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Review Article

Bacterial and Antimicrobial Susceptibility in Bloodstream Infections

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ABSTRACT

Bloodstream infections (BSI) are considered among the top ten causes of death globally. Among various microorganisms, bacteria are majorly responsible for the onset of BSI. The study aimed to identify bacterial profile, antimicrobial susceptibility patterns, and factors associated with BSI-suspected patients, including incidence and mode of occurrence of common diseases, detection methods, disease mechanism, and treatment options. BSI can be further classified into sepsis and septic shock based on the degree of organ failure and the overall onset of drug-resistant bacteria-related mortality and morbidity**.** The prevalence of BSI is related to several variables such as the patient's age, immunity, mode of entry of virulence factors, and control and prevention strategies. BSI can typically be characterized by chills, low blood pressure, changes in mental state, fever, hypothermia, excessive sweating, and the possibility of organ malfunction. Falciparum Malaria, UTIs (Urinary Tract Infections), and Methicillin-resistant *Staphylococcus aureus* Bacteremia are common illnesses arising due to BSI. Treatments include routine vaccinations, oral therapies, bacteremia management for MRSA, and anti-staphylococcal treatment. However, treatment for bacteremia remains challenging despite advances due to the pathogenicity of the organism, weak response to antibiotics, and rising multidrug resistance. As a result, combinational therapy is receiving more attention for treatment.

1. INTRODUCTION

Bloodstream infections (BSI) are caused by pathogenic microorganisms which include bacteria, fungi, viruses, and protozoa leading to a mortality rate of 70% worldwide (Li *et al.*, 2022). BSI is caused by bacteria, viruses, protozoa, and fungus; bacteria, being the primary causative agent. The word "bacteremia" refers to the presence of live bacteria in blood without any bacterial proliferation. This condition can be temporary, sporadic, or continuous. When bacteria enter the circulation and actively multiply, it can lead to septicemia. Toxins that harm the host's organs can be released by these microorganisms. Based on the intensity and extent of organ failure, two stages of blood shock illness can be distinguished: sepsis and septic shock (Birru *et al.*, 2021). An estimate shows the incidence of BSI at between 113 and 204 cases per 100,000 individuals (Kern and Rieg, 2020). An independent association was shown between an increased risk of mortality and ineffective antibiotic therapy for bloodstream infections (Kadri *et al.*, 2021).

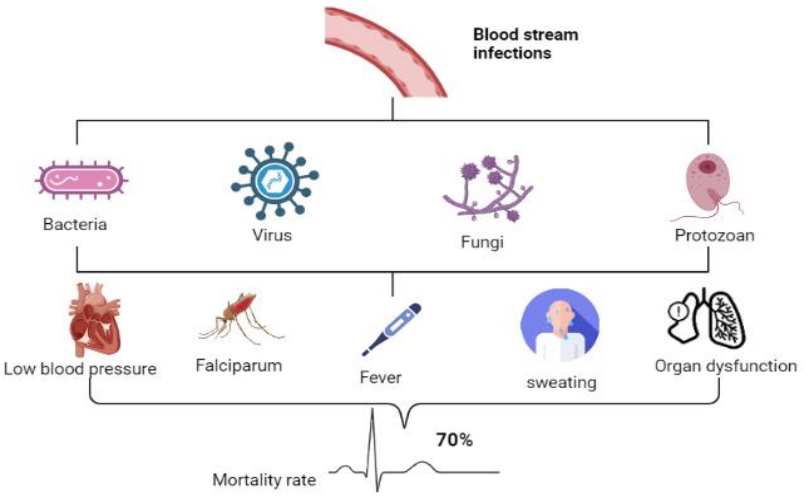

Figure 1. Bloodstream infections: causes, symptoms and mortality

The data on bacterial resistance and epidemiology associated with BSI can be a potential source to establish the most effective empirical antibiotic therapy. In the context of rising antimicrobial resistance (AMR), accurate monitoring is essential for identifying the distribution of bacterial species causing BSI and laying the foundation for appropriate empirical therapy (Chen *et al.*, 2022).

Antimicrobial resistance (AMR) arises from the defense mechanisms of microbes against antibiotics. After evaluating the data of about 12,000 articles, it was revealed that one thousand full-text articles comprised 109 studies in which AMR was associated with a 58% increase in the death risk from BSI, an increase in the chance of being admitted to the intensive care unit, an additional week spent in a hospital, and an increase in direct medical costs of around $12,000 in each instance (López-Cortés *et al.*, 2020). Lethality is on the rise which is caused by an insufficient dosage of antibiotics delivered during the first 24 hours (Costa and Carvalho, 2022). Based on research done over the past 10 years, urinary tract infections (UTIs) are the most often reported clinical infections in Pakistan (16.1%). In 2008 (30.11%) of the examinations, *Escherichia coli* was discovered, and they were all significantly resistant to first-line antibiotics. MRSA was found in 49% of all reported cases of *Staphylococcus aureus* (Bilal *et al.*, 2021). The present study aims to review and discuss bacterial and antimicrobial susceptibility profiles in bloodstream infections, incidence, and mode of occurrence, detection methods, disease mechanism, common diseases, and treatment options (Figure 1).

1.1 Bacterial Infections in Blood

Previous studies have shown that bloodstream infections acquired in the community and nosocomial settings are becoming far more common. The most frequently isolated bacteria linked to BSI globally have been identified to be *Streptococcus pneumoniae*, *S. aureus*, as well as *E. coli* (Browne *et al.*, 2020). Early diagnosis and prompt bacterial identification are critical for the successful treatment of BSI in normally sterile body fluids (Yang and Tao,

2023). Epidemiological statistics show that BSI can affect hematological patients at varying incidences (ranging from 9 to 40%), with a death rate close to 40%. Polymicrobial bloodstream infections (pBSIs) occur in a small number of cases, but there is very little data on their frequency, clinical presentation, and prognosis. A limited amount of available evidence suggests that many bacteria may be responsible for PBS. The bacteria that are most frequently found include coagulase-negative *Staphylococcus* species, particularly *Pseudomonas* species and *E. coli* (Facchin *et al.*, 2022). All age groups are affected by these diseases as the primary cause of sickness and mortality (Musicha *et al.*, 2017), with immunocompromised persons being the most affected (Israeli *et al.*, 2020). Such BSIs are widespread in hospitals and are serious illnesses that can be deadly (Deku *et al.*, 2019).

Every year, BSI impacts 30 million people worldwide, resulting in 6 million deaths, including 3 million babies, and 1.2 million cases of sepsis in children (Evans *et al.*, 2021). It is estimated that between 11% and 28% of people living in Eastern African countries have BSI. Hospital and laboratory monitoring records indicate that Ghana has 9.3% to 11.2% BSI rates (Deku *et al.*, 2019). (Foglia *et al.*, 2023). In previous years, BSI complications have been one of the top 10 causes of death worldwide. The hospital death rates associated with sepsis were 17% and 26%, respectively. Based on data from high-income nations, estimates of the number of sepsis cases worldwide are 31.5 million and 19.4 million serious sepsis cases, respectively, with 5.3 million deaths possible annually (Li *et al.*, 2022).

1.2 Bacterial Species involved in Blood Infections

Together with coagulase-negative bacteria, other possible microorganisms include *Klebsiella* species, *Pseudomonas aeruginosa*, *E. coli*, *Haemophilus influenzae*, and *Neisseria meningitidis*. Gram-positive bacteria include *Enterococcus faecium*, *Streptococcus agalactiae*, *S. aureus*, *S. pneumoniae*, and coagulase-negative *Staphylococci* (CoNS) (Deku *et al.*, 2019). Table 1 shows the list of major BSI-causing bacterial strains via the Sentinel Surveillance Program for Tracking Antimicrobial Resistance (SENTRY) program. The incidence of BSI is influenced by several variables, including the acquisition of virulence factors by pathogens in the bloodstream, the age of patients upon admission, and the high proportion of immunocompromised patients (Dargère *et al.*, 2018). Other factors that affect the incidence of BSI are related to the development and implementation of BSI prevention and control strategies (Ershova *et al.*, 2018).

1.3 Occurrence and Detection Methods

BSIs may be classified into three categories based on how they manifest: infections that overwhelm immune-competent hosts immunity, infections that affect individuals towards the end of their life, and infections that arise from pathological abnormalities that put them at risk for infection. A few symptoms associated with BSI include fever, chills, reduced vascular tone, altered mental status, hypothermia, lower blood pressure, hyperventilation, excessive sweating, and possible organ dysfunction.

The diagnostic methods used to identify bacteria and assess their responsiveness to different antibiotics play a significant role in controlling infectious diseases. Quick diagnostic response times have a critical role in the incidence of BSIs, as the duration between the onset of symptoms and the administration of appropriate antibiotics is negatively correlated with the patient's likelihood of survival. For effective antibiotic therapy and infection management, early identification of

Table 1. The rank order of pathogens causing BSI worldwide submitted to the SENTRY Program, 1997–2016 (Diekema *et al.*, 2019)

Rank	Pathogens			
	Hospital onset (n = 103,945)	**%**	**Community onset (n =102,638)**	**%**
1	*S. aureus*	21.3	*E. coli*	26.6
2	*E. coli*	15.6	*S. aureus*	22.4
3	*K. pneumoniae*	8.8	*K. pneumoniae*	7.2
4	*P. aeruginosa*	7.4	*S. pneumoniae*	5.2
5	*E. faecalis*	6.4	*E. faecalis*	4.7
6	*S. epidermidis*	4.8	*P. aeruginosa*	3.7
7	*E. faecium*	4.3	*E. cloacae*	2.4
8	*E. cloacae*	4.0	*S. agalactiae*	2.3
9	*A. baumanniia*	3.2	*S. epidermidis*	2.2
10	*S. marcescens*	2.1	*P. mirabilis*	2.0

pathogenic strains is essential which can cause infections in biofluids such as abdominal (ascitic, peritoneal, and biliary), cerebrospinal, pleural, synovial, and amniotic fluids. The conventional microbiological methods for isolating bacteria from biofluids include culture in enrichment broth and solid media (Deku *et al.*, 2019). These approaches might lead to a delay of up to 4 days in the detection and identification of pathogens. Rapid Gram staining offers quick identification data but has little diagnostic utility since a significant number of bacteria must be present to get a positive result (Rubio *et al.*, 2019).

For the identification of the bacterial genes within biological samples, multiplex polymerase chain reactions (PCR)-based molecular methods offer a fast alternative method. Centrifugation as well as filtration was employed to concentrate and enhance the detection of pathogens in larger amounts. However, pathogen recovery from bodily fluids remained insufficient until the development of blood culture (BC) bottles. The presence of blood culture bottles led to a reduction in the detection time as well as an increase in microbial identification. However, it could nevertheless take a minimum of 48 hours and perhaps longer for some pathogens, such as slow-growing yeasts and bacteria, to identify microbes from the positive bottles using traditional methods (Yang and Tao, 2023).

1.4 Immune System in Degradation of Bacteria

Upon breaching the innate immune system, the immune cells i.e., neutrophils, macrophages, and monocytes come into play and tend to destroy the invading pathogen. These immune cells are attracted to the site of microbial infection by chemotaxis. Serum proteins, such as opsonin, including the C3b component of complement and antibodies, are identified by specific receptors found in phagocytes as shown in Figure 2. These receptors facilitate the uptake of pathogens by phagocytic cells via the process of phagocytosis which involves the engulfment of the pathogen, formation of phagosome followed by phagolysosome which releases certain lysosomal microbicidal substances and enzymes for the pathogen degradation primarily attributed to the production of detrimental oxygen radicals. The intracellular bacteria responsible for leprosy,

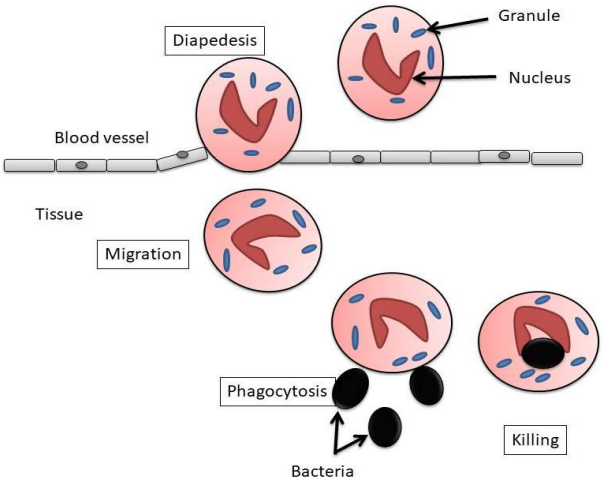

Figure 2. Schematic representation of the progressive steps involved in the identification and degradation of microbial pathogen

salmonellosis, brucellosis, listeriosis, and TB are ingested by macrophages, yet they retain their viability and ability to proliferate. In the aforementioned scenarios, the efficacy of antibodies is rendered futile, thereby emphasizing the exclusive reliance on cellular immunity for providing protection. Activated macrophages are the sole agents capable of eliminating and eradicating these pathogens (Verhoef *et al.*, 2019).

1.5 Pathogenesis of Shock

Sepsis, a prevalent inflammatory response triggered by a suspected or confirmed infection, leads to multiple organ failures and has the potential to culminate in mortality. The host response is initiated through the activation of families of pattern recognition receptors (PRRs) by pathogen-associated molecular patterns (PAMPs) present in viruses, bacteria, fungi, and parasites. The involvement of bacterial lipopolysaccharide (LPS), a crucial structural component of the bacterial cell wall, or endotoxin with various host cell systems has been implicated in the pathogenesis of septic shock in Gram-negative bacterial infections. The activation of host cells induced by endotoxins, specifically the production of interleukin-1 and Tumor necrosis factor alpha (TNF-α), has been identified as a significant contributor to the development of hemodynamic shock (Verhoef *et al.*, 2019).

1.6 Common Diseases Caused by Blood Infections

1.6.1 Urinary Tract Infections

Urinary tract infections (UTIs) are highly prevalent in both outpatient and hospitalized patients, with an annual occurrence exceeding 175 million cases (Fritzenwanker *et al.*, 2022). This substantial number underscores the significant burden imposed by UTIs on global healthcare systems. The presence of erythrocyturia and leukocyturia triggers an inflammatory response and infection caused by pathogenic bacteria, leading to UTIs. It is important to note that UTIs are commonly non-threatening and can be resolved without external intervention. UTIs are associated with significant morbidity and financial burden, especially among individuals with diabetes (Fritzenwanker *et al.*, 2022).

1.6.2 Methicillin-resistant S. aureus (MRSA) Bacteremia

A significant risk arises from BSI caused by *S. aureus*. *S.* aureus is accountable for a diverse range of infections, encompassing soft tissue, skin, joint, bone, prostate glands, and indwelling catheter-related infections. *S. aureus* plays a significant role in the occurrence of bacteremia in developed nations. Despite a decrease in the incidence of methicillin-resistant *S. aureus* (MRSA) infection during the previous decade, MRSA continues to exhibit inferior clinical outcomes compared to methicillin-sensitive *S. aureus* (MSSA). Metastatic diseases, including septic arthritis, osteomyelitis, and infective endocarditis (IE), often arise as a result of *S. aureus* bacteremia (SAB). Treating SAB can be a challenging task due to the potential occurrence of septic shock and sepsis as side effects. These complications can exacerbate the already complex nature of SAB treatment (Guo *et al.*, 2020).

1.6.3 Falciparum Malaria

Six percent of children hospitalized with critical falciparum malaria caused by *Plasmodium falciparum* in Africa are additionally diagnosed with bacteremia. It is recommended that alongside parenteral artesunate, children suffering from severe malaria should receive broad-spectrum antibiotics. Currently, it is not recommended for adults diagnosed with falciparum malaria to receive empirical antibiotics. The pathogens commonly associated with this condition include *Salmonella typhi, Hemophilus influenzae type b, Klebsiella pneumoniae, S. pyogenes,* and *S. aureus.* Patients with bacterial infections often exhibit severe renal failure, high malaria parasitemia, and jaundice (Phu *et al.*, 2020).

1.6.4 Bacteremia Infection Treatments

Studies have shown that timely identification and administration of appropriate antimicrobial therapy can significantly reduce both mortality and morbidity associated with BSI. On the contrary, the administration of antibiotic drugs may lead to noteworthy adverse effects, as evidenced by the fact that one out of every five hospital patients who receive parenteral antibiotics experiences an unfavorable medication event, with *C. difficile* infection being a particularly common occurrence. Furthermore, the unregulated and prolonged use of these drugs can contribute to the emergence of antimicrobial resistance, which poses a significant threat to public health (Sweeney *et al.*, 2019).

1.7 Treatment of BSIs

1.7.1 Oral Therapy

Converting Enterobacteriaceae -related bacteremia to oral treatment offers the potential to enhance the patient's quality of life by improving mobility, alleviating catheter-associated pain, reducing non-infectious adverse catheter events, decreasing the risk of infection, and lowering medical costs (Tamma *et al.*, 2019).

1.7.2 Routine Immunizations

As a consequence of perennial vaccinations, it is uncommon in the US to have bacteremia in a person who was healthy previously. The proportionate pertinent of *S. aureus*, *Salmonella* spp., as well as *E. coli* has grown as the prevalence of pneumococcal bacteremia has dwindled. Advanced proposals are required to treat a pyretic child who was normal previously in an outpatient environment (Woll *et al.*, 2018).

1.7.3 Bacteremia Management for MRSA Infection

Inceptive steps in the therapy of MRSA bacteremia include finding and eradicating of source of infection. After being diagnosed, a catheter must be withdrawn if that is the cause, as well as any incisions made, should also be

cleaned. In individuals reported with long-term or short-term catheter-related MRSA infections who acquire suppurative thrombophlebitis, the catheter must be withdrawn immediately from the patients having treatment for complex bacteremia; treatment using anticoagulation with the aid of heparin has just been delineated, but there is inadequate evidence to suggest it. Patients with methicillin-resistant *S. aureus* (MRSA) causing infective endocarditis (IE) with a synthetic valve should be checked out for valve reconstruction surgery as it must be done if the bacterial infection affects the native valve and if bacteremia is complicated or extensive. When bacteremia infection is immedicable, it is best to use CT or MRI imaging to locate any hidden infection sources and hence, to eliminate them by surgical debridement or drainage (Guo *et al.*, 2020).

1.7.4 Anti-Staphylococcal Treatment

In practice, anti-staphylococcal medication should be sustained for four to six weeks in patients with complex SAB and for around fourteen days in patients with simple bacteremia (Guo *et al.*, 2020). Anyone who had community-acquired *S. aureus* BSI should undergo echocardiography because *S. aureus* infectious endocarditis occurs in less than 10% of instances as well as up to 20% of cases that are contracted in community settings. It is recommended to treat MSSA BSI with anti-staphylococcal penicillin as well as MRSA bloodstream infection with daptomycin or vancomycin for a minimum of two weeks or up to four to six weeks intravenously (De Kraker, 2023).

1.7.5 Treatment Guidelines for Antibiotic Therapy for Bacteremia

Enterococcal and *Staphylococcal* bacteremia are customary in hospitalized or newly implanted patients and are linked to high rates of mortality and morbidity. Due to the toxicity of the pathogens, poor responsiveness to medicines as well as rising MDR (multidrug resistance) are frequent challenges in treatment. As a result, there is growing interest in using combination therapies to manage these infections. For this purpose, combined beta-lactam treatment is currently supported by in vitro findings but with minimal clinical evidence. The advantages of beta-lactam adjuvant treatment over monotherapy for the treatment of Gram-positive infections require further clinical research; however, combination treatment may be helpful in cases of infections that are resistant to regular antibiotic therapy (Nasir *et al.*, 2020).

Overuse, as well as abuse of antibiotics, is a factor in the development of antimicrobial drug resistance as well as unfavorable patient outcomes such as adverse medication responses, *C. difficile* infection, and related patient morbidities linked to antibiotics. The antimicrobial stewardship program's (ASP) (Palavecino *et al.*, 2020) main objectives are to maximize the effective use of antibiotics, enhance patient outcomes, limit unfavorable side effects of antibiotic usage, as well as lessen the establishment and transmission of multidrug-resistant diseases. To help healthcare centers to establish and carry out ASP and related activities, the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America issued recommendations in 2016. Additionally, the Joint Commission released regulatory guidelines for these programs in 2016 after the Center for Disease Control and Prevention (CDC) identified seven essential components for effective ASPs in the year 2014. These suggestions recommend that ASPs work closely alongside clinical microbiology (Palavecino *et al.*, 2020).

CONCLUSION

Bloodstream Infections (BSI) affect the local populace resulting in increased mortality and morbidity rates. A bacterial community that is

responsible for BSI includes *E. coli*, *Pseudomonas aeruginosa*, *Klebsiella* sp, *Haemophilus influenzae*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Enterococcus faecium*, *Staphylococcus aureus*, *Streptococcus pneumoniae* etc. Various therapies and methods have been devised for the treatment of BSI. Despite the advancements in public health and medical care, bacteremia remains a major reason for sickness and death. Still, treatment of bacteremia is difficult and it is high time to develop an in-depth understanding of the causative agents so that we can prevent and treat the deadly situations.

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CONFLICT OF INTEREST
The authors declare no conflict of interest.

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