RESEARCH NOTE

Role of superantigenic strains in the prognosis of community-acquired methicillin-susceptible *Staphylococcus aureus* bacteraemia

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ABSTRACT

Methicillin-susceptible *Staphylococcus aureus* (MSSA) strains can produce superantigenic toxins that may trigger a massive release of pro-inflammatory cytokines, which are involved in the onset of septic shock. This 1-year prospective pilot study assessed the role of the production of superantigenic toxins in the outcome of immunocompetent patients hospitalised for community-acquired MSSA bacteraemia. Thirty-seven patients were enrolled, of whom 14 died in hospital. Fourteen patients had septic shock, and the mortality rate in this subgroup was 56%. Twenty-seven (73%) isolates produced at least one superantigenic toxin, but this did not influence the rate of occurrence of septic shock or death.

Keywords Bacteraemia, cytokines, methicillin-susceptible *Staphylococcus aureus*, prognosis, septic shock, superantigenic toxins

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The high mortality rate associated with community-acquired methicillin-susceptible *Staphylococcus aureus* (MSSA) bacteraemia [1,2] appears to be influenced by the occurrence of septic shock [1–3]. Superantigenic toxins can trigger a massive release of pro-inflammatory cytokines, and these are involved in the onset of septic shock [4–6]. In a recent study, the presence of the enterotoxin A gene (*sea*) was correlated with the severity of infection [6]. However, the potential impact of the production of superantigenic toxins by MSSA on the rate of occurrence of septic shock and mortality remains poorly understood [7].

The present prospective observational study was performed during a 12-month period in a 1280-bed teaching hospital. All consecutive immunocompetent patients aged >18 years who had community-acquired MSSA bacteraemia were eligible. Patient characteristics and their Sequential Organ Failure Assessment (SOFA) scores [8] were recorded at enrolment. Septic shock was defined as a requirement for vasopressor therapy to maintain a mean blood pressure of ≥80 mmHg. Initial antibiotic therapy (delay in commencement, type and dose) was assessed for each patient. All patients were followed until hospital discharge or death.

The presence of genes for superantigenic enterotoxins (SEA, SEB, SEC, SED, SEE, SEH, SEG and SEI, and toxic shock syndrome toxin 1) and Panton–Valentine leukocidin (PVL) was detected by PCR as described previously [9]. As the *sed* and *sej* genes are located on the same mobile genetic element, *sed*-positive isolates were also considered to be *sej*-positive. Similarly, as the *seg*, *sei*, *selm*, *seln* and *selo* genes belong to the enterotoxin gene cluster (*egc*), isolates that were positive for the *seg* and *sei* genes were also considered to be positive for the *egc* gene cluster. The superantigenic activity of each isolate was confirmed by testing lymphocyte activation by means of flow-cytometry as described previously [10].

Results for survivors and for patients who died in hospital were compared. Qualitative variables were expressed as numbers and percentages, and were compared using the chi-square test or Fisher's exact test. Continuous variables were expressed as means ± standard deviation, and were compared using Student's *t*-test or the Mann–Whitney *U*-test. A multivariate analysis, based on a multiple logistic regression (SAS v.6.12; SAS Institute, Cary, NC, USA) was used to identify independent risk-factors for hospital

death. All risk-factors identified in the univariate analysis with p ≤0.20 were integrated with the production of superantigenic toxins in the multiple logistic regression model. ORs and 95% CIs were calculated for each risk-factor.

During the study period, 161 patients were admitted with MSSA bacteraemia and sepsis. Of these, 124 were excluded because the origin of bacteraemia was nosocomial (n = 78), or because they were undergoing dialysis (n = 15) or were immunosuppressed (n = 31). The mean SOFA score of the remaining 37 patients was 4.3 ± 4.4 (range 0–14). Twenty-three (62%) patients survived, and the mean length of hospital stay was 45 ± 37 days. Fourteen (38%) patients died in hospital after a mean interval of 16 ± 16 days following admission. On the basis of a subjective analysis of the clinical and biological data by two authors (AD and AH), death was attributed to MSSA bacteraemia for 11 patients, and to hepatic failure secondary to liver fibrosis for the three remaining patients. Mean age, gender, pre-existing morbidity and origin of infection were similar for survivors and non-survivors (Table 1). Initial antibiotic therapy was appropriate for 33 (89%) patients, with no difference between the study groups.

Among the MSSA isolates from blood culture, 27 (73%) produced at least one superantigenic toxin (one toxin, n = 3; two or more toxins, n = 24) and three produced PVL. Isolates from 11 (79%) of the 14 deceased patients produced at least one superantigenic toxin, whereas 16 (70%) of the 23 patients who survived were infected by strains that produced at least one superantigenic toxin (OR 1.60, 95% CI 0.34–7.59, p 0.55). The superantigenic toxins detected most frequently were enterotoxins SEG and SEI, indicating the presence of the *egc* gene cluster (Table 2). The distribution of superantigenic toxins was similar in the two study groups (Table 2). Fourteen patients in the study population developed circulatory failure, but superantigenic toxin production failed to influence the rate of occurrence of septic shock (OR 1.60, 95% CI 0.34–7.59, p 0.55). The SOFA score was the only independent parameter associated with hospital death (OR per additional point 1.36, 95% CI 1.03–1.78, p 0.028).

Table 1. Characteristics of the study population and risk-factors for methicillin-susceptible *Staphylococcus aureus* infection in survivors and non-survivors

	Survivors n = 23	Non-survivors n = 14	p
Age, years (range)	67 ± 15 (24–88)	59 ± 18 (32–84)	0.19
Male gender, n (%)	17 (74)	6 (43)	0.09
Medical history, n (%)			
Diabetes mellitus	11 (48)	7 (50)	1
Anti-inflammatory drugs	5 (22)	1 (7)	0.38
Intravenous drug use	1 (4)	0	1
Chronic underlying disease[a]	3 (13)	4 (29)	0.39
Origin of bacteraemia, n (%)			
Skin infection	15 (65)	11 (79)	0.48
Bone/joint infection	5 (22)	1 (7)	0.38
Urinary tract infection	2 (9)	2 (14)	0.62
Lung infection	1 (4)	0	1

[a]Chronic respiratory failure, chronic heart failure or hepatic cirrhosis with portal hypertension, defined according to Knaus *et al.* [11].

Table 2. Superantigenic toxin production by methicillin-susceptible *Staphylococcus aureus* blood culture isolates in survivors (n = 23) and non-survivors (n = 14)

Toxin production	Survivors n (%)	Non-survivors n (%)	p
One superantigenic toxin	16 (70)	11 (79)	0.71
Two or more superantigenic toxins	14 (61)	10 (71)	0.72
Enterotoxins			
SEA	2 (9)	3 (21)	0.35
SEB	1 (4)	2 (14)	0.28
SEC	3 (13)	2 (14)	1
SED	2 (9)	2 (14)	0.60
SEE	0	0	–
SEG	13 (57)	8 (57)	1
SEH	1 (4)	2 (14)	0.54
SEI	15 (65)	8 (57)	0.73
TSST-1	5 (22)	0	0.13
PVL	2 (9)	1 (7)	1

TSST-1, toxic shock syndrome toxin 1; PVL, Panton–Valentine leukocidin.

In a study conducted in a heterogeneous population with community- and hospital-acquired infections or colonisation caused by MSSA and methicillin-resistant *Staphylococcus aureus*, enterotoxin A was identified more frequently in isolates from patients who developed septic shock [6]. It was speculated that enterotoxin A could trigger the over-expression of inflammatory mediators that may, in turn, lead to the development of septic shock. In the present homogeneous, but limited, study population, comprising patients with community- acquired MSSA bacteraemia, production of superantigenic toxins failed to influence the rate of occurrence of septic shock or subsequent death. PVL was identified in only three of the 37 patients. Previous studies have reported substantially higher proportions of MSSA strains that produce PVL, albeit in different populations [12,13].

The mortality rate associated with *S. aureus* bacteraemia is highly variable, ranging from 3.6% to 83.3% [14], and is influenced by numerous factors that include methicillin susceptibility, the type of infection and the underlying disease [14–17]. In the present study, the hospital mortality

rate was as high as 38%, in keeping with reports published previously [1], and the risk of death increased with the number of organ dysfunctions, as evaluated by the SOFA score [18].

In conclusion, community-acquired MSSA bacteraemia in immunocompetent patients is associated with a high mortality rate. In the present pilot study, a large proportion (73%) of MSSA isolates produced a superantigenic toxin. Nevertheless, the production of superantigenic toxins failed to influence the development of septic shock or subsequent death. However, because of the limited number of patients included in the study, the statistical power was limited, and these preliminary data should be interpreted with caution.

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