Bloodstream infections as a marker of community-acquired sepsis severity. Results from the Portuguese community-acquired sepsis study (SACiUCI study)

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Abstract

The impact of bloodstream infection (BSI) on admission to hospital on the outcome of patients with community-acquired sepsis (CAS) admitted to intensive-care units (ICU) is largely unknown. We selected 803 adult patients consecutively admitted with CAS to one of 17 Portuguese ICU, in whom blood cultures were collected before initiation of antibiotic therapy during a 12-month period. A BSI was identified on hospital admission in 160 (19.9%) patients. Those with and without BSI had similar mean Simplified Acute Physiology Score (SAPS) II and age. The presence of BSI was independently associated with mortality in ICU (adjusted odds ratio 1.86; 95% confidence interval 1.20–2.89; p 0.005). On the 4th day in ICU, patients with BSI were found to be significantly more dependent on vasopressor support (p 0.002) but not on ventilatory support. Cumulative ICU mortality was significantly higher in BSI patients from the 9th day onwards. A seasonal variation of BSI isolates was noted: gram-negative BSI were more common in the summer, whereas in the winter, gram-positive infections were more frequent (p 0.024), without mortality differences.

Keywords: Blood cultures, bloodstream infection, community-acquired sepsis, intensive-care unit, septic shock
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Introduction

Despite great advances in the understanding of its pathophysiology, severe sepsis remains associated with high mortality, morbidity and costs [1]. Microbiological documentation, particularly of bloodstream infections (BSI), occurs in only a fraction of patients with community-acquired sepsis (CAS) [2].

The Surviving Sepsis Campaign guidelines [3] reinforce the need for obtaining blood cultures before starting antibiotic therapy in patients with CAS and with a high risk of dying to identify the causative microorganism and target antibiotic therapy. Our group, the SACiUCI (*Sepsis Adquirida na Comunidade e internada em Unidade de Cuidados Intensivos*) study group, had already shown that performing blood cultures in patients with severe sepsis and septic shock was independently associated with improved survival [4].

Hospital-acquired BSI is associated with excess length of stay, extra costs and excess mortality in critically ill patients [5]. However, data on BSI in patients with CAS is scarce. Furthermore, it is not known if the presence of a BSI by itself, complicating an identifiable focus of CAS, e.g. pneumonia or peritonitis, increases the risk of death.

In this study, we evaluate the impact of BSI on the mortality of patients with severe CAS.

Methods

The SACiUCI study is a prospective, multi-centre, observational study designed to evaluate the epidemiology of CAS in

patients admitted to Portuguese intensive-care units (ICUs). A detailed description of the study has been previously published [4,6,7]. Briefly, all patients older than18 years, newly admitted to the 17 participating ICUs, were consecutively enrolled during a 12-month period and followed up until death or hospital discharge. The study design was approved by the local Hospital Ethics Committees. Informed consent was waived because of the study's observational nature.

Patients with CAS, defined as the onset of infection before hospital admission or not present at admission but that became evident in the first 48 h, were eligible for further analyses. Presence of sepsis, severe sepsis or septic shock was defined according to the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference criteria [8]. The presence of healthcare-associated infection (HCAI) was defined at hospital admission according to the presence of the following criteria: home infusion therapy or wound care; chronic dialysis or chemotherapy within 30 days; hospitalization for 2 days or more in the preceding 90 days; residence in a nursing home or extended-care facility [9]. Episodes of CAS were divided according to the primary infection focus. All data were managed by the Department of Biostatistics and Medical Informatics at the University of Porto, where a dedicated database for SACiUCI had been created.

All patients consecutively admitted with CAS who had blood cultures collected before initiation of antibiotic therapy constituted our study population. Data collection included demographic data and co-morbid diseases, clinical and laboratory data from hospital admission to the 5th ICU day (including C-reactive protein and temperature). The Simplified Acute Physiology Score (SAPS) II was computed for all included patients [10]. The days of ICU and hospital discharge were recorded. Microbiological and clinical infectious data were reported, along with the antibiotics prescribed. The microorganism's sensitivity to the antibiotics prescribed on the day of hospital admission was available in 343 of the 364 patients with positive microbiological cultures. Blood culture collection on the day of hospital admission and its results were closely scrutinized. Blood cultures with isolated microorganisms considered most likely to be contaminants were considered negative for further analyses. Patients' ICU and hospital outcomes, either discharge or death, were our primary outcome measures. Comparison between survivors and non-survivors was performed.

Statistical analysis

A single investigator in each participating centre performed data entry. Consistency of data was assessed with a rechecking procedure of a 10% random sample of patients (see Acknowledgements). Data were screened in detail (see Acknowledgements) for missing information and for implausible and outlying values.

Continuous variables were expressed as median (interquartile range) or mean ± SD according to data distribution. Comparisons between groups were performed with two-tailed unpaired Student's *t* test or Mann–Whitney *U* test for continuous variables according to data distribution. Fisher's exact test and chi-squared test were used to test association between categorical variables as appropriate.

A multiple logistic regression was fitted to assess the impact of BSI on mortality in patients with CAS, adjusting for age, SAPS II, sepsis severity, the presence of HCAI, and primary infection focus. Adjusted odds ratios (AOR) with 95% CI were computed.

The Hosmer and Lemeshow test was used to check goodness-of-fit.

Cumulative mortality for each day in the ICU was calculated for CAS patients either with or without BSI.

Data were analysed using PASW Statistics v.18.0 for Mac (SPSS, Chicago, IL, USA). All statistics were two-tailed, and significance level was defined as $p < 0.05$.

Results

General description and outcomes

A total of 897 patients with CAS were included. In 94 patients, blood cultures were not performed on the day of hospital admission, resulting in 803 patients for analysis (age 58.4 ± 17.8 years; 65.3% male). At ICU admission their mean score on SAPS II was high, 47.9 ± 17.9, and 51% of the patients were in septic shock (Table 1). The overall ICU and hospital mortalities were 29% and 37%, respectively.

In 160 patients with CAS (19.9%) blood cultures returned positive. Patients with and without BSI had similar mean age and SAPS II. Nevertheless, the rate of septic shock at ICU admission was higher in patients with BSI (Table 1), although not reaching statistical significance (58.8% versus 50.5%, p 0.086).

The main primary focus of infection in our patient population was the lung (60.6%); however, among the patients with BSI, only 36.9% had a lower respiratory tract primary infection focus. In contrast, despite the fact that the urinary tract was the primary infection focus in only 7.8% of CAS patients, it was present in 16.3% of the BSI episodes ($p < 0.001$) (Table 1).

In the multivariable analysis, the presence of BSI at hospital admission was found to be independently associated with ICU mortality, 39.4% versus 26.4%, (AOR 1.86; 95% CI

TABLE 1. Baseline characteristics of community-acquired sepsis patients at intensive-care unit admission

	Total (*n* = 804)	No BSI (*n* = 644)	BSI (*n* = 160)	p-value
Age, years	58.4 ± 17.8	58.8 ± 18	56.8 ± 17.6	0.419§
Males	525 (65.3%)	426 (66.1%)	99 (61.9%)	0.309*
SAPS II	47.9 ± 17.9	47.7 ± 17.6	48.3 ± 18.7	0.814§
Primary admission diagnosis				
Medical	637 (79.2%)	504 (78.3%)	133 (83.1%)	**0.034***
Trauma	35 (4.4%)	34 (5.3%)	1 (0.6%)	
Surgery	132 (16.4%)	106 (16.5%)	26 (16.3%)	
Community-acquired sepsis primary infection focus				
Lung	487 (60.6%)	428 (66.5%)	59 (36.9%)	**<0.001***
Urinary	63 (7.8%)	37 (5.7%)	26 (16.3%)	
Intra-abdominal	135 (16.8%)	105 (16.3%)	30 (18.8%)	
Other	119 (14.8%)	74 (11.5%)	45 (28.1%)	
HCAI	189 (23.5%)	139 (21.6%)	50 (31.3%)	**0.010***
Antibiotic adequacy[a]	280 (81.6%)	157 (78.9%)	123 (85.4%)	0.3*
Temperature (°C)	37.5 (1.5)	37.5 (1.4)	37.8 (1.7)	**0.010§**
C-reactive protein (mg/dL)	19.4 (18.5)	18.4 (18)	22.3 (18.2)	**0.007****
WBC ($\times 10^3/mm^3$)	12 (11)	12 (10)	13 (13)	0.286**
Sepsis severity				
Sepsis	67 (8.3%)	59 (9.2%)	8 (5.0%)	0.086*
Severe sepsis	318 (39.6%)	260 (40.4%)	58 (36.3%)	
Septic shock	419 (52.1%)	325 (50.5%)	94 (58.8%)	
ICU LOS (days)	9 (10)	9 (10)	9 (13)	0.962**
Hospital LOS (days)	19 (19)	19 (18)	18 (12)	0.111**
ICU mortality	233 (29.0%)	170 (26.4%)	63 (39.4%)	**0.001***
Hospital mortality	297 (37.2%)	225 (35.1%)	72 (45.6%)	**0.015***

*Chi-square test, **Mann–Whitney *U* test, §Student's *t*-test.
[a]Only patients with positive microbiological cultures and susceptibility antibiotic testing results available were included.
Significant p-values are indicated in bold.
Patients included with blood cultures performed on the day of hospital admission; data presented as mean ± SD, median (interquartile range) or *n* (%).
BSI, bloodstream infection; HCAI, healthcare-associated infection; ICU, intensive-care unit; LOS, length of stay; SAPS II, Simplified Acute Physiology Score II; WBC, white blood cell count.

1.20–2.89; p 0.005; Hosmer and Lemeshow test: p 0.482; $\chi^2 = 7.52$).

In the sub-groups of patients with the primary focus of infection in the lung (*n* = 486) or intra-abdominally (*n* = 135), the presence of BSI at hospital admission was also associated with an increased risk of dying while in the ICU (42.4% versus 27.2%; p 0.016 and 46.7% versus 25.7%; p 0.028, respectively).

Clinical course

In Table 2, we present the mortality rate at day 4 of ICU stay and the persistence of organ support dependence in CAS patients who were still alive (*n* = 754). We found that the presence of BSI was associated with a higher rate of vasopressor support dependence (40.9% versus 27.1%, p 0.002) but not of ventilatory support. Mortality rate was not different at that time-point. Finally, despite the fact that ICU mortality and hospital mortality were higher in patients with BSI at hospital admission, this difference only became significant from the 9th day of the ICU stay (Fig. 1).

TABLE 2. Mortality of community-acquired sepsis patients according to the presence or absence of bloodstream infection at day 4 in the intensive-care unit stay and the need for ventilatory and vasopressor support of those still alive

	Total (*n* = 804)	No BSI (*n* = 644)	BSI (*n* = 160)	p-value*
Mortality at day 4	87 (11)	66 (10)	21 (13)	0.298
Patients alive at day 4				
With ventilatory support	544 (78)	436 (78)	108 (79)	0.887
With vasopressor support	210 (30)	154 (27)	56 (41)	**0.002**

*Chi-square test.
Data presented as *n* (%).
BSI, bloodstream infection.
Siginificant p-values are indicated in bold.

BSI microbiology

The microorganisms isolated from blood cultures are listed in Table 3. One single agent was found in 80.6% of BSI. One hundred gram-positive bacteria were isolated in blood cultures, mainly *Streptococcus pneumoniae* and methicillin-sensitive *Staphylococcus aureus*. Roughly the same number of gram-negative bacteria (93) were identified. Enterobacteriaceae, essentially *Escherichia coli* and also *Klebsiella pneumoniae*, were the commonest.

The adequacy of empirical antibiotic prescription at hospital admission was 81.6%. Concerning only patients with a BSI we found an adequacy rate of 85.4%. The ICU mortality of those BSI patients who receive adequate empirical antibiotic therapy was 41.5%, lower than, although not significantly different from, those with inadequate antibiotics, 52.4% (p 0.49).

No significant association was found between the type of microorganism responsible for the BSI and mortality. The ICU mortality of patients with gram-negative BSI was 33.3%, with gram-positive BSI was 49.3%, and with mixed microorganisms BSI was 38.9% (p 0.176).

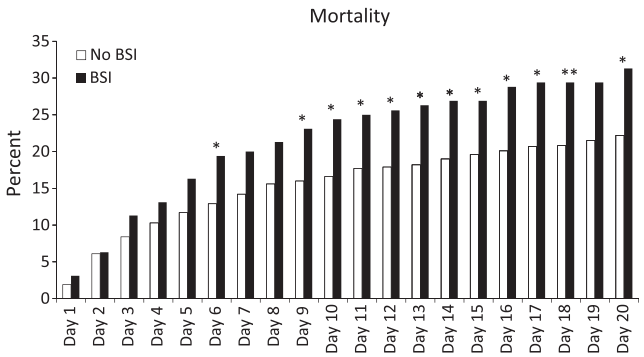

FIG. 1. Cumulative mortality of patients with community-acquired sepsis according to the presence of positive blood cultures on the day of hospital admission. A significantly higher mortality was noted from the 9th day onwards in patients with bloodstream infection. Chi-square test; *p <0.05.

TABLE 3. Main microorganisms isolated in bloodstream infections

Species	*n*
All gram-negative	93
Aeromonas hydrophila	1
Burkholderia cepacia	1
Citrobacter species	5
Eikenella corrodens	1
Enterobacter aerogenes	1
Enterobacter cloacae	1
Escherichia coli	44
Haemophilus influenzae	4
Klebsiella pneumoniae	15
Klebsiella species	2
Morganella morganii	1
Proteus mirabilis	4
Providencia species	1
Pseudomonas aeruginosa	7
Salmonella species	2
Serratia marcescens	1
Stenotrophomonas maltophilia	2
All gram-positive	100
Enterococcus faecalis	14
Enterococcus faecium	4
Staphylococcus aureus[a]	36
Coagulase-negative *Staphylococcus*	6
Streptococcus species	6
Streptococcus pneumoniae	34
All fungi	5
Candida albicans	2
Candida non-*albicans*	2
Cryptococcus neoformans	1

Including all microorganisms isolated in the blood cultures; there were 31 polymicrobial bloodstream infections.
[a]Four were methicillin-resistant *Staphylococcus aureus.*

Seasonal variation of BSI microbiology

Patients with a monomicrobial BSI who were admitted during the winter were more likely to have a gram-positive infection, whereas those admitted in the summer were more prone to gram-negative agents (p 0.024) (Table 4). This seems to be largely the result of the different primary infection foci, namely more lung infections in the winter and a relative increase in the proportion of both intra-abdominal and urinary tract infections during the rest of the year.

Discussion

In our study we found that the presence of BSI in patients with CAS was independently associated with both ICU and hospital mortality. However, this difference became significant relatively late in the clinical course, only after the 9th day of ICU stay. We also report a seasonal variation in microbiological isolates in CAS patients, with gram-positive microorganisms more frequent during the winter and gram-negative organisms more common in the summer.

In a population-based study, the incidence of BSI was found to be 15.7/100 000 patients per year [11] and was associated with risk factors for severe infection, namely age over 65 years, male gender, cancer, alcoholism, diabetes, lung disease and admission to an urban hospital. In another cohort of 3901 patients with CAS, the incidence of BSI at hospital admission was 8.2% [12]. In that study the major clinical predictors of BSI were high temperature (>39.5°C), the presence of a central venous line and the suspicion of endocarditis. The authors concluded that it was possible to safely reduce the collection of blood cultures in 26.7% without compromising safety. In fact, of a sub-group of 30 low-risk patients discharged home (25 with an antibiotic prescription) who were ultimately found to have a BSI, only seven had deteriorated when they returned for a second hospital evaluation [13]. In contrast, in our cohort of CAS patients the performance of blood cultures was independently associated with lower mortality [4]. However, all our patients needed ICU admission. Similarly in a study of 209 patients with community-acquired pneumonia [14], blood cultures only proved to be useful, providing guidance for antibiotic

TABLE 4. Seasonal distribution of isolated microorganisms in bloodstream infections

	Total (*n* = 160)	Spring (*n* = 42)	Summer (*n* = 46)	Autumn (*n* = 34)	Winter (*n* = 38)	p-value*
Microorganism						
Gram-negative	60 (38)	15 (36)	24 (52)	14 (41)	7 (18)	**0.024**
Gram-positive	71 (44)	17 (40)	17 (37)	12 (35)	25 (66)	
Mixed[a]	29 (18)	10 (24)	5 (11)	8 (24)	6 (16)	

*Chi-square test; [a]Includes polymicrobial mixed infections.
Siginificant p-values are indicted in bold.

therapy, in patients with a high (> III) Pneumonia Severity Score class [15].

The overall mortality of patients with community-acquired BSI ranges between 39 and 42% [11,16,17], slightly lower than our mortality rate (45.6%), reinforcing the severity of our patient population.

However, it is not clear if the presence of BSI increases disease severity itself or if it is only a marker of disease severity. In a cohort of 2076 infected surgical patients [18], the presence of BSI (17.5%) was not independently associated with mortality. The authors matched the patients with or without BSI according to their primary site of infection, APACHE II score, age and class of infecting organism [18]. According to that model, the presence of a hospital-acquired BSI was not associated with increased mortality, neither in pneumonia nor in abdominal infections. In contrast, in our study addressing only patients with CAS, the presence of BSI was independently associated with ICU and hospital mortality, even after adjusting for disease severity. Similar findings were noted in a recent study of patients with necrotizing fasciitis [19], especially when associated with group A streptococcus. Another study noted an independent association between BSI and the risk of developing septic shock in a cohort of patients admitted to a medical ward with new onset fever (OR 2.09, p 0.18) [20].

Initial early and adequate antibiotic therapy is considered of the utmost importance for the treatment of critically ill patients with sepsis [21]. In fact Ibrahim *et al.* [22] found a close relationship between initial antibiotic inadequacy and mortality in patients with BSI admitted to an ICU (AOR 6.9, p <0.001). In our study, 18.4% of patients with CAS at hospital admission (14.6% of patients with a BSI) received initial inadequate antibiotic therapy, although this did not significantly impact mortality. An initial antibiotic policy adjusted to the patients' risk factors (including the presence of HCAI) and to the severity of the disease, may have contributed to this high rate of antibiotic adequacy.

The most common isolated pathogens in patients with CAS and BSI in our study (Table 3) and in others [11,17] were, as would be expected, methicillin-sensitive *Staphylococcus aureus*, *Escherichia coli* and *Streptococcus pneumoniae*. Nevertheless, the observed hospital mortality was still over 40%, increasing with sepsis severity. In another prospective multicenter study, addressing ICU patients, with community-acquired and hospital-acquired BSI, the overall mortality rate was 38.7%. Age, illness severity and the presence of immunosuppression, but not inadequate initial antibiotic therapy (OR 0.89; 95% CI 0.61–1.3; p 0.55), were the identified mortality risk factors [16].

In Table 4 we present the seasonal variation of the agents responsible for BSI. *Streptococcus pneumoniae* was found to be more common during the winter, which was probably related to the lower temperature and also to the increased circulation of respiratory winter virus, especially respiratory syncytial virus and influenza virus [23]. On the other hand, *Escherichia coli* BSI were shown to be more prevalent in hot weather, during summer [24,25], as in our study.

In our study the presence of a BSI in CAS patients at hospital admission was associated with high mortality. Patients with BSI may have a larger burden of microorganisms, responsible for greater clinical severity and a high early mortality risk. However, in our study, this difference in mortality of patients with and without BSI only became statistically different after day 9 of ICU stay (Fig. 1).

Nevertheless, at day 4 the patients with BSI were more often dependent on vasopressors, probably reflecting a high clinical severity or a slower resolution of infection (Table 2). This dependence on vasopressors has been classified elsewhere as response failure and shown to be associated with increased mortality [26].

Both temperature and C-reactive protein were significantly higher at ICU admission in patients with BSI, but with substantial overlap of values, precluding their use for diagnosis. However, daily monitoring of C-reactive protein concentration may prove to be useful. A recent study from our group clearly showed that the C-reactive protein trend helps to identify CAS patients who are not responding to antibiotic therapy, who had an increase risk of dying, as early as the first days of antibiotic therapy [7].

Our study has several important strengths. It is one of the largest multi-centre epidemiological studies evaluating BSI in critically ill patients with CAS. It prospectively evaluated patients admitted with CAS for a 12-month period, allowing the evaluation of effects related to seasonal variation. All

patients were followed until death or hospital discharge, which unveiled differences in cumulative mortality through time. Data quality has been evaluated through an external audit randomly reviewing selected patient protocols. However, we recognize that our study has some limitations. Its non-randomized, observational design may have induced some unknown bias in the treatment of patients with CAS, especially as ICU admission criteria were defined by local policy and not by protocol. Furthermore, we have no data concerning antibiotic therapy before hospital admission or CAS patients not admitted to ICU.

Conclusion

In CAS patients receiving early appropriate antibiotic therapy, BSI at hospital admission was independently associated with late resolution of sepsis and increased ICU and hospital late mortality, noted after 9 days of ICU stay. There was a seasonal variation in the agents responsible for BSI.

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Authorship

JG-P and PP contributed to the study conception and design and participated in data analysis and drafted the manuscript. CL supervised data analysis, drafted the manuscript and takes responsibility for archiving the data. AHC conceived the study, participated in its design and coordination, participated in data analysis and helped to draft the manuscript. All authors read and approved the final manuscript.

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