 to May 1999 and January 2000 to August 2002, thus representing all SAB cases in various patient materials with various geographical locations. Originally 1226 SAB patients were identified of whom 430 were accepted when taking into account the exclusion criteria.[16] These patients had at least one *S. aureus*-positive blood culture within a median time of three days after sampling of the first positive blood culture. Each patient provided a written informed consent. All MRSA cases were excluded ($N = 6$). Other exclusion criteria have been described earlier.[16] All patients were prospectively followed for three months. Data collection included age, gender, underlying diseases or predisposing factors, place of acquisition of SAB, infection focus and antibiotic treatment. Duration of hospitalisation, need for surgery and documentation of infection foci verified by bacteriological, radiological or pathological investigations or clinical suspicion only were included. Radiological and laboratory findings and time to defervescence (axillary temperature below 37.5 °C) were recorded.

Definitions

Underlying diseases were classified according to McCabe and Jackson.[17] The guidelines of the Infectious Diseases Society of America[18] were used to define central venous catheter (CVC) infections. Endocarditis was defined according to the modified Duke criteria.[19] SAB was defined as HA if the first *S. aureus*-positive blood culture was obtained ≥48 h after hospital admission or if obtained within two days of admission with a preceding hospital discharge within seven days, or if the patient had attended haemodialysis or was a resident in a long-term care facility during the previous two months. SAB was classified as CA if the positive blood culture was obtained within two days of admission and there were no hospitalisations within the preceding seven days.

Antibiotic therapy

Detailed information on antimicrobial therapy has been supplied.[16]

Outcome

The primary outcome was regarded as the CF at 28 days and at three months. Secondary outcome was regarded as the number of complications (primarily deep infection foci), decrease in serum C-reactive protein (CRP) concentration and time to defervescence.

Statistical analysis

Pearson's χ^2-test was used to compare categorical variables and independent samples (Student's) *t*-test for non-categorical variables, and odds ratios (OR) with 95% confidence intervals (CIs) were calculated. Univariate risk factors for CF with $P < 0.1$ were entered into a binary logistic regression analysis. CF and time to defervescence survival estimates were calculated with the Kaplan–Meier method. All tests were two-tailed and $P < 0.05$ was considered to be significant.

Results

Patients and underlying factors

Of the 430 SAB episodes, 54% were healthcare-associated (Table I). Patients with HA-SAB were significantly older and more often had a fatal underlying disease such as cardiovascular disease, diabetic complication, chronic renal failure and dialysis treatment, heart valve disease, malignancy, immunosuppressive treatment and connective tissues or rheumatic disease as compared to patients with CA-SAB. On the contrary, liver disease, chronic alcoholism, injection drug abuse and human immunodeficiency virus were associated more often with CA-SAB. Predisposing factors such as surgical procedures within three months or foreign body implantation within one year before SAB and CVC were significantly more common among HA-SAB whereas the prevalence of chronic skin disease or wounds was significantly higher among CA-SAB (Table I).

Haemodynamic state during the first week

On the day of positive blood culture, equal numbers of patients with HA-SAB and CA-SAB suffered from severe sepsis (6% vs 7%, $P = 0.89$), septic shock (3% for both groups) or were treated at intensive care unit (15% vs 16%, $P = 0.76$). Within the first week no difference between HA-SAB and CA-SAB was observed in the occurrence of severe sepsis (13% for both groups), septic shock (4% vs 7%, $P = 0.30$) or need for intensive care unit (21% vs 23%, $P = 0.59$).

Infection foci

Within three days after onset of SAB, a deep infection focus was found significantly less frequently in patients with HA-SAB compared to CA-SAB (69% vs 84%, $P < 0.01$) and the prevalence increased only slightly during three months of follow-up (80% vs 87%, $P = 0.045$). Among patients with HA-SAB, there was significantly more often infection of permanent foreign body, CVC, peripheral catheter or mediastinitis compared to CA-SAB, whereas deep-seated abscesses and osteomyelitis were observed significantly less frequently in HA-SAB (Table II). No significant difference was detected in the frequency of pneumonia, endocarditis, septic arthritis or cutaneous infection foci between the groups. The occurrence of SAB without foci remained low for HA-SAB and CA-SAB at three days (3% vs 6%, $P = 0.29$) and within three months (2% vs 5%, $P = 0.16$).

Antibiotic therapy

All patients were treated with an antibiotic effective against the isolated *S. aureus* strain on the day of the first positive blood culture. Most patients received a β-lactam antibiotic and vancomycin was used in 12% of patients.

Outcome

The overall CF at 28 days was 13% and 18% at three months. Twenty-eight-day CF did not differ between HA-SAB and CA-SAB (14% vs 11%, $P = 0.40$) but three-month CF differed significantly (22% vs 13%, $P = 0.023$) (Figure 1). Risk factors for dying within 28 days according to multivariate analysis were age, chronic alcoholism, immunosuppressive treatment within six months, ultimately or rapidly fatal underlying diseases, severe sepsis at the onset of SAB, *S. aureus* pneumonia and endocarditis (Table III). No difference between the groups concerning the time to defervescense was observed ($P = 0.77$) but mean serum CRP was significantly lower for HA-SAB compared to CA-SAB ($P < 0.05$) on the day of positive blood culture.

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