



Bacterial Spectrum and Antimicrobial Susceptibility Patterns in Septicemia Suspected Patients

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Authors

Soheila Erfani, MD^{1*}
Majid Zare Bidaki, PhD²
Effat Alemzadeh, PhD²
Azadeh Ebrahimzadeh, PhD^{2*}

¹Nuclear Medicine Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

²Infectious Diseases Research Center, Birjand University of Medical Sciences, Birjand, Iran

* Correspondence

Infectious Diseases Research Center, Birjand University of Medical Sciences, Birjand, Iran.
Email: MR14436@yahoo.com.
Infectious Diseases Research Center, Birjand University of Medical Sciences, Birjand, Iran.
Email: AlemzadehEffat@bums.ac.ir

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ABSTRACT

Background: In this comprehensive study, the prevalence of sepsis, a potentially life-threatening condition, was investigated among 477 patients displaying sepsis symptoms. **Materials & Methods:** A detailed questionnaire was used to capture the patients' demographic information and clinical treatment outcomes. The E-test method was employed to determine the susceptibility of Gram-positive bacteria to vancomycin and Gram-negative bacteria to cefepime, ceftriaxone, and imipenem.

Findings: Among the participants, 40 patients (8.6%) were diagnosed with septicemia, a condition whose prevalence significantly increased with age ($p = .001$). Out of 40 patients with positive blood cultures, 14 (35%) were infected by Gram-positive bacteria, while 26 (65%) were infected by Gram-negative bacteria. *Acinetobacter lwoffii* and *Staphylococcus epidermidis* were identified as the most common causes of sepsis among Gram-negative (30.7%) and Gram-positive (57.1%) bacteria, respectively. Gram-negative bacteria exhibited the highest resistance to ceftriaxone (38.4%) and the highest susceptibility to imipenem (84.6%) in both laboratory and clinical settings. Gram-positive bacteria demonstrated the high susceptibility to vancomycin (78.5%), with only four patients exhibiting resistance to vancomycin in both laboratory and clinical settings. Encouragingly, there was a 77.5% concordance between laboratory and clinical antibiotic susceptibility testing results.

Conclusion: Based on these findings, vancomycin and imipenem are recommended as the preferred antibiotics for Gram-positive and Gram-negative bacteria, respectively. Given the high concordance (77.5%) between laboratory and clinical results, it is suggested to perform antibiogram test using E-test method on blood culture isolates in septicemia cases to guide appropriate antibiotic treatment.

Keywords: Septicemia, Clinical resistance, Bacterial agents, E-test method, Antibiotic

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Introduction

Bacteria, fungi, viruses, and protozoa are all capable of causing bloodstream infections (BSI). Among these pathogen groups, bacteria are the most common culprits [1]. Sepsis, a condition characterized by the rapid multiplication of bacteria in the bloodstream, poses a significant risk as these bacteria could release toxins that harm the host's organs. BSI could be categorized into two stages based on the severity and extent of organ failure: sepsis and septic shock [2, 3]. Studies conducted in developed countries have shown that Gram-positive bacteria are frequently implicated in sepsis cases. The most prevalent Gram-positive organisms identified in these studies include *Staphylococcus aureus*, *Enterococcus* species, and *Streptococcus pneumoniae*. On the other hand, Gram-negative bacteria such as *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas* species are also commonly found in sepsis cases [4-8]. However, it is important to note that the bacteriology of bloodstream infections could vary significantly in low and low-middle income countries due to regional and population differences [7]. Regardless of age, gender, or location, diarrheal disorders have been identified as the most common underlying cause of sepsis, with approximately 9.21 million cases attributed to diarrheal diseases [3]. Bacterial bloodstream infections are a major cause of mortality and morbidity worldwide, with mortality rates ranging from 4 to 41.5% depending on factors such as severity, age, sex, and other risk factors [9]. The elderly population is particularly vulnerable to BSI due to weakened immune systems often associated with comorbid conditions [3, 10]. The increasing incidence of BSI-related morbidity and mortality could be attributed to changing epidemiological patterns, inadequate antimicrobial guidelines, the

rise of antibiotic resistance, and limited diagnostic facilities [11]. Global studies have reported a rise in the number of BSI cases [12]. In Europe and North America, population-based studies have estimated 1,200,000 and 575,000–677,000 BSI incidents per year, respectively [6]. Additionally, a recent meta-analysis revealed the prevalence of community-onset BSI, ranging from 14.6% in Africa to 2.9% in Europe [13]. Sub-Saharan Africa, in particular, faces a significant burden of illness and mortality among adults due to bloodstream infections [3, 14]. Arbitrary use of antibiotics, particularly for self-treatment of suspected infections, and limited awareness of drug resistance have contributed to the rapid spread of resistant bacteria. Consequently, treating BSIs has become increasingly challenging for physicians, as definitive therapies are only occasionally effective [15, 16].

Objectives: In light of these concerns, this study aimed to investigate the bacterial profile and antimicrobial susceptibility patterns among patients with suspected septicemia in Valiasr hospital, the largest hospital in northeastern Iran, specifically Birjand, in 2020. By identifying the prevalent bacteria and their susceptibility to antibiotics, it is hoped to help develop effective treatment strategies for septicemia cases in this region.

Materials and Method

Study design and data collection: This hospital-based cross-sectional study was conducted in Valiasr hospital situated in South Khorasan province in Iran, specifically Birjand city. This study aimed to delve into the realm of septicemia by enrolling 477 patients exhibiting symptoms associated with this condition. These eligible patients formed the foundation of the current investigation. To ensure ethical practices, written informed consent was obtained from each participant

before inclusion in the study. Also, relevant socio-demographic information, such as age and sex, was collected from the participants. Furthermore, all individuals underwent thorough examinations conducted by experienced and trained physicians as part of the research process.

Blood sample collection, culture, and identification: In this study, 10 mL of venous blood from each participant was aseptically collected into sterile blood culture bottles containing tryptic soy broth (TSB) at a ratio of 1:10 to 100 mL. The samples were promptly transported to the microbiology laboratory for further analysis, including culture and antimicrobial susceptibility testing. It is important to note that blood samples were collected prior to the initiation of any antibiotic treatment. In the laboratory, all culture broths were incubated at 37 °C and examined daily for signs of microbial growth. These signs included uniform or subsurface turbidity, hemolysis, broth coagulation, surface floccular deposits, pellicle formation, and gas production. The incubation period lasted up to seven days to allow sufficient time to detect any potential growth. For further analysis and identification of bacterial growth, subcultures of blood cultures were performed using aseptic techniques. The subcultures were plated on various agar media, including blood agar, chocolate agar, MacConkey agar, and mannitol salt agar, all from Oxoid Ltd, UK. The blood agar, MacConkey agar, and mannitol salt agar plates were incubated aerobically at 37 °C for 18 to 24 hours. In contrast, the chocolate agar plates were incubated in a candle jar, generating approximately 10%-5 CO₂, at the same temperature for 24 to 48 hours. Bacterial growth in the subcultures was identified based on their characteristic appearance, including colony morphology, Gram reaction, and specific biochemical reactions. Standard methods

and identification panels were employed to accurately determine the species of bacterial isolates.

Antimicrobial susceptibility testing: To determine the susceptibility and resistance of bacteria isolated from patients' blood samples, the E-test method was employed. In this study, E-test strips (Liofilchem, Italy) were used to assess the minimum inhibitory concentration (MIC) of cefepime, ceftriaxone, imipenem, and vancomycin. The process involved several steps. Firstly, bacterial growth was observed on 10 cm plates containing Müller-Hinton agar medium. Then pure bacterial colonies were collected and mixed with sterile physiological saline solution using a sterile swab. This step ensured the formation of a uniform bacterial suspension. To standardize this approach, a control concentration with a turbidity equivalent to 0.5 McFarland was prepared from fresh microbial cultures. Using a sterile swab, the bacteria were cultured on Müller-Hinton agar medium from four different directions. Once the bacteria were fully absorbed into the culture medium, the E-test strips containing a concentration gradient of each antibiotic were carefully placed on Müller-Hinton agar medium. It is crucial to note that the E-test strips remained stationary throughout the incubation process. The culture plates were then incubated at 37 °C for 24 hours without moving the E-test strips. Following the incubation period, the plates were examined, and the numbers were recorded next to the intersection of the non-growth halo with the E-test strip. These numbers represented the quantitative values of the minimum inhibitory concentrations (MIC). By employing the E-test method and analyzing the MIC values obtained, the susceptibility and resistance profiles of the bacteria isolated from the blood samples were determined. This information was crucial

for evaluating their response to cefepime, ceftriaxone, imipenem, and vancomycin.

Data analysis: The data were analyzed using SPSS software V. 19. Descriptive indicators including mean, standard deviation, frequency, and percentage were reported.

Findings

General characteristics: During the study period, a total of 477 patients with suspected septicemia were admitted to Valiasr hospital. Among them, 237 (49.7%) were male, resulting in an overall sex distribution ratio of 1:1. The age group of 70-90 years included 148 (31%) patients. Out of the 477 blood samples processed by culture, 40 (8.6%) culture sets showed bacterial growth. Among the blood culture-positive cases, 16 (40%) were male, and 24 (60%) were female, resulting in a male-to-female ratio of 1:1.5. Chi-square test results indicated no significant difference in the frequency of sepsis between male and female patients ($p = .21$). In the age distribution analysis, it was observed that the age groups of 70-90 (21 of 40, 52.5%) and older than 90 years (4 of 40, 10%) had the highest number of positive cases. These findings indicated a significant correlation between septicemia and older age ($p = .001$) (Table 1).

Bacteriological profiles and distribution of bacterial isolates among blood culture-positive patients:

A total of nine bacterial pathogens were identified in 477 blood culture sets analyzed in this study. Among these organisms, 4 (44.5%) were Gram-positive bacteria, including *S. epidermidis*, *S. aureus*, *S. pneumoniae*, and *Micrococcus* species. The remaining 5 (55.5%) were Gram-negative bacteria, which consisted of *A. lwoffii*, *K. pneumoniae*, *K. oxytoca*, *E. coli*, and *Morganella morganii*. Among patients with blood culture-positive results ($n=40$), the most frequently isolated bacteria were *S. epidermidis* and *A. lwoffii*, each accounting for 20% of cases ($n=8$), followed by *E. coli*, which was identified in 17.5% of cases ($n=7$) (Table 2).

Antimicrobial resistance/susceptibility patterns of the bacterial isolates: Table 3 presents the antimicrobial resistance/susceptibility profiles of the isolates.

- G-negative bacteria: *A. lwoffii* displayed the highest susceptibility (62.5%) to imipenem and considerable resistance (62.5%) to ceftriaxone. Both *K. pneumoniae* (80%) and *K. oxytoca* (100%) exhibited the highest susceptibility to imipenem. However, *K. pneumoniae* isolates (60%) showed resistance to ceftriaxone, while *K*

Table 1) Characteristics of patients with suspected septicemia and patients with sepsis-positive blood culture

Characteristics	Total (%) N=477	Positive (%) N= 40	Negative (%) N=437	Chi Square	P Value
Age					
13-30	112 (23.5)	2 (5)	110 (25.17)	15.64	.001
30-50	86 (18)	4 (10)	82 (18.76)		
50-70	110 (23.1)	9 (22.5)	101 (23.11)		
70-90	148 (31)	21 (52.5)	127 (29.06)		
>90	21 (4.4)	4 (10)	17 (3.89)		
Sex					
Male	237 (49.7)	16 (40)	221 (50.57)	1.56	.21
Female	240 (50.3)	24 (60)	216 (49.43)		

Table 2) Bacteriological profiles and distribution of bacterial isolates

Isolated Organism (Total =9)	Frequency	Percentage (%)
G-negative		
<i>Acinetobacter lwoffii</i>	8	20
<i>Klebsiella pneumoniae</i>	5	12.5
<i>Klebsiella oxytoca</i>	5	12.5
<i>Escherichia coli</i>	7	17.5
<i>Morganella morganii</i>	1	2.5
Total	26	65
G-positives		
<i>Staphylococcus epidermidis</i>	8	20
<i>Staphylococcus aureus</i>	4	10
<i>Streptococcus pneumoniae</i>	1	2.5
<i>Micrococcus species</i>	1	2.5
Total	14	35

oxytoca isolates (20%) showed resistance to ceftriaxone and cefepime. *E. coli* isolates demonstrated 100% sensitivity to both imipenem and cefepime, and only a low level of resistance (14.3%) was detected for ceftriaxone. On the other hand, *M. morganii* demonstrated a high level of susceptibility (100%) to ceftriaxone, imipenem, and cefepime, without exhibiting any resistance to these antibiotics.

- G-positive bacteria: *S pneumoniae* exhibited 100% sensitivity to vancomycin, ceftriaxone, imipenem, and cefepime. Also, 75% of *S. aureus* isolates displayed sensitivity to vancomycin, while 25% showed intermediate sensitivity. *S. epidermidis* isolates also demonstrated 75% sensitivity and 12.5% resistance to vancomycin. *Micrococcus species*, on the other hand, exhibited a high level of sensitivity to vancomycin (100%).

Discussion

The dynamic nature of the bacterial pattern in septicemia emphasizes the importance of understanding the profile of bacteria and their antibiotic resistance/susceptibility

patterns. This knowledge is crucial for designing appropriate interventions [17]. In this study, the prevalence of sepsis cases was 8.6%, which is lower compared to other studies conducted in Uganda (12.6%) and Nigeria (18.0%) [18, 19]. The fluctuation in prevalence could be attributed to factors such as the size of the study population, the duration of the study, the number of blood samples taken, and the presence or absence of clinical indications. Additionally, factors like clinical care received, antimicrobial agents used, nature of patients, geographical locations, and sample size might have also contributed to the observed variations [3, 7]. Interestingly, this study revealed a female preponderance in the prevalence of sepsis, with a female to male ratio of 60 to 40%. However, no statistically significant association was found between gender and sepsis ($p = .21$). This finding aligns with the results of other studies [20, 21]. One possible reason for this gender difference could be attributed to differences in the immune system between males and females. Angele et al. (2014) and Liu et al. (2014) demonstrated that females produced more estrogen than males, which positively affected the function of their immune system. Expanding on this finding, estrogen has been shown to enhance the immune response by promoting the production of antibodies and activating immune cells. This hormonal advantage in females may contribute to their ability to mount a stronger immune response against bacterial infections, potentially leading to a lower prevalence of sepsis in females compared to males. Further research is needed to explore the intricate interactions between hormones, the immune system, and the development of sepsis to gain a comprehensive understanding of this phenomenon [21, 22].

Among the 40 culture-positive cases in this study, the highest number of isolates

Table 3) Antimicrobial resistance /susceptibility patterns of bacterial isolates from blood cultures of patients

Bacterial Species	Total N		VAN N (%)	CTR N (%)	CFP N (%)	EMP N (%)
G-positive						
<i>Staphylococcus epidermidis</i>	8	S	6 (75)	NT	NT	NT
		I	1 (12.5)			
		R	1 (12.5)			
<i>Staphylococcus aureus</i>	4	S	3 (75)	NT	NT	NT
		I	1 (25)			
		R	0			
<i>Streptococcus pneumoniae</i>	1	S	1 (100)	1 (100)	1 (100)	1 (100)
		I	0	0	0	0
		R	0	0	0	0
<i>Micrococcus species</i>	1	S	1 (100)	NT	NT	NT
		I	0			
		R	0			
G-negative						
<i>Acinetobacter lwoffii</i>	8	S	NT	1 (12.5)	4 (50)	5 (62.5)
		I		2 (25)	0	0
		R		5 (62.5)	4 (50)	3 (37.5)
<i>Klebsiella pneumoniae</i>	5	S	NT	1 (20)	3 (60)	4 (80)
		I		1 (20)	0	0
		R		3 (60)	2 (40)	1 (20)
<i>Klebsiella oxytoca</i>	5	S	NT	3 (60)	4 (80)	5 (100)
		I		1 (20)	0	0
		R		1 (20)	1 (20)	0
<i>Escherichia coli</i>	7	S	NT	6 (85.7)	7 (100)	7 (100)
		I		0	0	0
		R		1 (14.3)	0	0
<i>Morganella morganii</i>	1	S	NT	1 (100)	1 (100)	1 (100)
		I		0	0	0
		R		0	0	0

*Key: S = sensitive; I = intermediate; R = resistant. NT: no tested. VAN: vancomycin, CTR: ceftriaxone, CFP: cefapime, EMP: imipenem

(n=21) was found in the age group of 70-90 years, accounting for 52.5% of all cases. In the age group of 50-70 years, nine isolates were found, representing 22.5% of culture-positive cases. These findings indicate a significant increase in the prevalence of infection with advancing age ($p = .001$). In other words, as individuals grow older, their susceptibility to septicemia increases. This finding aligns with the results of previous research conducted by Finfer and Machado (2016), reporting a higher frequency of sepsis cases in the age group of 61-80 years [23]. It is important to note that the reasons

behind this age-related increase in sepsis prevalence are multifactorial. Factors such as decreased immune system function, presence of comorbidities, weakened physiological reserves, and increased exposure to healthcare settings may contribute to higher susceptibility among the elderly. Additionally, age-related changes in the microbiome and organ dysfunction could further exacerbate the risk of developing septicemia. Understanding the age-specific patterns of sepsis prevalence is crucial for tailoring preventive strategies and providing appropriate clinical care

for different age groups. The elderly, in particular, may require closer monitoring and targeted interventions to mitigate the risk of septicemia [23].

In this study, it was observed that Gram-negative bacteria were the predominant causative agents of sepsis, accounting for 65% of all cases, while Gram-positive organisms accounted for 35%. These findings are consistent with the results of several other studies conducted in different regions. For example, studies conducted in Uganda (53.2%)^[18] and Jalandhar (India) (58.2%)^[24] have reported similar results, with Gram-negative bacteria being the most commonly isolated pathogens.

In contrast, studies conducted in Ethiopia^[3] and Southwest Ethiopia^[7] have reported Gram-positive bacteria as the dominant group. This variation in etiological agents across different countries may be attributed to differences in the types of pathogens present, patient population characteristics, sample size, study duration, and geographical location^[25-27]. Further analysis in this study revealed that the most common causes of septicemia were *S. epidermis* and *A. lwoffii*, each accounting for 20% of cases. Additionally, 17.5% of septicemia cases were caused by *E. coli*, while the lowest prevalence was associated with septicemia infections caused by *M. morgani*, *S. pneumoniae*, and *M. luteus*, each accounting for 2.5% of cases. These findings are consistent with the results of previous studies, reporting *S. epidermidis* as the most commonly isolated bacterial agent.

Furthermore, studies conducted in various settings have consistently identified *E. coli* and *S. epidermidis* as the most frequently isolated bacteria in blood cultures, which aligns with the current study findings. Understanding the common etiological agents of sepsis is crucial for guiding appropriate empirical antibiotic therapy

and infection control measures^[21-23, 28-30]. This study yielded important findings regarding the antibiotic resistance and susceptibility patterns of Gram-negative and Gram-positive bacteria causing sepsis. Gram-negative bacteria showed the highest resistance (62.5%) to ceftriaxone and complete susceptibility to imipenem (100%). Similarly, Gram-positive bacteria exhibited the highest susceptibility (100%) to vancomycin. These results align with the findings of a study conducted by Munita and Arias (2016)^[31], reporting high resistance to ceftriaxone and low resistance to imipenem. The high susceptibility to imipenem could be attributed to its relatively novel status as an antibiotic and cautious prescribing practices under the guidance of infectious disease specialists. On the other hand, the high resistance to ceftriaxone might be linked to its overuse in unnecessary cases and its widespread prescription by both specialist and non-specialist physicians in outpatient settings.

In conclusion, this study provides valuable insights into the prevalence of sepsis in Birjand with an overall rate of 8.6%. *S. epidermidis*, *A. lwoffii*, and *E. coli* were identified as the most common causative agents of sepsis. Based on the antimicrobial susceptibility test results, it could be inferred that imipenem and vancomycin are effective drugs against Gram-negative and Gram-positive bacteria, respectively. These findings have important implications for clinical practice, as they highlight the need for prudent antibiotic prescribing practices and the importance of regular monitoring of resistance patterns. By using appropriate antibiotics based on susceptibility testing, healthcare providers could optimize treatment outcomes and minimize the development of antibiotic resistance. Ongoing surveillance of antimicrobial resistance is crucial to inform empirical

treatment guidelines and ensure effective management of septicemia.

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Ethical consideration: Before commencing the research project, it was ensured that all patients were fully informed about the aim of the study. Informed consent was obtained from each participant, emphasizing the importance of their voluntary participation. All individuals were reassured that their personal information would be treated with utmost confidentiality and privacy. To ensure ethical practices, the research study received the approval of the Research Assistant of Birjand University of Medical Sciences, with the assigned code: IR.BUMS.REC.1398.181.

Conflicts of Interest: The authors declare that they have no conflict of interest.

Consent to participate: Patients were satisfied to participate in the study.

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