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Short Communication

Predictors of early mortality in very elderly patients with bacteremia: a prospective multicenter cohort

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SUMMARY

Objectives: The proportion of very elderly people in the population is increasing, and infectious diseases in this patient group may present with specific characteristics. The objective of this study was to investigate the outcome predictors of bacteremia among the very elderly.
Methods: This was a multicenter prospective cohort study of bloodstream infections (BSI) in patients ≥80 years old in 15 hospitals in Spain. The outcome variables were 14-day and 30-day mortality. Multivariate analysis was performed.
Results: One hundred and twenty episodes were included. Mortality was 22% (n = 26) on day 14 and 28% (n = 34) on day 30. In the univariate analysis, the variables associated with mortality were neutropenia, recent surgery, Pitt score ≥2, intensive care unit (ICU) admission, severe sepsis or shock, and abdominal, unknown, and respiratory tract sources. In the multivariate analysis, variables associated with mortality on day 14 were high-risk source (abdominal, unknown, and respiratory tract sources; odds ratio (OR) 7.9, 95%

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confidence interval (CI) 1.8–33.9), Pitt score ≥2 (OR 5.6, 95% CI 1.3–23.3), inadequate empirical treatment (OR 11.24, 95% CI 1.6–80.2), and severe sepsis or shock at presentation (OR 5.3, 95% CI 1.4–20.7); the interaction between empiric treatment and high-risk source was significant. On day 30, mortality was independently related to a high-risk source (OR 2.92, 95% CI 1.1–7.5) and presentation with severe sepsis or shock (OR 3.81, 95% CI 1.2–12.4).

Conclusions: Presentation with severe sepsis or shock and a high-risk source of BSI were independent predictors of 14-day and 30-day mortality. Inadequate empirical treatment was also a predictor of early mortality in patients with a high-risk source.

1. Introduction

Octogenarians comprise the fastest growing segment of the population, which is expected to double by the year 2030 in Spain.[1] In a previous report, the incidence of sepsis among individuals over 85 years of age was 26.2 cases per 1000 population, which is >100-fold higher than that noted for individuals between 5 and 14 years of age.[2] Thus, the management of sepsis and bacteremia in very old persons has become a public health concern.

Frequent co-morbidities, long-term institutionalization, declining functional status, altered immune function, and the increasing accessibility of healthcare resorts may explain why this population segment is particularly susceptible to bacterial infections. Furthermore, the mortality rates of most of these infections are at least three times higher among the elderly than among younger adult patients with the same disease.[3,4] Several host factors are described as contributing to increased morbidity and mortality: age-related state of reduced physiological reserve, chronic underlying diseases, poor tolerance of invasive procedures, poor response to antimicrobial therapy, and higher rates of adverse reactions to drugs, including antibiotics.[5] There are, however, other variables leading to worse outcomes, such as a greater risk of nosocomial infection and delayed diagnosis and therapy, which are potentially modifiable. The clinical presentation of older patients with sepsis is often atypical, making diagnosis difficult.

Recent evidence has shown that many older patients respond well to selected interventions when these are initiated in time,[6] hence knowledge of the characteristics and predictors of bloodstream infections (BSI) among the very elderly may lead to a better and more specific management of this population. Several studies have found elderly patients with bacteremia to be at higher risk of death after controlling for potential confounders.[3,7,8] However, there is little information concerning patients over 80 years of age. Therefore, the objective of this study was to determine the general features and independent factors affecting the outcome of BSI among the very elderly.

2. Methods

We followed the STROBE recommendations for reporting observational studies.[9]

2.1. Study design and patient selection

Our study analyzed a prospective cohort that included all consecutive adult in-patients aged ≥80 years with clinically significant BSI in 15 public hospitals (10 tertiary and five community) in Andalusia, Spain, between October and December 2006 (to March 2007 in community centers). This sub-analysis forms part of the SAEI/SAMPAC/REIPI Bacteremia Project, the overall characteristics of which have been published previously.[10] In brief, cases were included by daily review of the positive cultures processed by the microbiology laboratory of each participating center. Blood cultures were performed, processed, and interpreted in accordance with the recommendations of the Spanish Society of Infectious Diseases and Clinical Microbiology;[11] episodes caused by potential contaminants (such as coagulase-negative staphylococci) were included only when isolated from at least two different blood culture sets. Susceptibility results were interpreted in accordance with the Clinical and Laboratory Standards Institute (CLSI) recommendations.[12] Patients were followed for 30 days by an infectious disease physician, who collected the clinical data. Centers for Disease Control and Prevention (CDC) criteria were used to define the source of bacteremia.[13]

The study was approved by the Ethics Committee of the Hospital Universitario Virgen Macarena, which waived the need to obtain informed consent.

2.2. Variables and definitions

The data collected included the following: demographics, acquisition category (nosocomial if the episode occurred more than 48 h after admission, and all other episodes considered as community-onset, then sub-classified as healthcare-associated or community-acquired, according to the criteria used by Friedman et al.[14]), type of hospital, ward of admission, presence of underlying chronic disease and its severity according to the Charlson index,[15] vascular or urinary catheter at onset, endoscopic procedures performed during the preceding week and major surgery in the preceding 3 months, antimicrobial use in the preceding 3 months, source of BSI using CDC criteria,[13] severity of illness the day before the onset of bacteremia (day −1) using the Pitt score,[16] severity of systemic inflammatory response syndrome (SIRS) according to predefined criteria on day 0,[17] etiology, and treatment. Empirical therapy (i.e., administered before the susceptibility data were known) was considered adequate when an active antimicrobial agent (based on susceptibility data) was administered at the recommended dose within the first 24 h after the blood cultures were performed. Pathogens were considered multidrug-resistant (MDR) if they showed acquired non-susceptibility to at least one agent in three or more antimicrobial categories.[18] The outcome variables were all-cause mortality on day 14 and day 30.

2.3. Statistical analysis

Univariate analyses were performed using the Chi-square test or Fisher's exact test and the Student's *t*-test and Mann–Whitney *U*-test for comparison of categorical and continuous variables, respectively. The association between different variables and mortality or inadequate treatment was estimated by calculating the crude relative risk (RR), with 95% confidence intervals (CI).

Multivariate analyses were performed by logistic regression. All variables associated with mortality by a conservative univariate analysis at a level of significance of <0.2 were included in the initial models. Variables were selected using a backward stepwise process; a *p*-value of <0.1 was used to delete variables in subsequent steps. Interactions were investigated. Model validity was evaluated by

Hosmer–Lemeshow test for estimating goodness-of-fit to the data and its discrimination ability using the area under the receiver operating characteristics (ROC) curve. All analyses were carried out using SPSS 15.0 software package (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Patient characteristics, clinical features, etiology, and mortality

One hundred and twenty episodes were included. Demographic, epidemiologic, clinical, and microbiological data are shown in Table 1. With respect to BSI acquisition, 53% of episodes were nosocomial, 26% healthcare-associated, and 21% community-acquired. Of the 31 patients with community-onset healthcare-associated episodes, 20 had been hospitalized during the previous year, five came from a nursing home (two of these had also been hospitalized previously), five were undergoing hemodialysis (one had also been hospitalized), and eight had received specialized home care (four of these had also been hospitalized in the previous year). The most frequent underlying condition was diabetes (31%, n = 37). Forty-two percent of BSI patients presented signs with a urinary catheter and 38% had taken antibiotics in the previous 3 months. The most common sources of BSI were urinary (26%, n = 31) and unknown (24%, n = 29).

Table 1
Characteristics, clinical features, etiology, and mortality of very elderly patients with bloodstream infections

	n (% of 120)
Male gender	58 (48)
Age, years, median (IQR)	83 (5)
Acquisition	
Community	25 (21)
Healthcare-related	31 (26)
Nosocomial	64 (53)
Ward of admission when blood cultures were taken	
Emergency department	56 (47)
Medical ward	43 (36)
Surgical ward	9 (7)
Intensive care unit	12 (10)
Charlson index, median (IQR)	2 (1)
Pitt score, median (IQR)	1 (2)
Severe sepsis or shock at presentation	33 (27)
Underlying diseases	
Cancer	22 (18)
Neutropenia	2 (2)
Diabetes	37 (31)
Chronic pulmonary disease	20 (17)
Renal insufficiency	16 (13)
Invasive procedures	
Urinary catheter	50 (42)
Nasogastric tube	13 (11)
Previous surgery	13 (11)
Previous antimicrobial use	46 (38)
Source	
Unknown	29 (24)
Urinary tract	31 (26)
Intra-abdominal infection	5 (4)
Biliary	17 (14)
Vascular catheter	14 (12)
Respiratory source	13 (11)
Skin and soft tissue infection	8 (7)
Other source	3 (2)
Etiology	
Escherichia coli	43 (36)
Staphylococcus aureus	11 (9)
Klebsiella pneumoniae	9 (7)
Enterococcus spp	6 (5)
Coagulase-negative staphylococci	25 (21)
Enterobacter spp	2 (2)
Pseudomonas aeruginosa	5 (4)
Streptococcus pneumoniae	2 (2)

IQR, interquartile range.

Regarding the etiology of the BSI, we described 120 episodes of which seven were polymicrobial. The most common microorganism was *Escherichia coli* (36%, n = 43), followed by coagulase-negative staphylococci (21%, n = 25). Among the latter, 30% were catheter-related BSI and up to 40% of unknown source; of these, five occurred in patients with a peripheral intravenous line. Only 9% of episodes were caused by *Staphylococcus aureus* (n = 11), and 54% (n = 6) of these were methicillin-resistant. Among Gram-negative organisms (n = 68), 19% (n = 13) were cefotaxime-resistant and 37% (n = 25) fluoroquinolone-resistant. One episode was caused by *Bacteroides fragilis* but was monomicrobial.

Empiric antimicrobial treatment was adequate in 73% (n = 89) of episodes. All-cause mortality was 22% (n = 26) on day 14 and 28% (n = 33) on day 30.

3.2. Variables associated with 14- and 30-day mortality

An analysis of the demographics, epidemiological and clinical factors associated with 14- and 30-day mortality in very elderly patients with BSI is set out in Table 2. In the univariate analysis, 14-day mortality was significantly higher when the patient presented with neutropenia, had had a surgical procedure in the previous month, a Pitt score ≥2, severe sepsis or shock, or the patient had been admitted to the ICU (43% vs. 19%, p = 0.04). Similar variables were associated with mortality on day 30. On day 14, mortality in tertiary hospitals was 24% and in community hospitals was 16% (p = 0.33); on day 30 these percentages were 29.5% and 25%, respectively (p = 0.62). No significant differences were found.

Regarding the etiology, there was higher mortality for episodes caused by Gram-positive microorganisms compared to Gram-negative microorganisms (26% vs. 16% on day 14, and 32% vs. 23% on day 30), although the differences were not statistically significant. There was only one episode caused by a fungus and one by an anaerobic microorganism and both patients died before day 14. The mortality rates on days 14 and 30, respectively, among the most prevalent pathogens were: *E. coli*, 14% and 23%; coagulase-negative staphylococci, 24% and 28%; *S. aureus*, 18% and 36%; and *Klebsiella pneumoniae*, 0.

We also analyzed the prevalence of antimicrobial-resistant pathogens and their association with mortality; 13% of episodes (n = 16) were caused by resistant pathogens. On days 14 and 30, mortality rates for multidrug-resistant (MDR) pathogens were 25% and 32%, respectively, and for non-MDR, 21% and 25%, respectively. The differences were not significant. Among Gram-negatives, mortality was higher when the microorganism was resistant to cefotaxime (23% vs. 14% on day 14, and 31% vs. 22% on day 30) or was fluoroquinolone-resistant (25% vs. 12% on day 14, and 40% vs. 17% on day 30), although these differences were not significant.

Mortality rates associated with the source of BSI are shown in Figure 1. The lowest mortality rates on day 14 occurred for urinary (10%), catheter-related (14%), and biliary sources (18%). These sources were categorized as 'low-risk sources' for the multivariate analysis. The highest mortality rates were seen in intra-abdominal infections other than biliary (40%) and in patients with an unknown source (35%).

An exploratory multivariate analysis of variables associated with 14- and 30-day mortality was then performed. The variables introduced in the logistic regression models were: neutropenia, a surgical procedure in the previous month, Pitt score ≥2, severe sepsis or shock, ICU admission, high-risk BSI, and inadequate empirical treatment. Interactions between empirical treatment and source, Pitt score ≥2, and severity of SIRS were also studied. Variables independently associated with mortality on day 14 were the following: high-risk source (odds ratio (OR) 7.9, 95% CI 1.8–33.9), Pitt score ≥2 (OR 5.6, 95% CI 1.3–23.3), inadequate empirical treatment (OR 11.24, 95% CI 1.6–80.2), and severe sepsis or shock

Table 2
Univariate analysis of demographics, predisposing factors, clinical factors, and etiology related to mortality on days 14 and 30

Variable	No. deaths on day 14 /No. exposed (%)	RR (95% CI)	*p*-Value	No. deaths on day 30/No. exposed (%)	RR (95% CI)	*p*-Value
Type of acquisition						
Community	8/25 (32)	2.0 (0.7–5.3)	0.2	10/25 (40)	1.8 (0.8–4.0)	0.2
Healthcare-related	5/31 (16)	Ref.	-	7/31 (23)	Ref.	-
Nosocomial	13/64 (20)	1.3 (0.5–3.2)	0.6	17/64 (27)	1.2 (0.6–1.5)	0.7
Charlson score ≥2						
No	11 /56 (20)	Ref.		15/56 (27)	Ref.	
Yes	15/64 (23)	1.2 (0.6–2.4)	0.6	19/64 (30)	1.5 (0.8–2.9)	0.2
Neutropenia						
No	24/118 (20)	Ref.		32/118 (27)	Ref.	
Yes	2/2 (100)	4.9 (3.4–7.0)	0.04	2/2 (100)	3.7 (2.7–4.9)	0.02
Previous surgery						
No	19/107 (18)	Ref.		25/107 (23)	Ref.	
Yes	7 /13 (54)	3.0 (1.6–5.8)	0.003	9/13 (69)	3.0 (1.8–4.9)	0.001
Previous antibiotics						
No	16/73 (22)	Ref.		21/73 (29)	Ref.	
Yes	10/46 (22)	1.0 (0.5–2.0)	1	13/46 (28)	1.0 (0.5–1.8)	1
Urinary catheter						
No	13/70 (19)	Ref.		16/70 (23)	Ref.	
Yes	13/50 (26)	1.4 (0.7–2.8)	0.3	18/50 (26)	1.6 (0.9–2.8)	0.1
Pitt score						
0–1	4/69 (6)	Ref.		9/69 (13)	Ref.	
≥2	22/51 (43)	7.4 (2.7–20.3)	<0.001	25/51 (49)	3.8 (1.9–7.3)	<0.001
ICU admission						
No	20/106 (19)	Ref.		27/106 (25)	Ref.	
Yes	6/14 (43)	2.3 (1.1–4.7)	0.04	7/14 (50)	2.0 (1.1–3.6)	0.06
Severity of SIRS						
Sepsis	9/88 (10)	Ref.		15/88 (17)	Ref.	
Severe sepsis or septic shock	17/32 (53)	5.2 (2.6–10.4)	<0.001	19/32 (59)	3.5 (2.0–6.0)	<0.001
Empiric therapy						
Adequate	16/88 (18)	Ref.		23/88 (26)	Ref.	
Inadequate	10/32 (31)	1.7 (0.7–3.4)	0.1	11/32 (34)	1.3 (0.7–3.4)	0.4

RR, relative risk; CI, confidence interval; Ref., reference; ICU, intensive care unit; SIRS, systemic inflammatory response syndrome.

at presentation (OR 5.3, 95% CI 1.4–20.7); the interaction between empirical treatment and a high-risk source was significant (p = 0.06). In this model, the p-value for the Hosmer–Lemeshow goodness-of-fit test was 0.58, with an area under the ROC curve of 0.87 (meaning good predictive ability). On day 30, mortality was independently related to a high-risk source (OR 2.92, 95% CI 1.1–7.5) and presentation with severe sepsis or shock (OR 3.81, 95% CI 1.2–12.4). The Hosmer–Lemeshow goodness-of-fit test was 0.27 for this model, with an area under the ROC curve of 0.77 (meaning moderate predictive ability).

4. Discussion

We described the features of patients aged ≥80 years with bacteremia and identified predictors of short-term mortality. Some features of the population are remarkable. In our cohort, 26% of the episodes were community-onset healthcare-associated and 53% were nosocomial. In some earlier studies in this population, community acquisition was the most common, although the healthcare-associated category was not taken into account in some of these studies.[19] Previous or present care in healthcare facilities may facilitate the acquisition of exogenous bacteria, and invasive procedures, which are increasingly being performed in very old people, may compromise the natural barriers of innate immunity and create a portal of entry for healthcare-acquired and nosocomial BSI. However, because of the unspecific clinical presentation of sepsis in the very elderly, some true community BSI may have been misclassified as nosocomial due to delayed diagnosis. It is essential to make a careful evaluation of older patients for subtle signs of systemic inflammatory response syndrome, since such patients pose particular challenges for the diagnosis of sepsis. They are often initially diagnosed as having delirium, weakness, anorexia, malaise, urinary incontinence, or falls,[5,6] which are common clinical expressions of infection in elderly patients. In one recent study, fever was blunted or absent in half of the elderly patients studied.[19]

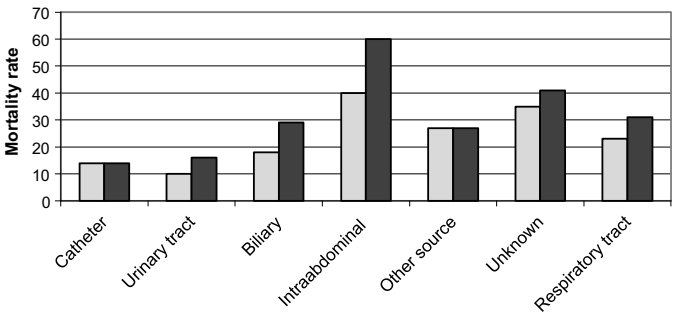

Figure 1. Mortality rates according to the source of bloodstream infection; gray bars indicate 14-day mortality, black bars indicate 30-day mortality.

Regarding co-morbidity, the median Charlson index score was 2. Previous studies have observed higher Charlson scores in patients with BSI aged between 65 and 80 years compared to those older than this.[19,20] This may be explained in terms of a natural selection of healthier patients, although the possibilities of a selection bias due to limited diagnostic effort (including blood cultures) in the very elderly with a worse basal status cannot be ruled out.

Another feature of note is that 41% of patients with a BSI had a permanent urinary catheter and the most frequent source of bacteremia, as expected, was the urinary tract;[6,19,20] this is concordant with the fact that *E. coli* was the most prevalent pathogen, followed by coagulase-negative staphylococci, which also highlights the importance of catheter-related BSI.

In terms of prognosis, mortality rates were 22% and 28% on days 14 and 30, respectively, higher than the mortality rates found in the all-ages cohort reported previously (18% and 22%, respectively).[3] Of note, only two patients were neutropenic and both died. Neutropenia has been shown previously to be associated with a worse prognosis in BSI in all age populations[21] and also in the elderly.[19] We also observed a high mortality rate when the BSI was due to a cefotaxime- or quinolone-resistant Gram-negative organism, but according to the multivariate analysis, this effect is more probably due to inadequate therapy. The high rate of previous antimicrobial use in our cohort should be mentioned as a potentially modifiable predictor of emerging resistance.[22–24]

In the multivariate analysis, apart from the variables representing acute severity of illness (severe sepsis or shock and Pitt score), we found inadequate empirical antimicrobial treatment to be a very strong independent predictor of early mortality. The interaction between empirical therapy and source indicated that the influence of empiric therapy was even more relevant when the source of bacteremia was classified as high-risk. It has been reported previously that in cases of urinary, catheter, or biliary infection, a high concentration of antibiotics in urine or other interventions, such as device removal, drainage, or are determinant in terms of the outcome.[25,26] On the other hand, abdominal, respiratory, and unknown sources have been related with a worse outcome in several studies.[27,28]

This study has several limitations. This was an observational study and thus subject to potential bias in the associations. However, our patients were followed prospectively and carefully, which is critical for the proper classification of exposure and outcome. We suspect that atypical clinical manifestations in the very elderly may have led to a delay in diagnosis and misclassification of the acquisition type, and may possibly have influenced the treatment and prognosis; this was not controlled in our study. The sample size, although similar to those of previous studies,[19,20] was insufficient to determine an association between some variables and mortality. Data regarding long-term (e.g. 3-month) survival, quality of life after sepsis, and nursing home requirements, were not considered. Future research efforts may be directed towards clarifying these aspects.

In conclusion, we described predictors of early mortality among very elderly patients with BSI. Inadequate empirical antimicrobial treatment was an important predictor of survival, particularly in high-risk sources. The early detection of sepsis and identification of risk factors for resistant organisms present challenges in these patients, and would contribute to better treatment and outcomes for the very elderly.

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Conflict of interest: JRB has been member of advisory boards for Merck, Pfizer, Novartis, and Janssen, has served as a speaker for Merck, Pfizer, Novartis, Astra-Zeneca, and Janssen, and has received research support from Novartis. All other authors declare no conflicts of interest.

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