

Impact of nosocomial polymicrobial bloodstream infections on the outcome in critically ill patients

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Abstract The aims of this study were to compare the clinical and microbiological characteristics from patients with polymicrobial bloodstream infections (BSI) to those from patients with monomicrobial BSI and to determine their influence on the prognosis. A prospective study was conducted on 371 nosocomial BSI in an intensive care unit (ICU). Seventy-five (20.2%) of them were polymicrobial. The mean APACHE II score at the onset of bacteremia in polymicrobial and monomicrobial BSI were 17.7 ± 6.6 and 18.9 ± 7.5 , respectively ($p=0.228$). Severe sepsis and septic shock were present in 68.0% and 50.6% of polymicrobial BSI and in 73.9% and 55.1% of monomicrobial BSI, respectively ($p=0.298$ and $p=0.494$, respectively). The length of stay and the length of stay post-infection were significantly longer in patients with polymicrobial BSI. APACHE II score at the onset of BSI, high-risk microorganisms, and septic shock were predictors of related mortality, but polymicrobial BSI and inadequate empirical antimicrobial treatment were not. Our findings suggest that the clinical and microbiological characteristics of polymicrobial BSI are not different from monomicrobial BSI, and polymicrobial BSI do not have any influence on the related mortality. However, they occurred in patients with a longer length of stay in the hospital and were associated with longer stays in the hospital after the episode of BSI.

Introduction

Nosocomial bloodstream infections (BSI) are among the most frequent and severe infections in intensive care unit

(ICU) patients, especially in those with severe sepsis and septic shock [1–4]. A great majority of polymicrobial BSI have a nosocomial origin, but the proportion of polymicrobial BSI in series of nosocomial infections in critical ill patients are relatively low [5, 6] and recent studies on these infections are scarce [7]. The differences in the clinical and microbiological features between monomicrobial and polymicrobial BSI in critically ill patients are not well established, and, most importantly, their impact on the prognosis remains unclear [8].

The aims of this study were: (1) to ascertain the clinical and microbiological characteristics of polymicrobial nosocomial BSI in an ICU, in comparison with hospital-acquired monomicrobial bacteremias and (2) to determine their influence on global and related mortality in hospital and on the length of stay.

Materials and methods

Study location and patients

The study was carried out in a university-affiliated urban teaching hospital with 600 beds: Hospital Universitario Dr. Peset in Valencia, Spain. During a period of 136 months (October 1998 to February 2010), all adult medical-surgical ICU patients with nosocomial-acquired bloodstream infection were prospectively analyzed.

Study design

A prospective cohort study was used. Its characteristics have been previously described [9]. We collected demographic, clinical, microbiological, hospital course, and outcome data. Patients were segregated according to the polymicrobial

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origin of bacteremia and hospital survival. Hospital-related mortality was the main outcome variable evaluated.

Definitions

A bacteremia was classified as nosocomial-acquired if the first positive blood culture occurred >48 h after hospital admission [10]. Each positive blood culture was categorized as either clinically significant or contaminant, taking into account organism identification, clinical signs and symptoms, number of positive blood cultures out of the total number drawn, results of other cultures, pathology findings, imaging results, and clinical course [11]. Organisms that are commonly recovered from the environment or the skin were judged to be contaminants, unless the clinical findings, the results of cultures of material from other body sites, and the number of positive sets (two or more) indicated a high probability of bloodstream infection [12]. Bacteremias considered as clinically nonsignificant or contaminants were excluded. Bacteremias were considered as polymicrobial when two or more microorganisms were isolated in the same set of blood cultures.

Sepsis, severe sepsis, septic shock, and multiple organ dysfunction syndrome were defined using established criteria [13]. A modified McCabe classification [14] was used to place the patients' underlying disease in the following categories: rapidly fatal, ultimately fatal, and nonfatal. Nosocomial BSI were defined according to criteria established by the Centers for Disease Control and Prevention (CDC) [15]. Respiratory and abdominal sources of bacteremia were considered as risk foci of infection, because these foci were associated with a higher mortality compared to other sources of bacteremia [5, 10]. *Enterobacteriaceae* other than *Escherichia coli*, *Pseudomonas aeruginosa*, and *Candida* spp. were considered to be high-risk microorganisms, due to having been reported to cause high mortality [5, 16].

Inappropriate empirical antimicrobial treatment (IEAT) was considered as the occurrence of bloodstream infection that was not effectively treated at the time when the causative microorganism and its antibiotic susceptibility were known, including the absence of antimicrobial agents directed at a specific class of microorganisms and the administration of an antimicrobial agent to which the microorganism responsible for the infection was resistant [9]. Mortality related to a bloodstream infection was predetermined to be present when a patient died during treatment for a nosocomial bloodstream infection and death could not be directly attributed to any other cause [17].

Statistical analyses

The χ^2 test was used to compare categorical variables. Continuous variables were compared using Student's *t*-test

for normally distributed variables and the Wilcoxon rank-sum test for non-normally distributed variables. Variables with a *p*-value ≤ 0.05 and a plausible biological relationship to the dependent outcome variable were further analyzed with a nonconditional multivariate analysis in order to determine the independent factors associated with hospital mortality. The results of the logistic regression analyses are reported as adjusted odds ratios with 95% confidence intervals. SPSS 15.0 software was used for the data analysis.

Results

During the study period, 12,742 consecutive eligible patients were evaluated. There were 509 episodes of ICU bacteremia; among these, 371 bacteremias (72.88%) were nosocomial and 75 (20.2% of nosocomial bacteremias) were polymicrobial. The epidemiological and clinical characteristics of the 371 nosocomial bacteremias according to the polymicrobial or monomicrobial infection are shown in Table 1. In two groups (polymicrobial and monomicrobial bacteremias), there were no differences in age, sex, underlying disease (chronic respiratory disease, diabetes mellitus, liver cirrhosis, neoplasia), APACHE II score at admission and at onset, the presence of severe sepsis, septic shock and multiorgan failure, and inadequate empirical antibiotic treatment. Length of stay in the ICU, length of stay in the ICU pre-infection, and length of stay in the ICU post-infection, days on mechanical ventilation, and the presence of high-risk microorganisms in blood cultures were significantly more frequent in the polymicrobial bacteremias group in the univariate analysis, whereas global mortality was more frequent in the monomicrobial bacteremias group (49.3% vs. 61.8%, *p*=0.049); there were no differences between the two groups.

The most common sources of polymicrobial bacteremias were respiratory (45.3%), unknown (24%), catheter-related (20%), and intra-abdominal (4%), without significant differences among monomicrobial bacteremias (Fig. 1). The systemic response in this group was classified as severe sepsis in 51 episodes (68.0%) and septic shock in 38 episodes (50.6%), with multiorgan failure in 50.6% of the cases.

A total of 154 microorganisms were isolated in the 75 episodes of polymicrobial bacteremia. The pathogens are listed in Table 2. There were 63 episodes with two microorganisms and 12 episodes with three microorganisms isolated. The microorganisms most frequently isolated in polymicrobial bacteremias were *Acinetobacter baumannii* in 34 episodes (45.3%), *Enterococcus* spp. in 32 episodes (42.7%), coagulase-negative staphylococci (CNS) in 23 episodes (30.7%), *Staphylococcus aureus* in 15 episodes (20.0%), and *Pseudomonas aeruginosa* in 12 episodes (16.0%), whereas in monomicrobial bacteremias, the

Table 1 Epidemiological and clinical characteristics of the 371 nosocomial bloodstream infections (BSI)

	Polymicrobial bacteremias <i>n</i> =75 (%)	Monomicrobial bacteremias <i>n</i> =296 (%)	<i>p</i> -value
Male/female	3.2:1	2.8:1	0.678
Age (years)	59.6±13.2	62.5±15.0	0.132
Diabetes mellitus	20 (26.6)	70 (23.6)	0.586
COPD	12 (16.0)	64 (21.6)	0.281
Liver cirrhosis	3 (4.0)	10 (3.4)	0.794
Neoplasia	9 (12.0)	24 (8.1)	0.290
APACHE II at admission	19.9±7.6	19.6±7.7	0.756
APACHE II at onset of BSI	17.7±6.6	18.9±7.5	0.228
Days on mechanical ventilation	13.9±15.1	10.2±13.0	0.042
Severe sepsis	51 (68.0)	219 (73.9)	0.298
Septic shock	38 (50.6)	163 (55.1)	0.494
Multiorgan failure	38 (50.6)	157 (53.0)	0.713
High-risk microorganisms	44 (58.6)	118 (39.8)	0.003
Length of stay (days)	55.5±45.3	39.4±36.6	0.001
Length of stay post-infection (days)	32.5±28.8	22.9±28.6	0.010
Length of stay in ICU (days)	37.6±31.2	27.3±28.9	0.007
Length of stay in ICU pre-infection (days)	17.6±19.6	11.4±13.2	0.001
Length of stay in ICU post-infection (days)	21.8±22.3	15.2±20.9	0.016
Inadequate empirical antibiotic treatment	32 (42.6)	123 (41.5)	0.861
Global mortality	37 (49.3)	183 (61.8)	0.049
Related mortality	11 (14.6)	49 (16.6)	0.692

Data are presented as the mean and standard deviation (SD) or as the number of patients and percentage for quantitative and qualitative cases, respectively

COPD chronic obstructive pulmonary disease; ICU intensive care unit

microorganisms most frequently isolated were *Acinetobacter baumannii* (25.0%), *Staphylococcus aureus* (14.5%), CNS (14.5%), *Enterococcus* spp. (10.5%), *Candida* spp. (9.8%), and *Escherichia coli* (5.7%).

Acinetobacter baumannii, *Enterococcus* spp., *Pseudomonas aeruginosa*, CNS, and *Klebsiella pneumoniae* were statistically more prevalent in the polymicrobial group by

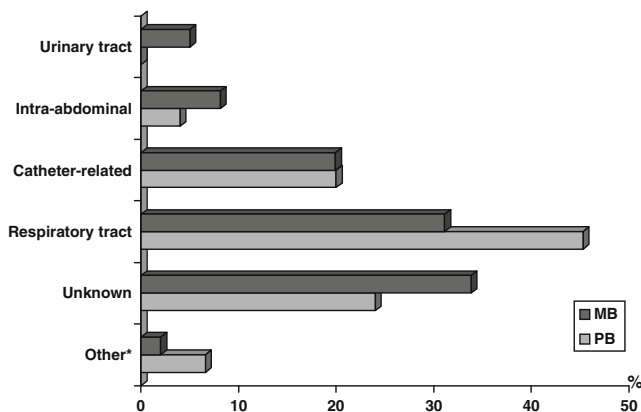


Fig. 1 Sources of polymicrobial (PB) and monomicrobial bacteremias (MB). *Soft tissue infections, endocarditis, pacemaker infections, meningitis

univariate analysis. The more frequent microorganism associations were *A. baumannii* + *Enterococcus* spp. (*n*=10, 13.15%), *Enterococcus* spp. + CNS (*n*=7, 9.21%), and *A. baumannii* + *S. aureus* (*n*=4, 5.26%).

Multivariate analysis demonstrated that the APACHE II score at onset, the presence of septic shock, and the isolates in cultures of high-risk microorganisms were independent factors associated with related mortality, but not polymicrobial bacteremia (Table 3).

Discussion

In our study, we found that over one-fifth of patients with nosocomial bacteremias were polymicrobial. This high figure points to the importance of polymicrobial BSI in ICUs. However, despite the clinical importance of polymicrobial BSI, studies on this subject are scarce and quite old [7, 18–22].

The clinical characteristics of our patients were similar to those previously described in other studies [19–21, 23]: a mean age of about 60 years, a higher proportion of men than women, frequent comorbidities, and diabetes mellitus being the most prevalent disease. We could not identify any

Table 2 Isolated microorganisms in polymicrobial and monomicrobial BSI

Microorganisms	Polymicrobial bacteremias <i>n</i> (%)	Monomicrobial bacteremias <i>n</i> (%)	<i>p</i> -value
<i>Acinetobacter baumannii</i>	34 (45.3)	74 (25.0)	0.001
<i>Enterococcus</i> spp.	32 (42.7)	31 (10.5)	0.000
<i>Pseudomonas aeruginosa</i>	12 (16.0)	16 (5.4)	0.002
<i>Escherichia coli</i>	8 (10.6)	17 (5.7)	0.129
CNS	23 (30.7)	43 (14.5)	0.001
<i>Staphylococcus aureus</i>	15 (20.0)	43 (14.5)	0.244
<i>Klebsiella pneumoniae</i>	8 (10.6)	11 (3.7)	0.028
<i>Candida</i> spp.	6 (8.0)	29 (9.8)	0.634
Gram-positive cocci ^a	5 (6.7)	9 (3.0)	0.141
Non-fermentative Gram-negative bacilli (except <i>E. coli</i>) ^b	10 (13.3)	13 (4.4)	0.004
Others ^c	2 (2.7)	4 (1.4)	0.420

^a *Aerococcus viridans*, *Streptococcus agalactiae*, *Streptococcus anginosus*, *Streptococcus bovis*, *Streptococcus mitis*, *Streptococcus pneumoniae*, *Streptococcus viridans*

^b *Citrobacter koseri*,
Enterobacter aerogenes,
Enterobacter cloacae,
Morganella morganii, *Proteus mirabilis*, *Proteus vulgaris*,
Serratia marcescens

^c *Clostridium* spp., *Haemophilus influenzae*, *Stenotrophomonas maltophilia*

clinical or epidemiological factor related to polymicrobial bacteremia in comparison with monomicrobial bacteremia. Few studies provided comparative data with monomicrobial bacteremias; Rello et al. [7] did so in intensive care patients without finding any predictor of polymicrobial bacteremia.

The length of stay in the hospital was longer in patients who developed nosocomial polymicrobial BSI compared to patients with monomicrobial BSI. As far as we know, there were no previous works which describe this finding. Interestingly, the length of stay, in both the ICU and in the hospital, after the episode of BSI was significantly longer in patients with polymicrobial BSI compared to monomicrobial BSI, which suggests a higher severity of polymicrobial BSI, not only in medical terms but also in cost.

It is widely accepted that intra-abdominal infections are the most frequent origin of polymicrobial bacteremias [5, 18, 22, 24]; however, in our series, abdominal origin was found in only 4% of cases. This could be due to the small

number of surgical patients admitted in our critical care unit. The sources of infection more frequently described in BSI are lower respiratory tract and unknown focus [24–26], in accordance with our results.

Nosocomial origin infections are caused frequently by Gram-negative bacilli [25], in the same way that polymicrobial bacteremias are [19, 22]. In recent years, there has been a shift in favor of Gram-positive organisms in BSI, and, even in some countries, its prevalence has overcome Gram-negative organisms [27–29]. We found that Gram-positive microorganisms caused 52.3% of polymicrobial BSI, probably due to a high prevalence of *Enterococcus* spp. and CNS from catheter and unknown origins in our setting. *A. baumannii* was the most prevalent microorganisms in both polymicrobial BSI (45.3%) and monomicrobial (25.0%) BSI. This high incidence of *A. baumannii* was due to a carbapenem-resistant outbreak in our ICU during the period of the study [9].

Table 3 Predictors of related mortality in BSI by logistic regression

	OR (95% CI)	<i>p</i> -value
Polymicrobial bacteremia	0.66 (0.27–1.58)	0.356
Risk foci	1.62 (0.82–3.20)	0.165
Inadequate empirical antibiotic treatment	1.93 (0.96–3.86)	0.065
High-risk microorganisms	3.64 (1.77–7.47)	0.000
APACHE II at onset of BSI	1.13 (1.07–1.19)	0.000
Septic shock	3.99 (1.36–11.69)	0.012
Multiorgan failure	2.41 (0.78–7.45)	0.128

OR odds ratio; CI confidence interval

BSI have a high mortality in the ICU, 35–60%, in severe sepsis and septic shock [6, 30, 31]. There is no consensus on whether polymicrobial BSI is a risk factor of mortality. Several studies have found a positive relationship between polymicrobial BSI [19, 32] and mortality in patients admitted and not admitted to the ICU, whereas Rello et al. [7] found no association in critical care patients. We found a lower global mortality in polymicrobial BSI. This low rate of mortality in polymicrobial BSI might be due to a significantly higher rate of CNS and *Enterococcus* spp. in these cases. However, this association was lost when we analyzed the related mortality.

The APACHE II score at the onset of bacteremia, septic shock, and high-risk microorganisms were all independent predictive factors of related mortality. On the other hand, no significant differences were found between IEAT and related mortality. These results are in contrast to findings in previous studies which found that IEAT was a predictor of mortality in community-acquired and nosocomial BSI [24, 33, 34]. But, however, these results did support previous findings in a study carried out by our group [9]. Related infection mortality was neither related to respiratory nor abdominal foci (high risk foci of mortality) nor polymicrobial BSI.

This study has some limitations. First, the data are from a single academic center, limiting its generalizability to other centers and settings. Second, despite the fact that stringent criteria were applied to each case of BSI caused by CNS, it is possible that some of our cases of polymicrobial BSI were monomicrobial, with CNS present as a contaminant. Third, the design of our study precluded us from collecting information about the time to antibiotic administration, which has been associated with better outcomes. Fourth, because the length of stay in the ICU and hospital is dependent on many factors, it is possible that some confounding variables were not analyzed. Our findings, however, provide significant information about the clinical and microbiological characteristics and prognosis of polymicrobial BSI in critically ill patients.

In summary, nosocomial polymicrobial bacteremias in intensive care represent a small but significant proportion of nosocomial BSI. They occur in patients with long-term hospitalization and are related to longer stays in the ICU and in the hospital compared to monomicrobial BSI. However, they were neither frequently IEAT nor did they have any influence on the mortality.

Conflict of interest The authors declare that they have no conflict of interest.

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