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Blood-Stream Infections: Causative Agents, Antibiotic Resistance and Associated Factors in Older Patients

Hoang-Van Quang[1,2], Le-Thi Kim Nhung[1], Pham-Thi Thanh Thuy[2], Phan Chau Quyen[2], Le Bao Huy[3], Ho Si Dung[2,4]

[1]Department of Internal Medicine, Medical Faculty, Nguyen Tat Thanh University, Ho Chi Minh City, Viet Nam

[2]ICU Department, Thong Nhat Hospital, Ho Chi Minh City, Viet Nam

[3]Department of Emergency Medicine, Thong Nhat Hospital, Ho Chi Minh City, Viet Nam

[4]Department of Internal Medicine, Pham Ngoc Thach University of Medicine, Ho Chi Minh City, Viet Nam

Corresponding author:
Ho Si Dung, MD. Department of Internal Medicine, Pham Ngoc Thach University of Medicine, Ho Chi Minh City, Viet Nam. E-mail: hodung.285@gmail.com. ORCID ID://http/www.orcid.org/0000-0002-2687-4975.

ABSTRACT

Background: The rate of multi-drug antibiotic resistance in nosocomial bloodstream infections in elderly patients is increasing. This study examined the data for bloodstream infections to gain a better understanding of bacterial antibiotic resistance. **Methods:** This was a retrospective study of 817 patients with the first positive blood culture between January 1, 2016 and December 31, 2019. **Results:** Moyen's age was 77.4 ± 9.8 years, male (52.4%) and SOFA 5.0 ± 4. ESBL(+) rate was 78/817 (9.5%). ESBL(+) rate for Escherichia coli and Klebsiella pneumoniae was 69/141 (48.9%) and 9/52 (17.3%), respectively. The most common isolates were Escherichia coli (17.3%), Stenotrophomonas maltophilia (13.7%), and Staphylococcus species (23.1%). The rate of septic shock and mortality accounted for 22.3% and 28.9%, respectively. Escherichia coli is highly sensitive to carbapenem, and resistant (>50%) with quinolone and aminoside. Klebsiella pneumoniae and Pseudomonas aeruginosa were highly sensitive to carbapenem. Acinetobacter baumannii was resistant to meropenem (75%). Stenotrophomonas maltophilia was sensitive to quinolone (13.8 %), and highly resistant to remaining antibiotics. Methicillin-resistant Staphylococcus aureus had a low resistance rate for vancomycin, teicoplanin, and linezolid. Multivariate analysis showed that the significant factors associated with mortality were age >75; SOFA >7; respiratory infection; intensive care unit treatment and presentation with septic shock. **Conclusion:** The mortality rate was still high, especially for antibiotic-resistant agents.

Keywords: Bloodstream infections, bacteremia, antibiotic resistance, prognostic factor.

1. BACKGROUND

Bloodstream infections (BSI) are common severe infections and have been one of the leading causes of death in older patients (1). In generally, BSI are more frequent in older than in younger patients and are associated with high hospitalization and mortality rate , especially in patients with many chronic diseases (2, 3). Many factors contributing to this difference include senescence of both humoral and cell-mediated immune systems; reduced physiologic reserve capacity; increased incidence of underlying illnesses; malnutrition; poor tolerance to invasive procedures; greater risk and incidence of nosocomial infections as well as the higher rate of multidrug-resistant organisms (3). Gram-negative bacteria are more common than Gram-positive pathogens in patients with BSI 65 years and older constitute 40% to 60%, in which Escherichia coli (E. coli) is the most common pathogen in the community-acquired BSIs (4, 5). Conversely, Staphylococcus aureus (S. aureus) is the most common bacteria for Gram-positive groups.

In recent years, the rate of antibiotic resistance remains still high, especially in nosocomial BSI. This association was found for 30-day mortality (6) 90-day mortality (3) and in-hospital mortality (7). In-hospital mortality rate for age cutoff 60-70 accounted for between 19% and 49% and for age cutoff ≥ 75 was 15% to 56% (.3, 7, 8). Many prognostic factors for mortality need to continue to be evaluated. In Vietnam, the data for BSI in elderly patients are very limited in multicenter studies. The previous studies usually had a small sample size and included both old and

young patients (9, 10). Thong Nhat Hospital is a national teaching geriatric hospital located in Ho Chi Minh City, Vietnam. The hospital has recorded a high patient volume (the average daily outpatient department attendants at around 4,000 patients). Number of elderly patients has a constant increase in the geriatric population have been associated with an increasing number of serious infections in older adults, including BSI. Severe infections in the elderly have become an important issue. Despite the great advances in medical science, BSI have a high mortality rate. The investigation results are very important to evaluate the epidemiology of pathogens and to treat them appropriately.

2. OBJECTIVE

This study aimed to determine the aetiologic agents, antibiotic susceptibility, outcomes, and factors associated with mortality of BSI.

3. MATERIAL AND METHODS

Study design and data collection

We conducted a retrospective study between January 1, 2016 and December 31, 2019 at Thong Nhat Hospital. The geriatric university hospital is a 1200-bed tertiary care medical center. The source population consisted of all patients ≥60 years of age admitted to the hospital during the study period and diagnosed with first BSI with positive blood culture accumulated by the Microbiology Laboratory from the Department of Laboratory Medicine of Thong Nhat Hospital. For all eligible patients, the following data were collected: demographic characteristics, multiple organ failure Sequential Organ Failure Assessment (SOFA), preexisting comorbid medical conditions, source of infection, initial vital signs, routine laboratory test results, admission, and final discharge diagnoses, and identity of microorganisms isolated from the blood cultures. Patient outcomes were in-hospital mortality or discharge from the hospital. Comorbidities were recorded according to the score proposed by Charlson et al. (1987) (11).

Study definition

BSI was defined as the isolation of gram-negative or gram-positive bacteria in a blood culture specimen. Clinically significant BSI was defined as at least one positive blood culture together with clinical features compatible with systemic inflammatory response syndrome, qSOFA(+), and SOFA ≥2.

Septic shock was defined as sepsis associated with evidence of organ hypoperfusion and a systolic blood pressure <90 or >30 mmHg less than the baseline or a requirement for the use of a vasopressor to maintain blood pressure and a serum lactate level greater than 2 mmol/L (18 mg/dL) despite adequate volume resuscitation (12).

Underlying diseases were defined as the medical diagnoses outlined in the individual medical file, based on the International Classification of Diseases-10 (ICD-10). Comorbid diseases included hypertension, diabetes, chronic cardiac failure, chronic coronary disease, chronic pulmonary disease, chronic hepatic disease, chronic renal disease, and immune deficiency.

The source of the bacteremia was determined based on the isolation of bacteria from the presumed portal of entry and clinical evaluation. The presence and source of a focal infection were classified by the final discharge diagnosis as lower respiratory tract infection, urinary tract infection (UTI), pancreaticobiliary tract infection, bacterial peritonitis, skin and soft-tissue infection, neurologic infection, and vascular catheter-related infection. Those without a localized source of bacteria after an extensive admission workup were classified as primary bacteremia. Vascular catheter-related BSI was defined as the presence of a positive blood culture result from at least one peripheral blood sample, a catheter tip culture positive for an identical microorganism with identical antibiogram, clinical signs of sepsis, and the absence of any other sources of sepsis

Nosocomial infection was defined as an infection that occurred >48 hours after hospital admission. Nosocomial BSI were defined according to the criteria proposed by the Centers for Disease Control and Prevention (13).

Organ failures assessed at the emergency department (ED) admission and during hospitalization after BSI were characterized as follows: (1) acute renal failure, a serum creatinine level >170 (μmol/L) or, in the case of preexisting renal dysfunction, a doubling of previous serum creatinine values, (2) acute hepatic failure, a bilirubin level >20 mmol/L, (3) altered level of consciousness, a Glasgow Coma Scale score of <14 or a decrease in the score of at least 3 if a primary central nervous system injury was present, (4) acute respiratory distress, PaO2/FiO2 ≤400, (5) hepatological failure, platelets ≤150 (103/mL), (6) shock, arterial systolic blood pressure <90 mmHg refractory to fluid repletion and requiring vasopressors to sustain a blood pressure of >90 mmHg (14).

Antibiotic susceptibility testing was performed according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) protocol since 2013 and prior according to the Clinical Laboratory Standard Institute (CLSI) guidelines using disc diffusion testing and the VITEK-system (.15, 16). Multi-Drug Resistance (MDR) was defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories. Extensive-Drug Resistance (XDR) was defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories (i.e. bacterial isolates remain susceptible to only one or two categories). Pan-Drug Resistance (PDR) was defined as non-susceptibility to all agents in all antimicrobial categories (17).

Statistical analysis

Statistical analysis was performed using SPSS Version 20.0. Descriptive statistics for categorical variables were performed by calculating frequencies and percentages. The variables were compared using the chi-square test or Fisher's exact test to observe the proportion differences. Binary univariate regression analysis was performed to identify factors associated with mortality. To evaluate independent predictors of in-hospital mortality, a multivariable Cox proportional hazards regression model was performed. All variables with p <0.05 at univariate analysis were further analyzed in multivariate binary

Variable	N (% of 817)
Sex	
Male	428 (52.4)
Female	389 (47.6)
Age, years (IQR)	77.4 (73.0)
SOFA score (mean ± SD)	5.0 ± 4.0
Multi-organ failure	2.6 ± 1.4
Cardiovascular	440 (53.9)
Respiratory	343 (42.0)
Hepatic	121 (14.8)
Renal	508 (62.2)
Hematologic	420 (51.4)
Neurologic	314 (38.4)
Acquisition	
Community	451 (55.2)
Nosocomial	366 (44.8)
Septic shock	182 (22.3)
Mechanical ventilation	319 (39.0)
Charlson index, median	3.7 (1.4)
Ward of admission	
Medical	474 (58.0)
Surgical	63 (7.70)
Intensive care unit	280 (34.3)
Underlying disease	
Hypertension	458 (56.1)
Diabetes	277 (33.9)
Coronary disease	196 (24.0)
Cardiac failure	253 (31.0)
Hepatic disease	44 (5.4)
Kidney disease	267 (32.7)
Immune deficiency	59 (7.2)
Chronic lung disease	36 (4.4)
Primary site of infection	
Catheter related	20 (2.4)
Pancreaticobiliary tract	21 (2.6)
Urinary tract	156 (19.1)
Lower respiratory tract	417 (51.0)
Peritoneum	76 (9.3)
Skin and soft tissue	62 (7.6)
Neurologic tract	8 (1.0)
Unknown	57 (7.0)

Table 1. Characteristics, clinical features, site of infection of elderly patients with BSI

regression. The strength of the association between prognostic variables and the outcome of interest was expressed as an Odd ratio, and their corresponding 95% confidence intervals were calculated. p-value <0.05 was considered statistically significant. Only the first episode of BSI was considered for the analysis.

Interpretation of the antimicrobial susceptibility results was carried out following CLSI 2018 guidelines (18). Antimicrobial sensitivity results were expressed in terms of sensitivity rates according to the CLSI M39 guidelines (19). To avoid the effect of repetitive isolation of strains on antimicrobial sensitivity, the first isolation of strains from the same site of infection in a patient was analyzed according to CLSI M39 guidelines (19).

4. RESULTS

Patient characteristics and comorbidity

Characteristics of patients with BSI, microbiological data are listed in Table 1. 817 patients aged 60 and older (mean 77.4, median 73.0, range 60-102) were identified; 428 patients were male (52.4%), 366 (44.8%) were nosocomial. Septic shock accounted for 182 patients (22.3%).

Variable	N (% of 817)	Mortality n (%)
Gram-negative bacteria	537 (65.7)	141/537 (26.2)
E. coli	141 (17.3)	26 (18.4)
K. pneumoniae	52 (6.4)	16 (30.8)
P. aeruginosa	15 (1.9)	4 (26.7)
A. baumannii	46 (5.6)	17 (37.0)
Burkholderia cepacia	60 (7.3)	12 (20.0)
Stenotrophomonas maltophilia	112 (13.7)	34 (30.4)
Achromobacter	23 (2.8)	3 (13.0)
Enterococcus	10 (1.2)	4 (40.0)
Sphingomonas paucimobilis	12 (1.5)	2 (16.7)
Salmonella	11 (1.3)	2 (18.1)
Other*	55 (6.8)	21 (38.2)
Gram-positive bacteria	280 (34.3)	95/280 (34.0)
Other *Staphylococcus spp.***	189 (23.1)	77 (40.7)
S. aureus	71 (8.6)	13 (18.3)
Streptococcus spp.	20 (2.4)	5 (25)
Antibiotic resistance		
Non multi-resistance	221 (27.1)	
Multi-resistance	596 (72.9)	
MDR	434 (72.8)	
XDR	152 (25.5)	
PDR	10 (1.7)	
ESBL(+)		
E. coli	69/141 (48.9)	
K. pneumoniae	9/52 (17.3)	

Table 2. Characteristics of pathogens in patients with BSI. ESBL, extended spectrum beta-lactamases; MDR, multi-drug resistance; PDR, pandrug resistance; XDR, extensive-drug resistance. *Other (Abiotrophia defective, Citrobacter koseri, Ochrobactrum anthropic, Roseomonas gilardii, Shigella group Morganella morganii, Pantoea agglomerans, Vibrio cholera, Brucella melitensis, Kocuria rhizophila, Chryseobacterium indologenes, Bordetella bronchiseptica, Proteus mirabilis, Cupriavidus pauculus, Ralstonia pickettii). **Other Staphylococcus spp. (Staphylococcus epidermidis, Staphylococcus hominis, Staphylococcus lugdunensis, Staphylococcus haemolyticus, Staphylococcus capitis, Staphylococcus saprophyticus, Staphylococcus xylosus, Staphylococcus cohnii, Staphylococcus caprae, Staphylococcus warneri).

Patients had rates of renal failure (62.2%), hematological failure (51.4%), cardiovascular failure (53.9%), and respiratory failure (42%). The number of patients treated in the medical ward, surgical ward, and intensive care unit (ICU) were 58%, 7.7%, and 34.3%, respectively. The most common medical comorbidities included hypertension (56.1%), diabetes mellitus (33.9%), chronic cardiac failure (31.0%), and chronic renal disease (32.7%). Charlson's comorbidity index was 3.7 ± 1.4.

Related to the source of infection, respiratory tract infection was most common (51%), followed by urinary tract (19.1%), peritoneum (9.3%), skin and soft tissue (7.6%). Neurologic tract, pancreaticobiliary tract and vascular catheter-related infection accounted for the low percentage (1%), (2.6%) and (2.4%), respectively. Site of infection was not observed with the rate (7%).

Etiology of bacteremia

Table 2 shows that the proportion of Gram-negative bacteria was 537 (65.7%) and Gram-positive bacteria was 280 (34.3%). For Gram-negative bacteria, E. coli was the most common agent, accounting for 17.3%, of which the rate of E. coli with positive extended spectrum beta-lactamase (ESBL(+)) was 69/141(48.9%). Followed by Stenotrophomonas maltophilia (13.7%), Burkholderia cepacia (7.3%). Klebsiella pneumoniae (K. pneumoniae) accounted for 52 (6.4%), in which the proportion of the bacteria with ESBL(+) was 9/52 (17.3%). For Gram-positive bacteria, other Staphylococcus species had a fairly high rate of 189/817 (23.1%). S. aureus accounted

	S. aureus (n=71)	*E. coli* (n=141)	*Stenotrophomonas maltophilia* (n=112)	*Burkhoderia cepacia* (n=60)	*K. pneumoniae* (n=52)	*A. baumannii* (n=46)
Meropenem	-	4.8	90.9	18.5	40.0	75.0
Imipenem	43.9	31.0	69.9	69.2	36.6	40.0
Ertapenem	12.5	-	6.7	12.5	5.9	-
Levofloxacin	-	81.8	13.8	8.0	20.0	16.7
Ciprofloxacin	41.4	66.9	9.8	86.0	36.7	37.8
Moxifloxacin	34.7	66.7	3.2	83.3	33.3	61.5
Tigecyclin	40.3	-	6.8	70.0	22.2	21.7
Gentamycin	44.9	40.6	88.8	98.1	22.0	62.2
Amikacin	-	7.7	75.0	96.4	13.6	76.9
Cefepim	-	37.3	83.7	50.9	38.5	63.9
Cefotaxim	-	57.7	97.2	91.7	42.9	79.3
Piperacillin	-	35.7	86.5	59.6	80.0	64.9
Ceftazidim	-	46.0	87.9	5.4	38.8	56.1
Norfloxacin	20	61.9	0	80.0	60.0	24.1
Fosfomycin	30.8	3.0	3.0	100	57.1	100
Trimethoprim	66.4	61.2	9.5	1.8	28.0	27.1
Tobramycin	0	45.0	96.7	100	83.3	62.1
Linezolide	0	-	-	-	-	-
Vancomycin	4.4	-	-	-	-	-
Teicoplanin	1.5	-	-	-	-	-
Aztreonam	-	100	100	100	0	89.3

Table 3: Percentage of antimicrobial resistance of bacteria isolated from patients with BSI.

for 71/817 (8.6%), and Streptococcus spp. had a very low rate (2.4%). The rate of non-multidrug-resistant bacteria was only 221 (27.1%). In contrast, the rate of multidrug resistance bacteria was relatively high at 596 (72.9%). Among multidrug-resistant bacteria, the ratio was as follows: MDR 434/596 (72.8%), XDR 152/596 (25.5%), PDR 10/596 (1.7%).

Antibiotic resistance of microorganisms

The antibiotic resistance patterns of the isolates are shown in Table 3. Antibiograms of common bacteria causing BSI were only performed on a few antibiotics depending using each isolate of bacteria. S. aureus had susceptibility to linezolid, low resistance vancomycin 4.4% and teicoplanin 1.5%. E. coli was only low resistant to meropenem 4.8%, but resistant to quinolones 66.7-81.8%, resistant to aminoglycoside 40-45%. K. pneumoniae was resistant to piperacillin 80%, tobramycin 83.3%, norfloxacin 60% and <40% for remaining antibiotics. Pseudomonas aeruginosa (P. aeruginosa) was resistant to moxifloxacin 100%, tigecycline 87.5%, cefotaxime 100%, fosfomycin 60% and <50% for remaining antibiotics. Acinetobacter baumannii (A. baumannii) was resistant to meropenem 75%, imipenem 40%, fosfomycin 100% and piperacillin 64.5%. Stenotrophomonas maltophilia was lowly resistant to levofloxacin 13.8%, ciprofloxacin 9.8%, moxifloxacin 3.2%, fosfomycin 3%, and highly resistant to remaining antibiotics. Burkholderia cepaciae was lowly resistant to meropenem 18.5%, levofloxacin 8%, ceftazidime 5.4%, and >70% for other antibiotics.

Table 3. Percentage of antimicrobial resistance of bacteria isolated from patients with BSI

Achromobacter is resistant to gentamycin 85.7%, Amikacin 33.3%, lowly resistant to other antibiotics. Sphingomonas paucimobilis is resistant to meropenem 72.7%, 100% resistant to imipenem, tigecyclin, gentamycin, amikacin, and fosfomycin, <50% for other antibiotics. Enterococcus is highly resistant to quinolones: ciprofloxacin 75%, norfloxacin, and moxifloxacin 100%.

In-hospital mortality rate and predictors

Table 2 shows the patient characteristics of hospital survivors (n=581) and non-survivors (n=236). In-hospital mortality rate of all patients were 28.9%. For each pathogen mortality rate, there was 36.9% (17/46) for A. baumannii, 26.6% (4/15) for S. aureus, 30.7% (16/52) for Klebsiella pneumonia, 18.4% (26 out of 141, 26/141) for E. coli, 34.6% (90/260) for Staphylococcus species, 25% (5/20) for Streptococcus spp., 20% (12/60) for Burkholderia cepacia, 40% (4/10) for Enterococcus, 30.4% (24/112) for Stenotrophomonas maltophilia and low rate for remaining bacteria. The mortality rate for Gram-negative bacteria 141/537 (26.2%) was lower than for Gram-positive bacteria 95/280 (34%).

Univariable analysis (Table 4) revealed that in the mortality group, the proportion of males, age, SOFA score, presentation of septic shock, ICU care, infection of the respiratory tract, multi-antibiotic resistance were significantly higher than those in the survivor group, with $p < 0.001$.

Compare to the survivior group, the non-survivor group had the significant higher rate of males, older age, SOFA score, septic shock, ICU care need, infection of the respiratory tract and multi-drug resistance.

The univariate analysis showed that males, age, SOFA score, septic shock, ICU care need, respiratory tract infection, and multi-antibiotic resistance were associated with the mortality risk,

Table 4. Factors associated with mortality based on univariable analysis

In Table 5, Age >75 (OR 1.82, 1.12-3.08, p=0.016); SOFA score >7 (OR 12.86, 7.03-23.54, p<0.001); presence of septic shock (OR 3.51, 1.88-6.56, p=0.007), ICU (OR 6.30, 6.70-10.74, p<0.001); primary respiratory infection (OR 1.91, 1.14-3.21, p=0.015) were identified as major independent predictors of mortality following multivariate Cox regression. In this analysis, nosocomial BSI, and antibiotic multi-resistance did not reach the level of significance.

Table 5. Factors associated with mortality in BSI based on multivariate analysis.

Characteristics	Survivors (%) 581 (71.1)	Non-survivors (%) 236 (28.9)	OR (95%CI)	p-value
Number of males	292 (50.26)	136 (57.63)	0.74 (0.5-1.0)	<0.001*
Age (year) (mean ± SD)	76.2 ± 9.6	80.3 ± 10		<0.001 #
SOFA score (mean ± SD)	3.0 ± 1.7	9.6 ± 4.1		<0.001 #
Underlying disease				
Hypertension	330 (56.8)	128 (54.2)	0.9 (0.7-1.2)	0.53*
Diabetes	202 (34.8)	75 (31.8)	0.8 (0.6-1.2)	0.46*
Coronary disease	143 (24.6)	53 (22.5)	0.9 (0.6-1.3)	0.53*
Cardiac failure	170 (29.3)	83 (35.2)	1.3 (1.0-1.8)	0.11*
Hepatic disease	30 (5.2)	14 (5.9)	1.2 (0.6-2.2)	0.73*
Kidney disease	196 (33.7)	71 (30.1)	0.8 (0.6-1.2)	0.33*
End-stage renal disease	11 (1.9)	5 (2.1)	1.1 (0.4-3.3)	0.79*
Immune deficiency	45 (7.8)	14 (5.9)	0.8 (0.4-1.4)	0.46*
Chronic lung disease	23 (3.6)	13 (5.1)	1.4 (0.7-2.8)	0.35*
Comorbid condition				
Septic shock	32 (5.5)	150 (63.6)	29.9 (19.2-46.6)	<0.001*
ICU care	146 (25.1)	206 (78.3)	20.5 (13.4-31.3)	<0.001*
Primary site of infection				
Catheter related	20 (3.4)	0 (0.0)	0.96 (0.95-0.98)	0.001*
Pancreaticobiliary	15 (2.6)	6 (2.5)	0.98 (0.38-2.57)	0.59*
Urinary	140 (24.1)	16 (6.8)	0.23 (0.13-0.39)	<0.001*
Respiratory	239 (41.1)	178 (74.4)	4.40 (3.13-6.17)	<0.001*
Peritonium	59 (10.2)	17 (7.2)	0.68 (0.39-1.21)	0.24*
Skin and soft tissue	48 (8.3)	13 (5.5)	0.63 (0.34-1.19)	0.02*
Neurologic	6 (1.0)	2 (0.9)	0.82 (0.16-4.09)	1.00*
Unknown	53 (9.1)	4 (1.7)	0.17 (0.06-0.48)	<0.001*
MDR				
Yes	412 (70.9%)	184 (78)		0.046*
No	169 (29.1%)	52 (22.0)		

Table 4: Factors associated with mortality based on univariable analysis. *χ2 tests; # Student's t-tests; SD, standard deviation.

5. DISCUSSION

This study was undertaken to evaluate the causative agents, antibiotic resistance, outcome as well as risk factors for mortality of BSI in elderly patients. We only investigated BSI in the elderly because this patient population was highly frail. Older patients with BSI often had a poor prognosis due to frequent comorbidities, altered immune function, long-term institutionalization, malnutrition, greater risk of nosocomial infection, and poor response to antimicrobial therapy. This could explain why this population segment was particularly susceptible to bacterial infections. To our knowledge, the current study is the largest on elderly patients in Vietnam. The mean age was 77.4 years, and the mortality rate accounted for 28.9%. In many countries, over half of all deaths now occur in hospitals, with the vast majority of in-hospital deaths occurring among the elderly and the very old (20). Previous studies showed that mortality rates of BSI are at least three times higher among the elderly than among younger adult patients with the same disease and have suggested that mortality depends on age cutoff (21). For age cutoff of 60-69 and ≥70, the death rate was 19% - 49% and 15% - 56%, respectively (7, 8). Studying 167 older patients with BSI in a French geriatric unit, Aurore Bulaud revealed that the mortality rate at 60 days was 32.3% and concluded that age is not a risk factor of mortality for BSI, and management of bacteremia has to be adapted to elderly (22). However, Ignacio Martin-Loeches identified that age was found to be an independent risk factor only in the very elderly group (13). Almost all investigations noted that increasing age was significantly associated with an increased odds ratio for attributable in-hospital death (8, 23). Our result identified that older age >75 was an independent factor associated with in-hospital mortality (OR 1.86, 1.12-3.08, p=0.016).

Risk factors	OR (95% CI)	**p-value**
Age (year) >75	1.86 (1.12 – 3.08)	0.016
SOFA score >7	12.86 (7.03-23.54)	<0.001
Septic shock	3.51 (1.88-6.56)	<0.001
Intensive care unit	6.30 (6.70-10.74)	<0.001
Primary respiratory infection	1.91 (1.14-3.21)	0.015

Table 5. Factors associated with mortality in BSI based on multivariate analysis.

In our study, it was noted that the community BSI rate accounts for 55.2%, and the nosocomial BSI rate is 44.8%. However, as an unspecific clinical presentation of sepsis in the very elderly, some true community BSI may have been misclassified as nosocomial due to delayed diagnosis. Rodriguez-Bano et. al. found that 58% of BSI were hospital-acquired infections, 24% were healthcare-associated and 18% were community-acquired in two similar hospital settings (24). The mortality rate of nosocomial BSI was usually higher than community BSI due to multidrug resistance. Gavazzi et al. (2002) found that community-acquired BSI was significantly more frequent in older patients and was independently associated with mortality. The author concluded that the elderly patients represented a frail population in the community (25). So, this population had significantly more acute respiratory failure, acute renal failure, septic shock, and altered mental status on admission (3). Patients were treated in ICU with high mortality 206/352 (58.5%). We

noted that SOFA >7 (OR 12.86, 7.03-23.54, p<0.001), and ICU care (OR 6.30, 6.70-10.74, p <0.001) were independent factors associated with mortality.

The mortality rate for gram-negative bacteria 141/537 (26.2%) was lower than for gram-positive bacteria 95/280 (34%). Crane et al. described a significantly higher 14-day mortality rate in nosocomial BSI compared to community-onset BSI (14% vs. 6%) and nosocomial BSI significantly associated with increases in 90-day mortality was noted in Kaye'study (26, 27).

The rate of septic shock in this investigation was 182/817 (22.3%) (Table 1). The mortality accounted for 150/182 (82.4%) for the elderly with septic shock. In several large studies, septic shock was present in 10-15% of patients aged 65 years and older, 39% of patients aged 85 years and older (6, 7, 28,29). In addition to being more common in older patients, severe sepsis and septic shock caused higher mortality in the elderly reaching 50-60% (29). Keith showed that BSI with (Systemic Inflammatory Response Syndrome) SIRS and BSI with SIRS and hypotension had mortality 40% and 49%, respectively (27). The other authors noted that the independent risk factor for mortality in BSI based on multivariate analysis was the presence of septic shock (6, 8, 30). Retamar et al. (2014) affirmed that severe sepsis and septic shock independently associated with short-term mortality on day 14 and day 30 for patients aged ≥85 years (30). The presence of septic shock was independently associated with in-hospital mortality in the multivariable analysis of our research with OR 2.84, 1.33- 6.05, p <0.001.

For source of BSI, the source of bacteremia was identified in 760/817 (93%) patients in UTI 156/817 (19.1%) and lower respiratory tract 417/817 (51%). In most other studies, the most common sources of infection were lower pulmonary infection and UTI. UTI is a common source of BSI that has been observed in this research. UTI was more common in older patients and very old patients reported in 26-51% of cases (21, 30). This was related to an indwelling urinary catheter. Even in the absence of an indwelling urinary catheter, higher rates of UTI in older patients could be secondary to incontinence or neurological disorders and to a higher rate of bacteremia associated with pyelonephritis (10). Our study reported respiratory tract as the source in 51% of the sources of BSI and primary respiratory infection was independently associated with mortality (OR 1.91, 1.14-3.21, p=0.015). These results were compatible with the results of other studies (31).

In Table 2, Gram-negative bacterial BSI-causing pathogens (65.7%) are higher than Gram-positive bacterial BSI-causing pathogens (34.3%). E. coli accounted for 17.3%, while S. aureus was 8.7%, compatible with the study of X. Zha (32). In another study in China, a 20-year surveillance study (1998-2017) revealed a compatible result. Lei Tian showed that the most common Gram-negative and Gram-positive pathogens were E.coli and S. aureus and the detection rate for methicillin-resistant S. aureus (MRSA) in hospitalized non-ICU patients increased from 8.4% in 1998–2002 to 63% in 2013–2017 (9).

For antibiotic resistance, the rate of pathogens and antibiotic resistance differ depending on the hospital and the region. The study population revealed ESBL(+) rate was 78/817 (9.5%). ESBL(+) for E. coli was 48.9% and for Klebsiella was 17.3%. Bacteria with ESBL(+) usually have high resistance to common antibiotics, but are sensitive to carbapenem. In the last decade, ESBL-producing pathogens were of great medical importance as these hydrolyse-lactam antibiotics. In recent years, the spread and incidence of ESBL pathogens have increased due to the overuse of expanded-spectrum cephalosporins in the hospital setting (32). About 80% of strains were resistant to penicillins and cephalosporins. Septicemia is a leading cause of mortality when caused by ESBL(+) strains. The enormous use of cephalosporins might become one of the major factors for the increasing rate of ESBL-producing microorganisms. E.coli rate with ESBL(+) was higher than Klebsiella rate with ESBL(+) identified in some investigations (9, 26). ESBL-producing pathogens are associated with mortality and have proved a controversial topic in different studies (33). However, ESBL-producing strains can prolong hospitalization times, increase medical expenditure, and inflict higher financial burdens on patients with these infections (34).

Dekinger et al. demonstrated that among patients aged 65 and older admitted to hospital, rates of MDR organisms are approximately 2-fold higher for MRSA and vancomycin-resistant enterococci and 3-fold higher for MDR Gram-negative bacteria compared to younger patients (35). Van Duin described the relationship between age and antimicrobial resistance in BSI by organism (36). Our investigation revealed the rate of antibiotic multi-resistance 596/817 (72.9%), of which the rate of MDR, XDR, PDR were 72%, 25.5%, 1.7%, respectively and antibiotic multi-resistance was not an independent prognostic factor of mortality. Leal et al. (2019) showed that 28.7% of BSI patients were caused by MDR Gram-negative bacteria. Age ≥ 60 was a risk factor for MDR bacteremia and K. pneumoniae was the most frequently observed causative agent and had the highest resistance level (37).

Third-generation quinolone such as levofloxacin was the cheapest amongst the most potent antimicrobial agents effective against both gram-negative and positive organisms. In this present study, quinolone had relatively high resistance to E. coli, Burkholderia cepaciae, and Sphingomonas paucimobilis but their resistance to other bacteria was low. In practice, quinolones were found to be the most potent empirical antibiotic for severe sepsis patients. However, these antibiotics induce a lot of resistance and their use must be limited and strictly supervised.

Our study identified that many bacteria had a high resistance to the third-generation cephalosporins, especially E. coli with ESBL(+), Burkholderia cepaciae, Sphingomonas paucimobilis, and Acinetobacter spp. The third-generation cephalosporins have been observed to become increasingly ineffective as shown in the published reports (31, 38). The enormous use of cephalosporins might become one of the major factors for increasing the rate of ESBL-producing microorganisms (35). Some previous studies have observed that

amongst aminoglycosides, even in the face of gentamicin resistance, amikacin might be recommended because of its good susceptibility patterns (32) We have found that gentamycin was sensitive to above 50% for S. aureus, E-coli, K. pneumoniae, S. aureus, while amikacin was more sensitive to K. pneumoniae, S. aureus than gentamycin. A research by Ho et al. at the same location demonstrated that Gram-negative pathogens still were sensitive to aminoglycosides, in line with current study (39). This antibiotic is probably less commonly used than the quinolone. In this investigation, some bacteria such as Acinetobacter sp, Stenotrophomonas maltophilia, Sphingomonas were highly resistant to Carbapenems but the carbapenems were found to be collectively effective for E. coli, S. aureus, K. pneumoniae, Burkholderia cepaciae, Achromobacter. However, the high cost of therapy with Carbapenems advocates the use of levofloxacin, amikacin as initial empirical therapy.

For Gram-positive isolates, we only performed antibiogram with vancomycin, linezolid, teicoplanin when blood cultures were positive for Staphylococcus species, especially S. aureus. We used antibiotics at the right dose and at the right time to limit resistance to antibiotics when suspected. The resistance rate for three antibiotics was low, approximately 0-4.4%. Some studies observed that S. aureus isolates were most sensitive to vancomycin, and teicoplanin glycopeptide antibiotics with a sensitivity rate of 100% (9, 12).

Limitations of the study

Several limitations of this study should be acknowledged. First, we performed a retrospective study, therefore some other pertinent information was not recorded. Second, it is a single-center study which limits its external validity. Third, there was a relatively small study sample, which can also influence its generalizability. Nevertheless, the sample size was large enough to demonstrate significant differences, so there was enough study power.

6. CONCLUSION

Tthe current study showed that BSI is often severe in older patients. The mortality rate is still high, especially for nosocomial BSI. It is very important to identify causative pathogens as well as antibiotic resistance to choose an appropriate treatment. The significant factors associated with mortality were age >75; SOFA >7; respiratory infection; ICU treatment and presentation with septic shock.

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REFERENCES

1. Yahav D, Eliakim-Raz N, Leibovici L, Paul M. Bloodstream infections in older patients. Virulence. 2016; (3): 341-352. doi: 10.1080/21505594.2015.1132142.
2. Reunes S, Rombaut V, Vogelaers D, Brusselaers N, Lizy C, Cankurtaran M, et al. Risk factors and mortality for nosocomial bloodstream infections in elderly patients. Eur J Intern Med. 2011; 22(5): e39-44. doi: 10.1016/j.ejim.2011.02.004.
3. Lee CC, Chen SY, Chang IJ, Chen SC, Wu S-CJM. Comparison of clinical manifestations and outcome of community-acquired bloodstream infections among the oldest old, elderly, and adult patients. Medicine (Baltimore). 2007; 86(3): 138-144.
4. Greenberg BM, Atmar RL, Stager CE, Greenberg SB. Bacteraemia in the elderly: predictors of outcome in an urban teaching hospital. J Infect. 2005; 50(4): 288-295. doi: 10.1016/j.jinf.2004.06.014.
5. Meyers BR, Sherman E, Mendelson MH, Velasquez G, Srulevitch-Chin E, Hubbard M, et al. Bloodstream infections in the elderly. Am J Med. 1989; 86(4): 379-384. doi: 10.1016/0002-9343(89)90333-1.
6. Hernández C, Fehér C, Soriano A, Marco F, Almela M, Cobos-Trigueros N, et al. Clinical characteristics and outcome of elderly patients with community-onset bacteremia. J Infect. 2015; 70(2): 135-143.
7. Wester AL, Dunlop O, Melby KK, Dahle UR, Wyller TB. Age-related differences in symptoms, diagnosis and prognosis of bacteremia. BMC Infect Dis. 2013; 13(1): doi: 10.1186/1471-2334-13-346.
8. Blot S, Cankurtaran M, Petrovic M, Vandijck D, Lizy C, Decruyenaere J, et al. Epidemiology and outcome of nosocomial bloodstream infection in elderly critically ill patients: a comparison between middle-aged, old, and very old patients. Crit Care Med. 2009; 37(5): 1634-1641.
9. Tian L, Zhang Z, Sun ZJAR, Control I. Antimicrobial resistance trends in bloodstream infections at a large teaching hospital in China: a 20-year surveillance study (1998-2017). Antimicrob Resist Infect Control. 2019; 8(1): 86.
10. Pien BC, Sundaram P, Raoof N, Costa SF, Mirrett S, Woods CW, et al. The clinical and prognostic importance of positive blood cultures in adults. The American journal of medicine. 2010; 123(9): 819-828.
11. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987; 40(5): 373-383. doi: 10.1016/0021-9681(87)90171-8.
12. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016; 315(8): 801-810.
13. Martin-Loeches I, Guia MC, Vallecoccia MS, Suarez D, Ibarz M, Irazabal M, et al. Risk factors for mortality in elderly and very elderly critically ill patients with sepsis: a prospective, observational, multicenter cohort study. Ann Intensive Care. 2019; 9(1): 26.
14. Jones AE, Trzeciak S, Kline JA. The Sequential Organ Failure Assessment score for predicting outcome in patients with severe sepsis and evidence of hypoperfusion at the time of emergency department presentation. Crit Care Med. 2009; 37(5): 1649-1654.
15. Testing TECoAS. Breakpoint tables for interpretation of MICs and zone diameters. Version 13.0 2023 [cited 2023 October 15]. Available from: http://www.eucast.org.
16. Gajic I, Kabic J, Kekic D, Jovicevic M, Milenkovic M, Mitic

Culafic D, et al. Antimicrobial Susceptibility Testing: A Comprehensive Review of Currently Used Methods. Antibiotics (Basel). 2022; 11(4).
17. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect. 2012; 18(3): 268-281. doi: 10.1111/j.1469-0691.2011.03570.x.
18. (CLSI) CaLSI. Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Eighth Informational Supplement. CLSI Document M100-S28 2023 [cited 2023 October 15]. Available from: https://clsi.org/standards/products/microbiology/documents/m100/.
19. (CLSI) CaLSI. Analysis and presentation of cumulative antimicrobial susceptibility test data. CLSI Document M39-A4 2022 [cited 2023 October 15]. Available from: https://clsi.org/standards/products/microbiology/documents/m39/.
20. Beckett CL, Harbarth S, Huttner B. Special considerations of antibiotic prescription in the geriatric population. Clin Microbiol Infect. 2015; 21(1): 3-9. doi: 10.1016/j.cmi.2014.08.018.
21. Rebelo M, Pereira B, Lima J, Decq-Mota J, Vieira JD, Costa JNJIaom. Predictors of in-hospital mortality in elderly patients with bacteraemia admitted to an Internal Medicine ward. 2011; 4(1): 1-9.
22. Burlaud A, Mathieu D, Falissard B, Trivalle CJAog. Mortality and bloodstream infections in geriatrics units. Archives of gerontology geriatrics. 2010; 51(3): e106-e9.
23. Crane SJ, Uslan DZ, Baddour LMJTAjom. Bloodstream infections in a geriatric cohort: a population-based study. 2007; 120(12): 1078-1083.
24. Rodríguez-Baño J, López-Prieto MD, Portillo MM, Retamar P, Natera C, Nuño E, et al. Epidemiology and clinical features of community-acquired, healthcare-associated and nosocomial bloodstream infections in tertiary-care and community hospitals. Clin Microbiol Infect. 2010; 16(9): 1408-1413. doi: 10.1111/j.1469-0691.2009.03089.x.
25. Gavazzi G, Mallaret MR, Couturier P, Iffenecker A, Franco A. Bloodstream infection: differences between young-old, old, and old-old patients. J Am Geriatr Soc. 2002; 50(10): 1667-1673. doi: 10.1046/j.1532-5415.2002.50458.x.
26. Zha X, Song Y, Jin Z, Shen Z, Wang Q, Hu X. Etiological and antibiotic resistance profile of bloodstream infections in 107 old patients. Chinese Journal of Infection and Chemotherapy. 2017; 17: 77-81. doi: 10.16718/j.1009-7708.2017.01.014.
27. Kaye KS, Marchaim D, Chen TY, Baures T, Anderson DJ, Choi Y, et al. Effect of nosocomial bloodstream infections on mortality, length of stay, and hospital costs in older adults. J Am Geriatr Soc. 2014; 62(2): 306-311.
28. Dafna Yahav ASVDYALFYA-GMP, Leonard L. Presentation of infection in older patients—a prospective study. Annals of Medicine. 2015; 47(4): 354-358. doi: 10.3109/07853890.2015.1019915 , note = PMID: 25856541.
29. Nasa P, Juneja D, Singh O. Severe sepsis and septic shock in the elderly: An overview. World J Crit Care Med. 2012; 1(1): 23-30.
30. Retamar P, López-Prieto MD, Rodríguez-López F, de Cueto M, García MV, González-Galan V, et al. Predictors of early mortality in very elderly patients with bacteremia: a prospective multicenter cohort. Int J Infect Dis. 2014; 26: 83-87. doi: 10.1016/j.ijid.2014.04.029.
31. Gea-Banacloche JC, Opal SM, Jorgensen J, Carcillo JA, Sepkowitz KA, Cordonnier C. Sepsis associated with immunosuppressive medications: an evidence-based review. Crit Care Med. 2004; 32(11 Suppl): S578-90. doi: 10.1097/01.ccm.0000143020.27340.ff.
32. Sarkar SK, Aritra B, Kishalay P, Mandal SM. A Retrospective Study on Bacteria Causing Blood Stream Infection: Antibiotics Resistance and Management. Indian Journal of Pharmaceutical Sciences. 2018; 80: 547-551.
33. Ben-David D, Kordevani R, Keller N, Tal I, Marzel A, Gal-Mor O, et al. Outcome of carbapenem resistant Klebsiella pneumoniae bloodstream infections. Clin Microbiol Infect. 2012; 18(1): 54-60. doi: 10.1111/j.1469-0691.2011.03478.x.
34. Leistner R, Gürntke S, Sakellariou C, Denkel LA, Bloch A, Gastmeier P, et al. Bloodstream infection due to extended-spectrum beta-lactamase (ESBL)-positive K. pneumoniae and E. coli: an analysis of the disease burden in a large cohort. Infection. 2014; 42(6): 991-997. doi: 10.1007/s15010-014-0670-9.
35. Denkinger CM, Grant AD, Denkinger M, Gautam S, D'Agata EM. Increased multi-drug resistance among the elderly on admission to the hospital--a 12-year surveillance study. Arch Gerontol Geriatr. 2013; 56(1): 227-230. doi: 10.1016/j.archger.2012.05.006.
36. van Duin D. Diagnostic challenges and opportunities in older adults with infectious diseases. Clin Infect Dis. 2012; 54(7): 973-978.
37. Leal HF, Azevedo J, Silva GEO, Amorim AML, de Roma LRC, Arraes ACP, et al. Bloodstream infections caused by multidrug-resistant gram-negative bacteria: epidemiological, clinical and microbiological features. BMC Infect Dis. 2019; 19(1): 609.
38. Chandel DS, Johnson JA, Chaudhry R, Sharma N, Shinkre N, Parida S, et al. Extended-spectrum beta-lactamase-producing Gram-negative bacteria causing neonatal sepsis in India in rural and urban settings. J Med Microbiol. 2011; 60(Pt 4): 500-507.
39. Ho DS, Dinh HC, Le TD, Ho DT, Ngo HT, Nguyen CD. Sputum culture and antibiotic resistance in elderly inpatients with exacerbation of chronic obstructive pulmonary disease at a tertiary geriatric hospital in southern Vietnam. Aging Clin Exp Res. 2023; 35(6): 1347-1356. doi: 10.1007/s40520-023-02401-2.