Coagulase-negative Staphylococcus bacteraemia accounts for one third of Staphylococcus bacteraemia in a French university hospital

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ORIGINAL ARTICLE

Coagulase-negative Staphylococcus bacteraemia accounts for one third of Staphylococcus bacteraemia in a French university hospital

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Abstract

Background: We sought to determine the epidemiological patterns of Staphylococcus bacteraemia, with a focus on the proportion of coagulase-negative Staphylococcus (CoNS) as compared to Staphylococcus aureus bacteraemia, and the prognosis. *Methods:* All patients with significant Staphylococcus bacteraemia at the university hospital in Reims in 2008 were included in the study. Data were retrieved retrospectively from the patient records using a standardized case investigation form. Quantitative variables were compared using the Mann–Whitney *U*-test and qualitative variables were compared using Fisher's exact test or Pearson's Chi-square test, as appropriate. Bivariate logistic regression was performed on both S. aureus and CoNS bacteraemia. All variables with a *p*-value of < 0.15 were entered into a multiple logistic regression model. *Results:* CoNS represented 31.6% of all strains isolated. The methicillin resistance rate was higher in CoNS (66.1%) than in S. aureus (19.1%) ($p < 0.0001$). CoNS were more frequently associated with intravascular catheters and neoplastic disease, whereas S. aureus was associated with chronic renal failure ($p < 0.0001$) and diabetes mellitus ($p = 0.004$). Mortality was 30.7% for S. aureus and 19.6% for CoNS bacteraemia ($p = 0.12$). Methicillin resistance was not associated with mortality ($p = 0.99$). Factors independently associated with mortality in CoNS and S. aureus bacteraemia were age and acute renal failure. The presence of severe sepsis/septic shock was only associated with mortality in S. aureus bacteraemia. *Conclusions:* CoNS represent one third of Staphylococcus bacteraemia. The mortality difference between CoNS and S. aureus bacteraemia was not statistically significant. Acute renal failure is associated with mortality in both S. aureus and CoNS bacteraemia.

Keywords: *Bacteraemia, coagulase-negative Staphylococcus, epidemiology, acute renal failure*

Introduction

There are numerous reports of infections due to methicillin-resistant Staphylococcus aureus (MRSA) in the USA [1,2]. The prevalence of MRSA is very different in Europe, with extreme differences between countries and facilities: from 2% [3] to 43% [4] of all Staphylococcus aureus bacteraemia.

The incidence of infective endocarditis (IE) due to S. aureus is also increasing [5], as well as the incidence of IE due to coagulase-negative Staphylococcus (CoNS) in the USA [6] and in Europe [7].

New anti-staphylococcal treatments have been developed because of the emergence of severe infections due to MRSA and because of reports of vancomycin treatment failure [8,9].

CoNS are known to be frequently less sensitive to vancomycin than S. aureus [10], but the prognosis for CoNS appears better than for S. aureus in meningitis [11,12] and endocarditis [7]. Little data exist comparing the mortality of CoNS bacteraemia with S. aureus bacteraemia [13], and the predictive factors for mortality are less well known in CoNS bacteraemia [14] than in S. aureus bacteraemia [15,16]. No predictive factors of complicated CoNS bacteraemia have been identified, although they have been investigated for S. aureus bacteraemia [17,18].

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We sought to determine the epidemiological patterns of Staphylococcus bacteraemia, with an emphasis on the proportion of CoNS bacteraemia as compared to S. aureus bacteraemia, and the prognosis of CoNS bacteraemia.

Methods

Materials

This study was conducted retrospectively in 2008 in a 1549-bed university hospital in Reims, France. All patients with significant bacteraemia in the adult surgery, medicine, and intensive care units (926 beds) were included. A significant bacteraemia was defined in the presence of 1 blood culture positive for S. aureus. For CoNS, bacteraemia was considered significant when criterion 2 of the definition of a laboratory-confirmed bloodstream infection as per the US National Nosocomial Infections Surveillance System and the National Healthcare Safety Network [2] was fulfilled (e.g. fever and 2 blood cultures drawn on separate occasions positive for CoNS, or fever and 1 blood culture from a central line positive for CoNS, with favourable outcome under appropriate antimicrobial therapy and no other argument for infection at another site).

Blood culture processing

Blood culture bottles were incubated on the BacT/ALERT 3D system (bioMérieux, Marcy l'Etoile, France). Positive bottles containing Gram-positive cocci in clusters were inoculated onto S. aureus ID select agar (SAID; bioMérieux) and sheep blood agar plates (Oxoid, Dardilly, France). After 18–24 h incubation at 37°C, bacterial colonies were further tested using the catalase test (bioMérieux), the Pastorex test (Bio-Rad, Marnes-la-Coquette, France), and the Vitek2 (bioMérieux) microbial identification system.

All bacterial growth identified on blood agar plates was further examined using antimicrobial susceptibility testing by the disk diffusion method, performed with an inoculum of 10^6 CFU/ml on Mueller–Hinton agar plates, in accordance with the recommendations of the Antibiogram Committee of the French Microbiology Society (CA-SFM) [19].

Detection of the *mecA* gene was performed using a polymerase chain reaction (PCR) as the methicillin resistance gold standard for all strains isolated.

Vancomycin minimum inhibitory concentrations (MICs) were determined by E-test method (bioMérieux) following the manufacturer's instructions.

Data collection

Demographic, epidemiological, clinical, and laboratory data were recovered retrospectively from the patient records, using a standardized case investigation form.

Definitions

Comorbidity corresponded to the presence of a pre-existing ongoing illness.

Immunodepression was defined as the presence of a primary or secondary immune deficiency (human immunodeficiency virus infection, solid organ transplant, malignant neoplasm treated or not, autoimmune disease, immunosuppressive agent, diabetes mellitus, renal insufficiency, liver cirrhosis, asplenia, obesity, under-nutrition, and chronic alcoholism).

Foreign material was defined as the presence of osteosynthesis material, an orthopaedic or valvular prosthesis, pace-maker device, central venous catheter, implantable chamber, surgical wound drain device, or urinary catheter.

The Charlson weighted comorbidity index and the criteria for sepsis, severe sepsis, and septic shock have been detailed elsewhere [20,21].

A bacteraemia was nosocomial when it occurred more than 48 h after admission. Healthcare-related bacteraemia has been defined elsewhere [22]. All other bacteraemia was community-acquired.

Intravascular catheter-related infection has been defined elsewhere [23].

A secondary site of infection corresponded to the presence of another site of infection due to the same Staphylococcus species, remote from the primary site of infection. Septic thrombosis was included as a secondary site of infection.

IE was defined using the modified Duke criteria [24].

All in-hospital deaths were attributed to the Staphylococcus bacteraemia.

Acute renal failure was defined as a 50% increase in the serum baseline creatinine level.

Statistical analysis

Quantitative variables were compared using the Mann–Whitney *U*-test and qualitative variables were compared using Fisher's exact test or Pearson's Chi-square test, as appropriate.

Bivariate logistic regression was performed on both S. aureus and CoNS bacteraemia. All variables with a p-value of < 0.15 were entered into a multiple logistic regression model. Statistical analyses were performed using Statview 5.0 software (SAS institute).

Results

Incidence

Two hundred and seven significant Staphylococcus bacteraemia episodes were observed in patients

hospitalized in the adult surgery, medicine, and intensive care units of the university hospital of Reims in 2008, giving an incidence of Staphylococcus bacteraemia of 2.74 per 1000 admissions. The incidence density was 0.77 per 1000 patient-days. One hundred and twenty-four episodes of bacteraemia were diagnosed in medicine units (59.9%), 51 in surgery units (24.6%), and 32 in intensive care units (15.5%).

Population characteristics

Patient records were unavailable for 6 patients. Population ($n = 201$) characteristics are shown in Table I. The most frequently retrieved sources of infection were intravascular catheters (58.3%), skin and soft tissues (17.9%), and surgical site infections (11.2%). The most frequent secondary sites of infection were osteoarticular (43.2%), septic thrombosis (35.2%), and cerebral emboli (8.1%).

Bacteriology

Two hundred and six Staphylococcus strains were isolated from 201 patients. CoNS represented 31.6% of all strains; the incidence of CoNS bacteraemia was 0.86 per 1000 admissions and the incidence density was 0.23 per 1000 patient-days. Of the CoNS, Staphylococcus epidermidis was the most frequently isolated species (90.7%). Staphylococcus warneri, Staphylococcus capitis, Staphylococcus haemolyticus, and Staphylococcus hominis accounted for the remaining 9.3%.

Thirty-four percent of Staphylococcus isolates were methicillin-resistant. The methicillin resistance rate was higher in CoNS (66.1%) than in S. aureus (19.1%) ($p < 0.0001$). Vancomycin MICs were determined only for 53 Staphylococcus strains (Table II). Sixty percent of S. aureus strains tested and 96.9% of CoNS strains tested had a vancomycin MIC of 2 mg/l or more. The median vancomycin MIC was 2 mg/l.

Outcome

The in-hospital mortality was 27.3% ($n = 55$). One hundred and forty patients experienced S. aureus bacteraemia and 43 died during hospitalization. The mortality rate was 30.7% for S. aureus bacteraemia. Factors significantly associated with mortality in S. aureus bacteraemia are shown in Table III.

Sixty-one patients experienced CoNS bacteraemia and 12 died during hospitalization (missing data = 1), giving a mortality rate of 19.6%. The difference

Table I. Population characteristics of the 201 patients who experienced Staphylococcus aureus and coagulase-negative Staphylococcus (CoNS) bacteraemia.

	S. aureus	CoNS	*p*-Value
Number of patients (%)	140 (100%)	61 (100%)	
Male	97 (69.2%)	45 (73.7%)	0.52
Comorbidity	134 (95.7%)	60 (98.3%)	0.67[a]
Immunodepression	113 (80.7%)	50 (81.9%)	0.83
Charlson weighted index of comorbidity > 3	83 (59.2%)	24 (39.3%)	0.009
Cardiac valvulopathy	39 (27.8%)	24 (39.3%)	0.10
Foreign material	63 (45.0%)	36 (59.0%)	0.06
Intravenous drug user	3 (2.1%)	1 (1.6%)	0.99[a]
Haematology ward hospitalization	5 (3.5%)	25 (40.9%)	< 0.0001
Neoplasm antecedent	37 (26.4%)	38 (62.3%)	< 0.0001
Chronic kidney disease antecedent	53 (37.8%)	3 (4.9%)	< 0.0001
Diabetes mellitus antecedent	54 (38.5%)	11 (18.0%)	0.004
Mean age (range), y	67.3 (22–96)	61.2 (16–86)	0.008
Mean Charlson weighted index of comorbidity (range)	3.34 (0–11)	2.72 (0–10)	0.08
Mean creatinine at time of admission[b] (range), µmol/l	154.6 (23–672)	87.3 (29–311)	0.01
Community-acquired	21 (15.0%)	8 (13.1%)	0.72
Healthcare-related	35 (25.0%)	12 (19.7%)	
Nosocomial	84 (60.0%)	41 (67.2%)	
Presence of septic shock or severe sepsis criteria	26 (18.5%)	5 (8.2%)	0.06
Definite source of bacteraemia	104 (74.2%)	47 (77.0%)	0.67
Catheter as a source of bacteraemia	35 (25.0%)	40 (65.5%)	< 0.0001
Skin infection as a source of bacteraemia	27 (19.2%)	1 (1.6%)	0.0009
Secondary site of infection	26 (18.5%)	11 (18.0%)	0.92
Infective endocarditis (IE)	6 (4.3%)	5 (8.2%)	0.31[a]

[a]Fisher's exact test.
[b]Data missing for 20 patients.

Table II. Vancomycin median minimum inhibitory concentration (MIC) for the 53 Staphylococcus strains tested in 2008.

	Number of strains	Vancomycin median MIC (mg/l)	Vancomycin MIC range mg/l
Staphylococcus	53	2	0.75–4
Methicillin-resistant strains	41	2	0.75–4
Staphylococcus aureus	20	2	0.75–2
MSSA	8	1.5	1–2
MRSA	12	2	0.75–2
CoNS	33	2	1.5–4
MSCoNS	4	2.5	2–3
MRCoNS	29	2	1.5–4

MSSA, methicillin-sensitive Staphylococcus aureus; MRSA, methicillin-resistant Staphylococcus aureus; CoNS, coagulase-negative Staphylococcus; MSCoNS, methicillin-sensitive coagulase-negative Staphylococcus; MRCoNS, methicillin-resistant coagulase-negative Staphylococcus.

between CoNS and S. aureus mortality did not reach significance ($p = 0.12$). Factors significantly associated with mortality in CoNS bacteraemia are shown in Table III.

The multiple logistic regression model is shown in Table IV.

Discussion

CoNS were found to represent one third of all Staphylococcus bacteraemia in the Reims hospital. This rate is important because there is no consensus concerning the management of CoNS bacteraemia. CoNS are always among the 4 most frequently isolated pathogens in bloodstream infections [25–28], but there are great differences between European countries. Another study from France [25], a country where the MRSA prevalence is high according to the European Antimicrobial Resistance Surveillance System (EARSS) data, reported a higher incidence of CoNS than S. aureus bacteraemia during the period 2005–2007. The definition of CoNS bacteraemia was not the same as that used in the present study, and the CoNS bacteraemia incidence was probably overestimated because skin contaminants were considered as genuine bacteraemia. A nationwide study from Finland [26], which is a country with a low prevalence of MRSA, reported an equal incidence of CoNS and S. aureus bacteraemia; however, the incidence of CoNS increased above that of S. aureus when only nosocomial bloodstream infections were taken into account [27]. Such data have been reported by Bourneton and colleagues [25], but we were not able to demonstrate a difference between the incidence of CoNS and S. aureus in nosocomial bacteraemia in our study. Finally, a recent nationwide study in England [28] reported that CoNS bacteraemia has constantly increased in incidence as compared to S. aureus bacteraemia since 2006, which suggests a major change in the epidemiology of Staphylococcus bacteraemia. Such data should be confirmed using a strict definition of CoNS bacteraemia [2].

Table III. Factors associated with mortality among patients experiencing Staphylococcus bacteraemia.

	Staphylococcus aureus				Coagulase-negative Staphylococcus			
Factor	Deceased patients ($n = 43$)	Survivors ($n = 97$)	Missing data	p-Value	Deceased patients ($n = 12$)	Survivors ($n = 48$)	Missing data	p-Value
Age, y	74.9	63.9	0	0.001	70.7	58.8	0	0.01
Charlson weighted index of comorbidity ≥ 3	30/43 (69.7%)	53/97 (54.6%)	0	0.09	6/12 (50.0%)	18/48 (37.5%)	1	0.51[a]
Community-acquired	8/43 (18.6%)	13/97 (13.4%)	0	0.42	1/12 (8.3%)	7/48 (14.6%)	1	0.99[a]
Presence of a secondary site of infection	11/43 (25.6%)	15/97 (15.4%)	0	0.15	2/12 (16.6%)	9/48 (18.7%)	1	0.99[a]
Presence of infective endocarditis (IE)	3/43 (6.9%)	3/97 (3.1%)	0	0.37[a]	2/12 (16.6%)	3/48 (6.2%)	1	0.25[a]
No definite source of bacteraemia	16/43 (37.2%)	20/97 (20.6%)	0	0.038	3/12 (25.0%)	10/48 (20.8%)	1	0.71[a]
Severe sepsis/septic shock	14/43 (32.5%)	12/97 (12.3%)	0	0.004	1/12 (8.3%)	4/48 (8.3%)	1	0.99[a]
Acute renal failure	28/42 (66.6%)	36/96 (37.5%)	2	0.001	9/12 (75.0%)	17/48 (35.4%)	1	0.01
Methicillin resistance	10/43 (23.2%)	17/97 (17.5%)	0	0.42	9/12 (75.0%)	33/48 (68.7%)	1	0.67

[a]Fisher's exact test.

Table IV. Factors significantly associated with mortality in the logistic regression model.[a]

		Multivariate analysis		
Staphylococcus aureus + CoNS	Bivariate analysis *p*-Value	OR	95% CI	*p*-Value
Age	<0.0001	1.04	1.01–1.07	0.001
Charlson weighted index of comorbidity ≥ 3	0.038	1.06	0.51–2.24	0.86
Community acquired	0.64			
Presence of secondary site of infection	0.25			
Presence of infective endocarditis (IE)	0.18			
No definite source of bacteraemia	0.04	1.81	0.83–3.96	0.13
Severe sepsis/septic shock	0.006	3.02	1.25–7.28	0.013
Acute renal failure	0.0001	3.06	1.49–6.25	0.002
CoNS species	0.12	0.86	0.38–1.95	0.71
Methicillin resistance	0.99			

CoNS, coagulase-negative Staphylococcus; OR, odds ratio; CI, confidence interval.
[a]The Hosmer and Lemeshow goodness of fit test gives $p = 0.39$.

The main limitations of this study are that it was carried out at a single centre and that the data were collected retrospectively, which may explain the low rate of IE and secondary sites of infection. The inclusion criteria for CoNS were very strict and we may have missed genuine cases of CoNS bacteraemia with only 1 positive blood culture.

Population characteristics

Patients experiencing CoNS bacteraemia were younger, had lower creatinine on admission, and less frequently had a Charlson weighted comorbidity index over 3 than patients with S. aureus bacteraemia. However, the Charlson weighted comorbidity index has not been validated for CoNS bacteraemia. The presence of an indwelling catheter is more frequently noted among patients with CoNS bacteraemia. CoNS are known for their pathogenesis in catheter-related infections [29]. The presence of an indwelling catheter is probably the reason why CoNS were more frequently isolated in the haematology ward and in patients with neoplasms in our study.

Bacteriology

S. epidermidis was the most frequently isolated CoNS, as previously reported [6]. CoNS were found to represent more than half of the methicillin-resistant strains in our facility. The methicillin resistance rate in S. aureus was only 19%. This value is far higher than the 2% rate reported in the study by Kaech et al. [3], but lower than the 43% rate in the study by Libert et al. [4]. This means that in our facility, methicillin class penicillin should be the reference treatment for 80% of the strains of S. aureus isolated. Methicillin class penicillin has been proven superior to vancomycin in methicillin-sensitive S. aureus (MSSA) bacteraemia [16,30]. There are no similar data available for CoNS bacteraemia.

Despite a very small sample size, the vancomycin MICs were far higher in our hospital than those reported from different countries. Seventy-five percent of MRSA had a vancomycin MIC ≥ 2 mg/l ($n = 9/12$), which is far higher than the rates of 9.7% ($n = 9/92$) [8] and 22.2% ($n = 92/414$) [9] reported in the literature. This means that the majority of our patients with MRSA bacteraemia are potentially at risk of vancomycin failure [8,9]. In this situation some authors suggest an increase in the dosage of vancomycin, as has been recommended in pneumonia [31]. However a high dosage vancomycin regimen exposes the patient to an increased risk of nephrotoxicity [32–34] and is not always associated with a better outcome [35]. In this situation, the new anti-staphylococcal drugs should be considered [36–38]. Ninety-six percent of methicillin-resistant CoNS had a vancomycin MIC of ≥ 2 mg/l ($n = 28/29$), which is also well above the rate of 53.3% found by Jones ($n = 3148/5902$) [10]. There are no specific data available concerning the management of such CoNS bacteraemia.

All these data concerning vancomycin MICs should be interpreted with caution: vancomycin MICs were determined for only 53 strains, because routine vancomycin MIC determination was not fully implemented in 2008. Thus too many data were missing, and taking into account vancomycin MICs when establishing risk factors for mortality would have been a selection bias.

Outcome

The in-hospital mortality rate was 30% for S. aureus bacteraemia as reported by Chang et al. [18]. Age, the presence of severe sepsis or septic shock, and the presence of acute renal failure have previously been reported [3] as risk factors for mortality in S. aureus bacteraemia. However, we used a different definition

of acute renal failure: a 50% increase in serum creatinine in our study versus an only 20% increase in the study of Kaech et al. [3]. A Charlson weighted index of comorbidity of ≥ 3 was not significantly associated with mortality in our study. This may be due to a sampling bias. Methicillin resistance was also not associated with mortality during S. aureus bacteraemia. Some of the studies included in the meta-analysis by Cosgrove and colleagues [15] found a similar result, however the pooled odds ratio was 1.93 (95% confidence interval (CI) 1.54–2.42) when MRSA and MSSA bacteraemia mortality were compared.

The in-hospital mortality was 19.6% for CoNS in our study. Data in the literature concerning mortality for CoNS bacteraemia show that mortality varies between 4.9% and 28% [39,40].

CoNS bacteraemia was found not to be significantly associated with a lower mortality when compared with S. aureus ($p = 0.12$), and CoNS species does not appear to be a predictive factor of mortality in our multivariate analysis combining S. aureus and CoNS bacteraemia. Data in the literature comparing the mortality from CoNS and that from S. aureus bacteraemia are scarce. Danese and colleagues [13] reported an odds ratio of 0.8 (95% CI 0.66–0.94) when comparing mortality due to CoNS and mortality due to S. aureus bacteraemia in haemodialysis patients. However, there were no differences in the in-hospital mortality between CoNS and S. aureus native valve endocarditis [6].

The factors associated with mortality among patients with CoNS bacteraemia are very different from those observed in S. aureus bacteraemia. Only age and acute renal failure were found to be common to S. aureus and CoNS bacteraemia. The presence of severe sepsis or septic shock was not found to be correlated with mortality in CoNS bacteraemia in our study, and we did not confirm the results obtained by Topeli and colleagues [14]. The deleterious role of acute renal failure in CoNS bacteraemia has only been reported once, in a study focusing on CoNS endocarditis [7].

In the multivariate analysis, CoNS were pooled with S. aureus and CoNS species was tested in that model. Multivariate analysis with patients experiencing CoNS bacteraemia only was not performed because of the relatively small number of patient deaths in CoNS bacteraemia. Factors independently associated with mortality in CoNS bacteraemia should be determined in studies with larger sample sizes.

This article provides data on the specific epidemiological features observed in our hospital, with a high proportion of CoNS bacteraemia (one third of all Staphylococcus bacteraemia). The CoNS strains were more frequently methicillin-resistant. A high vancomycin MIC of > 2 mg/l was frequently observed among tested strains.

The mortality rate was not statistically lower in CoNS bacteraemia when compared to S. aureus bacteraemia. Acute renal failure was found to be associated with mortality in both S. aureus and CoNS bacteraemia. More studies are needed concerning prognostic factors and the management of CoNS bacteraemia, as previously done for S. aureus [35,38].

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