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Short Communication

Staphylococcus epidermidis bloodstream infections are a cause of septic shock in intensive care unit patients



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ABSTRACT

Objectives: *Staphylococcus epidermidis* (SE) is a supposedly low-virulence agent, which may cause proven bloodstream infections (BSIs), with little-known consequences on intensive care unit (ICU) patients. We aimed at studying ICU patients diagnosed with BSIs caused by SE (SE-BSIs).

Methods: We constituted a retrospective cohort in two medical ICUs. SE-BSIs were defined by two or more independent SE-positive blood cultures of the same strain, within 48 hours, without concurrent infection.

Results: We included 59 patients; 58% were men ($n = 34$), with median age of 67 (interquartile range 60–74) years and a simplified acute physiology score II of 59 (36–74) points, and 56% were immunocompromised ($n = 33$). Among the 37 (63%) patients requiring norepinephrine initiation or increase at the onset of SE-BSI versus patients not requiring vasopressors (37%; $n = 22$), concomitant arterial lactate levels reached 2.8 (1.9–5.8) versus 1.5 (1.3–2.2) mmol/l ($P < 0.01$), whereas the mean blood pressure was 49 (42–54) versus 61 (56–65) mm Hg ($P = 0.01$) and the mortality was 46% ($n = 17$) vs 14% ($n = 3$) at day 28 ($P = 0.01$), respectively. Regarding antibiotics, the susceptibility rates toward linezolid and vancomycin were 71% ($n = 41/58$) and 100% ($n = 54/54$), respectively. At the time of SE-BSI, all but one patient had a central venous access device.

Conclusion: This work highlights SE-BSIs as a cause of septic shock, mostly in immunocompromised ICU patients, with increasing concerns about resistance to antibiotics and central line management.

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Introduction

Staphylococcus epidermidis (SE) is a gram-positive coccus that belongs to the family of coagulase-negative staphylococci (CNS) and is a highly frequent colonizing agent of the skin and mucous membranes [1,2]. Like most CNS, SE is classically a low-virulent agent and is, therefore, mainly considered a contaminant when found in bacteriological samples, leading to make the diagnosis of CNS bloodstream infection (BSI) only if two or more independent blood cultures are positive for the same species of CNS within 5 days in the absence of another concomitant infection [3]. SE can cause infections in certain circumstances, especially health care-associated infections [2] and is implicated in 31–38% of catheter-related BSIs [4,5].

In addition to indwelling devices, immunosuppression appears to be a determining risk factor for SE infections, which are frequently considered opportunistic infections [2]. SE is easily encountered in patients with neutropenic cancer [6], with frequent involvement of long-term central lines [5]. SE may also affect solid-organ transplant recipients treated with immunosuppressive therapy and can cause endocarditis even on native valves, suggesting virulence factors of some strains [7].

Apart from publications dealing with SE infections in postoperative intensive care unit (ICU) patients and increasing concerns about antibiotic resistance [8], the literature remains scarce on critically ill patients with BSI caused by SE (SE-BSI), particularly regarding the clinical repercussions and prognosis, despite the high proportion of immunocompromised patients and the frequent use of invasive devices in the ICU. We, therefore, conducted a retrospective study involving medical ICU patients with focus on their epidemiological characteristics and on the clinical outcomes after SE-BSI.

Methods

We constituted a retrospective cohort in the two separate medical ICUs of the University Hospitals of Strasbourg. All patients who had an SE-induced BSI, defined by two or more independent positive blood cultures within 48 hours during their intensive care stay, were included in the absence of concurrent infection. We defined early SE-BSI as a positive blood culture within the first 48 hours after ICU admission. An SE-BSI associated with significant hemodynamic consequence was defined as the need for norepinephrine initiation or increase in at least 0.1 µg/kg/min. Antibiotic susceptibilities were assessed using the disk diffusion method according to the guidelines of the European Committee on Antimicrobial Susceptibility Testing. The complete methods are detailed in the Supplementary Material.

Results

Study population

We included 59 patients with proven SE-BSI. A total of 53% (n = 31) of SE bacteremia occurred within the first 48 hours after ICU admission (early group). The baseline characteristics of the study population are summarized in Table 1, according to the significant hemodynamic consequence of SE-BSI or not. Patients were 58% male (n = 34), with a median age of 67 (60–74) years, and had a median simplified acute physiology score II of 59 (36–74) points. Most patients were immunocompromised (56%; n = 33), including 44% patients with active cancers (n = 26) and 17% with organ transplant (n = 10). The median lymphocyte count was 0.61 G/l (0.34–0.96) and nine patients (15%) presented with neutropenia. Patients had a history of cardiovascular disease in 47% of cases (n = 28) and 39% had diabetes (n = 23).

Staphylococcus epidermidis bloodstream infection hemodynamic consequences

Of the 59 patients with SE-BSI, 63% (n = 37) required the initiation or increment of norepinephrine dose of at least 0.1 µg/kg/min at the time of positive blood cultures. Patients requiring norepinephrine initiation or increment also had higher arterial lactate level at the onset of bacteremia, at 2.8 (1.9–5.8) versus 1.5 (1.3–2.2) mmol/l ($P < 0.01$), and a significantly lower mean blood pressure (49 [42–54] vs 61 [56–65] mm Hg [$P = 0.01$]). Patients with a hemodynamic consequence of SE-BSI required more invasive mechanical ventilation at the time of bacteremia (49% [n = 18] vs 18% [n = 4]; $P = 0.03$) and displayed a higher mortality, reaching 46% (n = 17) versus 14% (n = 3) at day 28 ($P = 0.01$).

Invasive devices

All but one patient had a central venous access device during their ICU stay, mostly inserted into the jugular vein (76%; n = 45). A total of 47% (n = 28) of patients had a dialysis catheter. Central venous catheter was removed in 53 patients, among which 25% (n = 13) were implantable venous access devices and peripheral intravenous central catheters. There were more implantable venous access devices and peripheral intravenous central catheters removed in the early group (44%, n = 11/25) than in the late group (7%, n = 2/28; $P < 0.01$).

Microbiological findings and antibiotics

The median time to positivity of blood cultures was 22.3 (17.0–27.6) hours. The rates of antibiotic resistance toward methicillin, gentamicin, and linezolid were 86% (n = 51/59), 71% (n = 42/59), and 29% (n = 17/58), respectively (Table 2). No strain was resistant to vancomycin. Vancomycin was used to treat SE-BSI in 64% (n = 38) of the patients. At a median starting dose of 2 (2–3) g/day, the maximal vancomycin serum concentration during the whole course of treatment reached a median of 39 (31–49) mg/l (Supplementary Material).

Discussion

To the best of our knowledge, this is one of the first works dealing with SE-BSIs in medical ICU patients not focusing on postoperative infections. Of major importance, our data show a high rate of hemodynamic failure at the time of SE-BSI. They also reinforce the importance of immunosuppression and of central venous access devices on the risk of developing an SE-BSI. In addition, our work confirms the concerns raised about resistance to oxazolidinones.

Our 59-patient series supports SE's ability to induce septic shock, contrasting with its often-described low virulence [5]. Septic shock is exceptionally mentioned in case reports [9]. Our patients requiring norepinephrine during BSI, without any detectable concurrent infection, also have a lower mean blood pressure and higher arterial lactate levels, meeting the Sepsis-3 diagnostic criteria for septic shock in most cases. Moreover, the mortality is higher in these patients with septic shock.

We remain cautious about the causality of septic shock. Our study is retrospective, which is its main limitation. Other concomitant culture-negative sepsis cannot be definitively excluded. However, SE's ability to induce septic shock is credible. Certain strains are superantigen-producing, which has been demonstrated for toxic shock syndrome toxin-1 [9] and enterotoxins A, B, C or C-like, G, and I; some works have developed a strong argument in favor of a genetic exchange from *Staphylococcus aureus* to SE [10].

Table 1

Characteristics of patients at baseline and at the time of blood cultures positive for *Staphylococcus epidermidis* according to the occurrence of hemodynamic instability.

n =	All patients	Hemodynamic instability ^a	No hemodynamic instability ^a	P-value
General characteristics				
Men	34 (58%)	20 (54%)	14 (64%)	0.47
Age (years)	67 (60–74)	67 (62–75)	66 (57–70)	0.32
Simplified acute physiology score II	59 (36–74)	61 (35–78)	54 (40–74)	0.87
Intensive care unit mortality	19 (32%)	16 (43%)	3 (14%)	0.02^F
Immunocompromised	33 (56%)	22 (59%)	11 (50%)	0.59
Active cancer	26 (44%)	16 (43%)	10 (45%)	0.87
Organ transplant	10 (17%)	6 (16%)	4 (18%)	1 ^F
Clinical presentation at time of positive blood culture				
Maximal temperature ^b (°C)	38.2 (37.5–38.8)	38.3 (37.5–39.0)	38.0 (37.5–38.7)	0.95
Mean blood pressure ^b (mmHg)	53 (48–60)	49 (42–54)	61 (56–65)	0.01
Systolic blood pressure ^b (mmHg)	79 (68–88)	74 (63–83)	92 (82–99)	<0.01
Sepsis-related organ failure assessment ^b	8 (6–13)	11 (6–15)	6 (3–10)	<0.01
Early bacteremia ^c	31 (53%)	23 (62%)	8 (36%)	0.06
Treatment changes related to bloodstream infection				
Norepinephrine ^a	37 (63%)	37 (100%)	0 (0.0%)	-
Mechanical ventilation ^d	22 (37%)	18 (49%)	4 (18%)	0.03^F
Modification of antibiotics	49 (83%)	33 (89%)	16 (73%)	0.15 ^F
Catheter withdrawal	53 (90%)	31 (84%)	22 (100%)	0.07 ^F
Positive catheter culture	22/53 (42%)	15/31 (48%)	7/22 (32%)	0.27
Biology at time of positive blood culture				
White blood cells (10 ⁹ /l) ^b	10.1 (5.6–13.8)	10.5 (6.8–15.6)	8.5 (5.2–12.7)	0.34
Lactate (mmol/l) ^b	2.2 (1.4–3.7)	2.8 (1.9–5.8)	1.5 (1.3–2.2)	<0.01
C-reactive protein (mg/l) ^b	107 (59–188)	125 (86–209)	75 (29–125)	0.04
Procalcitonin (µg/l) ^b	2.7 (1.4–8.5)	3.2 (1.3–9.0)	1.9 (1.8–3.6)	0.61

Footnotes: Results are expressed in n (%) or median (interquartile range 25–75), F: Fisher's exact Test.

^a Hemodynamic instability concomitant with blood cultures positive for *S. epidermidis* and defined by the implementation, resumption, or re-increment of norepinephrine of at least 0.1 µg/kg/min;

^b Most pejorative values within 24 hours of first blood culture positive for *S. epidermidis*;

^c First blood culture positive for *S. epidermidis* within 48 hours of intensive care unit admission;

^d Reintubation and/or resumption of invasive mechanical ventilation.

Table 2

Microbiological data of *Staphylococcus epidermidis* bacteremia according to the occurrence of concomitant hemodynamic instability.

n =	All patients	Hemodynamic instability ^a	No hemodynamic instability ^a	P-value
Resistances of <i>S. epidermidis</i> strains				
Vancomycin-R ^b	0/54 (0%)	0/34 (0%)	0/20 (0%)	1 ^F
Teicoplanin-R ^b	4/39 (10%)	2/23 (9%)	2/16 (13%)	1 ^F
Pristinamycin-R	8/58 (14%)	4/36 (11%)	4/22 (18%)	0.45 ^F
Rifampicin-R	9/59 (15%)	3/37 (8%)	6/22 (27%)	0.04^F
Linezolid-R	17/58 (29%)	10/36 (28%)	7/22 (32%)	0.74
Fosfomycin-R	23/55 (42%)	13/35 (37%)	10/20 (50%)	0.35
Clindamycin-R	34/59 (58%)	21/37 (57%)	13/22 (59%)	0.86
Fusidic acid-R	34/59 (58%)	18/37 (49%)	16/22 (73%)	0.07
Trimethoprim-sulfamethoxazole-R	39/59 (66%)	23/37 (62%)	16/22 (73%)	0.41
Erythromycin-R	39/59 (66%)	28/37 (76%)	11/22 (50%)	0.04
Gentamicin-R (KTG phenotype)	42/59 (71%)	24/37 (65%)	18/22 (82%)	0.16 ^F
Tobramycin-R (KT phenotype)	43/59 (73%)	25/37 (68%)	18/22 (82%)	0.23 ^F
Amikacin-R (K phenotype)	44/59 (75%)	26/37 (70%)	18/22 (82%)	0.32 ^F
Levofloxacin-R	49/59 (83%)	29/37 (78%)	20/22 (91%)	0.29 ^F
Methicillin-R	51/59 (86%)	30/37 (81%)	21/22 (95%)	0.24 ^F

Footnotes: Results are expressed in n (%). F: Fisher's exact test.

Abbreviations: R, resistant.

^a Hemodynamic instability concomitant with blood cultures positive for *S. epidermidis* and defined by the implementation, resumption, or re-increment of norepinephrine of at least 0.1 µg/kg/min;

^b Vancomycin and teicoplanin minimum inhibitory concentration are detailed in the Supplementary Material.

Through horizontal gene transfers, SE also evolves genetically along with host-related factors, and immunosuppression helps transform SE from a commensal agent into an opportunistic pathogen [1]. The high incidence of SE-BSI in oncological patients [6] and in solid-organ transplant recipients [7] has been previously described [2] and could explain the observed lymphopenia.

The interest in SE is reinforced by the expansion of antibiotic resistances in ICUs, with our 29% linezolid resistance being consistent with the literature [8]. Of note, most patients experienced an overdose of vancomycin during treatment, exposing them

to nephrotoxicity, and raising concerns about the relatively small therapeutic arsenal against methicillin-resistant strains.

Finally, invasive devices play a key role in the pathogenesis of SE-BSIs. Therefore, CNS rank first in ICU-acquired central line-associated BSIs according to the European Centre for Disease Prevention and Control, with SE ranking first in immunocompromised patients, which is in agreement with our results.

Altogether, this work raises several perspectives. A prospective study is needed to further investigate host-related factors, such as lymphopenia. In parallel, the factors associated with SE and its

virulence, including the production of toxins, must be studied. Ultimately, these data should lead to clinical trials aimed at testing new anti-infectious strategies against SE-BSIs.

Declarations of competing interest

The authors have no competing interests to declare.

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Ethical approval

Data were collected in accordance with the advice of the local academic ethics committee (Reference: CE-2022-13).

Author contributions

All authors participated in the writing and editing of the manuscript. RCJ, PM, MS, JK, JH, and FM included the patients. RCJ, HM and JD performed the statistical analyses. AG and TL performed the microbiological analyzes.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.ijid.2023.07.014](https://doi.org/10.1016/j.ijid.2023.07.014).

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