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REVIEW

A review of bloodstream infections–pathogens, pathogenesis, diagnostic strategies, treatment methods–challenges and future aspects

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Abstract

Purpose Bloodstream infections (BSIs) remain a major cause of morbidity and mortality worldwide and continue to represent a substantial challenge to modern healthcare systems. These infections arise when pathogenic microorganisms gain access to the bloodstream, triggering systemic inflammatory responses that may progress to sepsis, septic shock, multi-organ dysfunction, and death. This review provides a comprehensive overview of the historical development, epidemiology, pathogenesis, diagnosis, treatment, and future perspectives of BSIs. The major bacterial, fungal, viral, and parasitic pathogens associated with BSIs are discussed, with particular emphasis on their virulence attributes, mechanisms of immune evasion, antimicrobial resistance, and clinical significance.

Methods A comprehensive literature review was conducted using peer-reviewed publications, clinical guidelines, surveillance reports, and systematic reviews published between 2010 and mid-2026. Evidence related to bacterial, fungal, viral, and parasitic bloodstream pathogens, host-pathogen interactions, diagnostic modalities, antimicrobial resistance mechanisms, and emerging therapeutic and diagnostic innovations was critically evaluated and integrated.

Results BSIs continue to impose a substantial healthcare burden, driven by increasing antimicrobial resistance, delayed diagnosis, and diverse pathogen-specific virulence mechanisms. Bacterial pathogens remain the predominant cause of BSIs, whereas Candida species represent the leading fungal agents. Advances in molecular diagnostics, metagenomic sequencing, biomarker-guided testing, and artificial intelligence-assisted analyses have substantially improved rapid pathogen detection and therapeutic decision-making. Precision medicine, genomic surveillance, and novel antimicrobial agents show considerable promise for enhancing clinical management and addressing multidrug-resistant infections.

Conclusion Bloodstream infections remain a major global health challenge due to their complex pathogenesis, increasing antimicrobial resistance, and high associated mortality. Improving patient outcomes requires early and accurate pathogen identification, prompt initiation of targeted antimicrobial therapy, effective antimicrobial stewardship, and continuous epidemiological surveillance. The integration of next-generation diagnostics, artificial intelligence-assisted pathogen detection, genomic surveillance, and precision medicine has the potential to transform BSI diagnosis and management by enabling rapid, individualized therapeutic interventions.

Keywords Bloodstream infections · Pathogenesis · Diagnosis · Molecular diagnostics

Introduction

Bloodstream infections (BSIs) are clinically significant conditions defined by the presence of viable pathogenic microorganisms in the bloodstream, typically confirmed through positive blood cultures in patients exhibiting systemic signs of infection [1–3]. Under normal physiological conditions, blood remains sterile; therefore, the detection of microorganisms indicates a breach in host defense mechanisms and the establishment of an active infectious process [3, 4]. Bloodstream infections (BSIs) encompass a spectrum of conditions that differ in origin, pathogen type, and

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pathophysiological implications. BSIs may be categorized as primary, when no identifiable source is detected, or secondary, when they arise from infections at other anatomical sites such as the respiratory, urinary, or gastrointestinal tract [2].

Primary bloodstream infections are defined as infections in which microorganisms are detected in the blood in the absence of a recognizable primary source elsewhere in the body [5]. Mechanistically, primary BSIs are most commonly associated with direct intravascular entry of pathogens, particularly through medical devices such as central venous catheters. These infections are strongly linked to biofilm formation on catheter surfaces, where microorganisms adhere, proliferate, and periodically release planktonic cells into circulation. Recent clinical and epidemiological studies further confirm that catheter-related bloodstream infections constitute a major proportion of primary BSIs and are associated with high morbidity, mortality, and antimicrobial resistance [6, 7]. The absence of a secondary infectious focus and the central role of the vascular compartment in sustaining infection distinguish primary BSIs as a unique clinical entity.

In contrast, secondary bacteremia arises when microorganisms enter the bloodstream from a defined primary site of infection, such as the lungs, urinary tract, or intra-abdominal region. In this context, the bloodstream functions primarily as a conduit for microbial dissemination rather than the site of initial infection. Recent studies and reviews consistently demonstrate that the majority of bloodstream infections originate from such secondary sources, highlighting the importance of identifying the primary focus for effective management [8, 9]. The pathogenesis of secondary bacteremia involves microbial proliferation at the primary site, disruption of epithelial or endothelial barriers, and subsequent invasion into the vascular system. Once in the bloodstream, pathogens can disseminate to distant organs and trigger systemic inflammatory responses that may progress to sepsis. Importantly, recent critical care reviews emphasize that outcomes in secondary bacteremia are closely linked to timely source control, underscoring the clinical importance of distinguishing it from primary BSI [10].

Systemic viral infections introduce a distinct but related concept of bloodstream involvement through viremia, defined as the presence of viral particles or viral genomes in the blood. Unlike bacteria, viruses generally do not replicate within the bloodstream itself; instead, the circulatory system serves as a transport medium facilitating dissemination from the initial site of infection to target organs. The biological significance of viremia lies in its direct association with disease severity, as higher levels of circulating viral load are correlated with increased systemic involvement and adverse clinical outcomes. Modern virological and clinical studies have demonstrated that the magnitude and persistence of viremia play a central role in determining disease progression across multiple viral infections, thereby establishing the bloodstream as a critical compartment for viral pathogenesis rather than merely a passive transit route [3].

The inclusion of viral infections such as human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV) within the broader conceptual framework of bloodstream involvement is increasingly supported by contemporary research. Although traditional definitions of BSIs have focused on acute bacterial or fungal infections characterized by active microbial proliferation in the bloodstream, chronic viral infections are distinguished by persistent viremia, in which viral particles continuously circulate in the blood over prolonged periods. This sustained presence is not incidental but plays a central role in disease pathogenesis, as circulating viral load directly influences immune activation, systemic inflammation, and long-term clinical outcomes. Recent studies emphasize that bloodstream pathogen burden, irrespective of microbial type, is a key determinant of disease progression, thereby supporting the inclusion of chronic viral infections within an expanded definition of bloodstream-associated infectious processes [11].

These distinctions support a more precise conceptual framework in which bloodstream involvement in infectious diseases is not treated as a single uniform entity but rather as a continuum of biologically distinct processes. Primary bloodstream infections represent conditions in which the vascular compartment itself serves as the principal site of infection, whereas secondary bacteremia reflects the hematogenous spread of pathogens from established peripheral foci. In parallel, systemic viral infections characterized by viremia highlight the role of the bloodstream as a dynamic conduit for dissemination and host–pathogen interaction, even in the absence of intravascular replication. Chronic viral infections such as HIV, HBV, and HCV are characterized by the sustained presence of viral particles in the bloodstream (viremia), which contributes to their systemic dissemination and long-term pathogenesis. However, these infections are not categorized as bloodstream infections in the clinical sense applied to bacteremia or candidemia. BSIs typically refer to acute conditions involving the invasion and multiplication of bacteria or fungi in the blood, usually confirmed by blood culture and often associated with sepsis. In contrast, HIV, HBV, and HCV represent chronic systemic viral diseases with distinct diagnostic approaches and therapeutic strategies, and their presence in blood reflects viral replication dynamics rather than an acute bloodstream infectious process [12, 13]. This integrated and mechanistically grounded perspective provides a clearer basis for distinguishing between these entities while aligning with

current advances in infectious disease research, thereby strengthening diagnostic classification and informing targeted therapeutic strategies.

The clinical importance of BSIs lies in the central role of the circulatory system in maintaining homeostasis and enabling immune surveillance. Once pathogens enter the bloodstream, they can disseminate rapidly to distant organs, increasing the risk of systemic complications. The progression and severity of these infections are governed by complex host–pathogen interactions, including microbial virulence, pathogen load, and host immune responses [3, 14]. In severe cases, BSIs may progress to sepsis, a life-threatening condition characterized by dysregulated host responses and organ dysfunction [1, 15].

Microorganisms gain access to the bloodstream through multiple routes, including translocation from infected tissues, breaches in skin or mucosal barriers, and invasive medical procedures such as catheterization or surgery [2, 16]. Although transient entry of microbes into the bloodstream may occur and be rapidly cleared by the immune system, persistent invasion can lead to clinically significant infection and systemic manifestations.

BSIs are broadly classified based on the type of pathogen involved, including bacteremia, viremia, fungemia, and parasitemia. Bacteremia, defined as the presence of viable bacteria in the bloodstream, represents the most frequently encountered form and may be transient, intermittent, or persistent depending on the source and host immune status [2]. Common bacterial pathogens associated with BSIs include *Staphylococcus aureus*, *Escherichia coli*, and *Klebsiella pneumoniae*, with clinical manifestations often including fever, chills, tachycardia, hypotension, and altered mental status (Fig. 1) [2, 17].

Viremia refers to the presence of viruses in the bloodstream and plays a critical role in the systemic dissemination of viral infections. It may occur as primary viremia following initial infection or as secondary viremia after replication in target tissues [18]. Clinical manifestations vary but commonly include fever, headache, myalgia, fatigue, and rash, as observed in infections such as chikungunya and dengue (Fig. 1) [19]. The magnitude of viral load is an important determinant of disease severity, with higher levels associated with worse clinical outcomes, as demonstrated in dengue and SARS-CoV-2 infections [20–22].

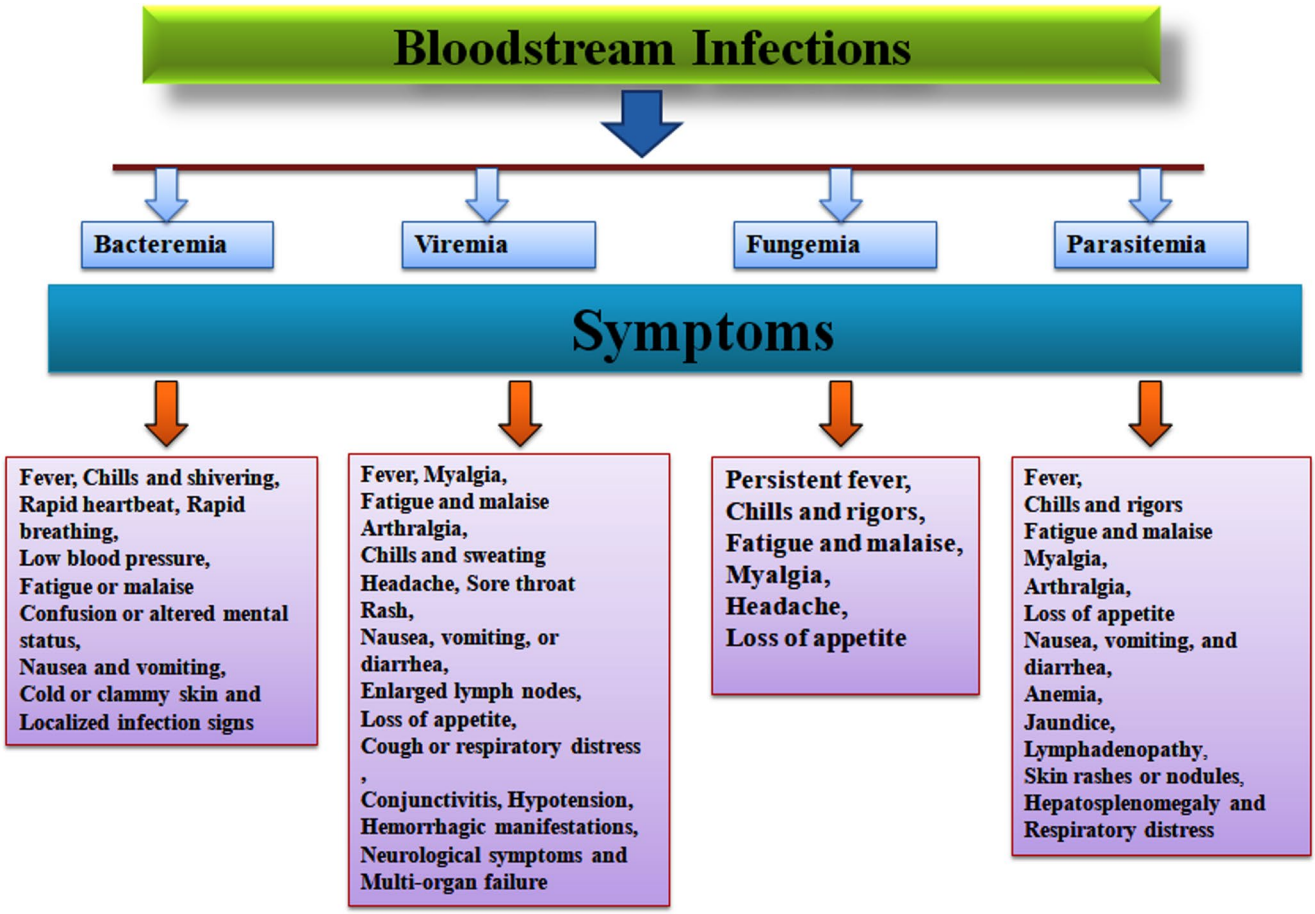

Fig. 1 Different signs and symptoms of bloodstream infections caused by Bacteria, viruses, fungi and parasites

Parasitemia denotes the presence of parasites in circulating blood and is a defining feature of diseases such as malaria and babesiosis. It serves as an important indicator of disease severity and treatment response [23]. In malaria, clinical manifestations include fever, chills, headache, myalgia, and malaise, often occurring in cyclical patterns associated with parasite replication (Fig. 1) [24, 25]. Disease severity is influenced by parasite burden and host immunity, with complications such as anemia, organ dysfunction, and cerebral involvement reported in severe cases [26–30]. Babesiosis, caused by *Babesia microti*, presents with similar clinical features and can be severe in immunocompromised individuals [31].

Fungemia, defined as the presence of fungi in the bloodstream, is most commonly associated with *Candida* species and occurs predominantly in critically ill or immunocompromised patients [32]. Clinically, it is characterized by persistent fever and systemic signs that do not respond to antibacterial therapy. Emerging pathogens such as *Candida auris* have further complicated the epidemiology of fungal BSIs due to their multidrug resistance and high transmissibility [33]. Invasive fungal infections may progress to involve deep organs and are associated with high mortality [34].

BSIs represent a major global health challenge due to their significant contribution to morbidity and mortality across both community and healthcare settings. Recent analyses indicate that bloodstream infections and associated antimicrobial resistance contribute substantially to global mortality, particularly in low- and middle-income countries [35, 36]. The emergence of multidrug-resistant and hypervirulent pathogens, including *Klebsiella pneumoniae*, further complicates treatment and clinical outcomes [37, 38]. In addition, environmental factors such as climate change are influencing the distribution of opportunistic pathogens, including *Aspergillus fumigatus*, thereby expanding the geographical risk of invasive infections [39]. Beyond clinical impact, BSIs impose a substantial economic burden due to prolonged hospitalization, increased intensive care requirements, and higher treatment costs. Antimicrobial resistance has further intensified this burden, with studies reporting significantly increased healthcare costs associated with resistant infections [40]. These challenges highlight the urgent need for improved diagnostic tools, effective antimicrobial stewardship, and strengthened global surveillance systems to mitigate the impact of bloodstream infections.

Highlights of the history of BSIs

The understanding of blood as a conduit for infectious agents has evolved profoundly over centuries. Initially, ancient and medieval medical thought attributed illness to supernatural forces or imbalances in bodily humors, with blood being central to health and often subjected to practices like bloodletting [41]. The concept of bloodstream transmission was entirely absent. This began to shift with key scientific milestones. Antonie van Leeuwenhoek's 17th-century microscopic observations of microorganisms laid the foundation for microbiology [42], while the 19th-century-germ theory proposed by Louis Pasteur and Robert Koch, has revolutionized the medical science by linking specific microbes to disease [43].

Joseph Lister's introduction of antiseptic techniques demonstrated the role of microbes in surgical infections, further validating germ theory. Around the same time, the discovery of *Plasmodium* spp. by Laveran and Ross clarified the parasitic nature of malaria and highlighted blood as a transmission route [44]. Other bacteria such as *Treponema pallidum* and causative agents of puerperal fever and endocarditis were also identified as blood-transmissible pathogens [45].

The early 20th century marked a turning point with the advent of blood culture methods, offering direct detection of pathogens in blood and greatly enhancing diagnostic precision. Attention shifted toward viruses by the mid-20th century. The 1960 s discovery of the Australia antigen by Baruch Blumberg led to identification of hepatitis B virus (HBV), transforming blood screening and vaccine development [46, 47]. Hepatitis C virus (HCV) followed in 1989, discovered through molecular cloning, emphasizing the need for improved diagnostic tools like PCR [48, 49].

The emergence of HIV in the 1980 s brought global attention to viral BSIs, prompting major reforms in transfusion safety, infection control, and antiviral research [50]. These advances collectively redefined how bloodstream infections are understood, diagnosed, and managed, laying a critical foundation for modern infectious disease control. These scientific milestones have transformed the understanding and management of BSIs. From speculative origins to the use of advanced molecular diagnostics, the historical trajectory underscores the importance of continuous innovation and vigilance in safeguarding blood-related healthcare practices.

Methodology: literature search and selection framework

Problem statement regarding the cure of BSIs

Bloodstream infections (BSIs) remain a critical healthcare burden, especially with the growing prevalence of antimicrobial-resistant pathogens. The high mortality and morbidity rates associated with BSIs are compounded by the increasing inefficacy of conventional antibiotics due to

resistance mechanisms developed by ESKAPEEc organisms and other multidrug-resistant bacteria [51]. Despite significant advancements in medical science, blood-related microbial diseases continue to pose a substantial threat to global health. Challenges persist in several key areas:

(i)Timely and Accurate Diagnosis Early and accurate diagnosis of bloodstream infections and other blood-related microbial diseases is crucial for initiating appropriate treatment and improving patient outcomes [52]. However, traditional molecular diagnostic methods, such as blood culture, PCR and next-generation sequencing can be time-consuming, and newer molecular diagnostic techniques may not be readily available in all settings as also low- and middle-income settings due to high costs and infrastructural constraints [53]. Therefore, there is a critical need for scalable, rapid, and affordable diagnostic solutions to improve early detection and clinical outcomes in diverse healthcare environments.

(ii) Antimicrobial Resistance The rising prevalence among bacterial, fungal, and parasitic pathogens has become a major concern, particularly in the context of blood-related infections. It the treatment of conditions, leading to higher rates of treatment failure, prolonged hospital stays, and increased mortality [54]. Recent studies highlight the increasing resistance to key antibiotics such as carbapenems and cephalosporins in pathogens like *Klebsiella pneumoniae* and *Escherichia coli*, which are frequent culprits in bloodstream infections [49]. Additionally, the emergence of multidrug-resistant fungal pathogens, including *Candida* spp., has further complicated clinical outcomes [55]. Efforts to their mitigation include improving antimicrobial stewardship, enhancing infection control measures, and developing novel therapies to address resistant pathogens. However, the growing resistance underscores the urgent need for continued research and global cooperation to combat this escalating threat [56].

(iii) Emerging and Re-emerging Infections Emerging and re-emerging blood-related microbial diseases present significant global health challenges, exacerbated by factors such as climate change, antimicrobial resistance, and healthcare practices [57]. The increasing incidence of fungal infections, notably those caused by *Aspergillus fumigatus* and *Aspergillus flavus*, has been linked to rising global temperatures, which create favorable conditions for these pathogens to expand their habitats and pose severe health risks [58]. Similarly, the emergence of multidrug-resistant organisms like *Elizabethkingia anophelis* has been observed in intensive care units, leading to heightened mortality rates due to limited effective treatments. The COVID-19 pandemic has further influenced the epidemiology of bloodstream infections, with studies indicating shifts in resistance patterns and infection rates in intensive care settings [54]. These developments underscore the critical need for enhanced surveillance, innovative therapeutic strategies, and robust infection control measures to mitigate the impact of these evolving pathogens.

(iv) Management in Vulnerable Populations Bloodstream infections (BSIs) pose significant risks to vulnerable populations, including neonates, the elderly, immunocompromised individuals, and patients requiring central venous catheters (CVCs). Effective management strategies are crucial to mitigate morbidity and mortality in these groups. In neonates, particularly those in neonatal intensive care units (NICUs), strict adherence to aseptic techniques during catheter insertion and maintenance is vital [59]. A recent update by the Centers for Disease Control and Prevention (CDC) advises against routine prophylactic antimicrobial infusions to decrease bacterial central line-associated bloodstream infections (CLABSIs) in NICU patients, emphasizing the importance of infection prevention bundles [60]. Addressing these challenges requires a comprehensive understanding of the epidemiology, pathogenesis, diagnosis, treatment, and prevention of blood-related microbial diseases.

The present review provides a comprehensive overview of blood-related microbial diseases, focusing on BSIs caused by diverse microbial agents. It explores the epidemiology, clinical impact, and underlying mechanisms of conditions such as bacteremia, viremia, fungemia, and parasitemia. The review highlights key pathogens and their virulence factors that enable them to invade the bloodstream, evade the immune response, and cause systemic illness. The pathogenesis of these infections often leads to severe complications like sepsis and multiorgan failure, particularly in immunocompromised individuals and those with medical devices.

Diagnostic approaches are evaluated, ranging from traditional culture techniques to advanced molecular tools like PCR and next-generation sequencing for faster and more accurate pathogen detection. The review also assesses therapeutic strategies, including antimicrobial, antifungal, and antiviral treatments, while acknowledging the growing challenge of multidrug resistance and limited new drug development. Key barriers include diagnostic delays, inappropriate treatments, and limited access to care in low-resource settings. Emphasis is placed on improving diagnostics, developing novel therapies, and strengthening stewardship programs to effectively manage and reduce the global burden of BSIs.

Search strategy

A structured literature search was undertaken to identify relevant studies on BSIs, encompassing their etiology, pathogenesis, diagnosis, treatment, and emerging challenges. The search strategy combined controlled vocabulary (e.g., MeSH terms in PubMed) with free-text keywords to maximize sensitivity and specificity. Core search terms included "bloodstream infection," "bacteremia," "viremia," "fungemia," "parasitemia," "antimicrobial resistance," "diagnosis," "treatment," and "future aspects," which were systematically combined using Boolean operators. To ensure comprehensive coverage, backward and forward citation tracking of key articles was also performed. The methodological approach was aligned with established guidance for narrative reviews to ensure transparency and reproducibility [61, 62].

Databases and information sources

The literature search was conducted across multiple major biomedical and interdisciplinary databases, including PubMed/MEDLINE, Scopus, and Web of Science, which collectively index high-quality peer-reviewed journals in clinical medicine, microbiology, and public health [63, 64]. To capture recently published or in-press articles not yet indexed in these databases, supplementary searches were performed using Google Scholar. In addition, relevant reports such as CDC, and datasets from recognized international health organizations were consulted where appropriate to support epidemiological synthesis.

Time frame of literature inclusion

The literature included in this review was selected with a deliberate emphasis on contemporary evidence reflecting current clinical and epidemiological understanding of bloodstream infections (BSIs). The majority of cited studies were published between 2015 and 2026, a period marked by substantial advances in antimicrobial resistance surveillance, molecular diagnostics, and global burden estimation. Earlier studies were incorporated selectively where required to establish foundational concepts, particularly in areas such as sepsis definitions, pathogen biology, and host–pathogen interactions. This approach ensured that the review remains anchored in current evidence while retaining essential historical context, consistent with best practices for narrative synthesis [65].

Eligibility criteria (inclusion and exclusion)

To ensure methodological rigor and relevance, studies were selected based on predefined eligibility criteria aligned with the scope of bloodstream infections and related systemic diseases.

Studies were included if they met the following criteria:

(i) publication in peer-reviewed journals, including original research, systematic reviews, or meta-analyses;
(ii) direct relevance to bloodstream infections, including microbial etiology, pathogenesis, clinical manifestations, diagnostic approaches, antimicrobial resistance, or treatment strategies;
(iii) large-scale epidemiological investigations, multicenter cohort studies, or structured surveillance datasets reporting incidence, mortality, or resistance trends.

Studies were excluded if they met any of the following conditions:

(i) non-English language without accessible translation;
(ii) isolated case reports or small case series lacking generalizability;
(iii) conference abstracts or preliminary reports without full methodological description;
(iv) studies with insufficient methodological transparency or lacking direct relevance to bloodstream infections.

This selection strategy was designed to prioritize high-quality, generalizable evidence while minimizing bias from underpowered or poorly described studies.

Data synthesis and use of global surveillance data

Given the narrative design of this review, evidence was synthesized using a thematic and integrative approach, allowing comparison across heterogeneous study designs without formal meta-analysis. Particular attention was given to global and regional surveillance data, which form the basis for epidemiological conclusions and summary tables.

Data describing the global burden, pathogen distribution, and antimicrobial resistance patterns of BSIs were derived from well-established international surveillance platforms and large-scale analytical studies [37, 66–70]. Preference was given to datasets characterized by standardized case definitions, large sample sizes, multicenter participation, and recent publication, thereby ensuring robustness and

cross-regional comparability. The integration of these surveillance systems allows for a more reliable assessment of global trends in bloodstream infections and antimicrobial resistance, as widely recognized in contemporary infectious disease research.

Common microbial pathogens and their pathogenesis in bloodstream infections

Pathogens responsible for BSIs include bacteria, fungi, viruses, and parasites, each using unique mechanisms to infect and persist in the host. *Staphylococcus aureus*, a Gram-positive organism, contributes to BSIs by producing enzymes and toxins that disrupt blood vessels and evade immune defenses [71]. *Escherichia coli*, a Gram-negative bacterium, releases endotoxins such as lipopolysaccharides, which can provoke intense immune responses leading to septic shock [72]. Opportunistic fungi, notably *Candida albicans* and the emerging *Candida auris*, often infect immunocompromised patients and are difficult to treat due to antifungal resistance [73]. Viral pathogens like hepatitis B virus and HIV persist in the bloodstream and interfere with immune function, increasing transmission risk [72]. Parasitic organisms such as *Plasmodium* spp., which cause malaria, invade red blood cells and circulate in the bloodstream, leading to severe systemic complications. Understanding how these microbes cause disease is vital for improving diagnostic tools, treatment protocols, and infection control strategies.

Bacterial pathogens

Bacterial pathogens remain the most significant causative agents of BSIs globally, with both Gram-positive and Gram-negative bacteria implicated. Among Gram-positive organisms, *Staphylococcus aureus*—particularly methicillin-resistant strains (MRSA)—is a leading cause of hospital-acquired BSIs, often associated with indwelling medical devices and surgical procedures [74, 75]. *Streptococcus pneumoniae* and *Enterococcus faecalis* are also common, the latter showing increasing multidrug resistance. On the other hand, Gram-negative bacteria are also prevalent, especially in community-acquired infections and urinary tract-related BSIs. These pathogens have shown alarming resistance to third-generation cephalosporins and carbapenems, largely due to extended-spectrum β-lactamase (ESBL) and carbapenemase production [71]. *Pseudomonas aeruginosa* and *Acinetobacter baumannii* are increasingly responsible for nosocomial BSIs and are notable for their multidrug resistance profiles and association with high mortality rates [76]. Rapid diagnostic techniques, such as MALDI-TOF mass spectrometry and PCR-based assays, have improved pathogen identification and resistance profiling, leading to more targeted therapies. However, empirical treatment guided by local antibiograms remains critical in the initial management of suspected BSIs. Overall, understanding the evolving epidemiology of bacterial pathogens in BSIs is crucial for improving patient outcomes, guiding antimicrobial stewardship, and informing public health interventions. The pathogenesis of bacterial BSIs involves a complex interplay of bacterial virulence factors (e.g., adhesins, toxins, biofilms) and the host immune response, which can lead to localized infection, systemic inflammation, and organ dysfunction. Below table (Table 1) is showing some common examples of bacteremia, their pathogenesis and disease caused.

Viral pathogens

Viral bloodstream infections, though less frequently identified than bacterial or fungal ones, play a significant role in causing systemic illness and complications, particularly in immunocompromised individuals. Viremia, the presence of viruses in the bloodstream, is a critical phase in the pathogenesis of many viral diseases. The specific consequences of viremia depend on the target organs of the virus and the host immune response. Among the most clinically significant viral pathogens are members of the *Herpesviridae* family, including cytomegalovirus (CMV), Epstein-Barr virus (EBV), and herpes simplex virus (HSV). These viruses can enter the bloodstream during primary infection or reactivation, especially in transplant recipients, patients undergoing chemotherapy, and individuals with HIV/AIDS. CMV viremia is often a precursor to severe diseases such as CMV colitis, pneumonitis, and retinitis [85]. For example, in dengue infection, viremia is associated with fever, headache, and potentially severe hemorrhagic complications [86]. In HIV infection, persistent viremia leads to the depletion of CD4+T cells, resulting in immunodeficiency and susceptibility to opportunistic infections [87]. Research continues to focus on understanding viral entry into the bloodstream, mechanisms of viral replication within blood cells or endothelial cells, and the host factors that influence the duration and magnitude of viremia. [87]. Another important group is the hepatitis viruses—especially hepatitis B (HBV) and hepatitis C (HCV)—which can circulate in the blood and contribute to systemic inflammation, liver failure, and increased risk of hepatocellular carcinoma. Human immunodeficiency virus (HIV) itself is a prominent example of a viral agent that causes BSIs by targeting CD4+T cells, leading to progressive immune system deterioration. Arboviruses like dengue virus, chikungunya virus, and Zika virus are also known to cause viremia during the acute phase of infection, leading to systemic symptoms and complications such as hemorrhagic fever and shock [87]. Advances in

Table 1 Representing the major pathogens of bacterial BSIs, their pathogenesis, resistance mechanisms, regional mortality and diagnostic yield

Bacterial Pathogen	Resistance Mechanisms	Regional Mortality	Pathogenesis	Diagnostic Yield	Citation
Escherichia coli	ESBL production (CTX-M), MDR plasmids	Europe (hospital cohort): more than 10% mortality in ESBL (Extended-Spectrum Beta-Lactamase)	Utilizes adhesins, toxins, and siderophores to invade initial sites, overcome host barriers, and survive in the bloodstream; certain strains produce extended-spectrum β-lactamases (ESBLs) conferring antibiotic resistance.	Blood culture-confirmed BSI; ESBL strains associated with prolonged hospitalization	[77]
Klebsiella pneumoniae	Carbapenem resistance, hypervirulent strains	China cohort: high 28-day mortality 30% (significantly elevated in severe KP-BSI)	Through the formation of lipopolysaccharide (LPS), capsular polysaccharide (CPS), fimbriae, siderophore system, allantoin utilization and secretion system, etc.	Isolates Cultured on blood agar plates for clinical data of 90 cases	[78]
MBL-producing *Escherichia coli*	Metallo-β-lactamase (NDM, VIM)	France multicenter (2023–2025): 26.3% mortality in-hospital in 30-days	Enzyme-mediated β-lactam resistance, rapid systemic spread, immune activation	Culture-confirmed BSI; resistance delays effective therapy	[79]
Staphylococcus aureus	MDR increasing; MRSA prevalent in BSI cohorts	BSI-associated mortality significantly increased in hospitalized cohorts e.g. in North America 700,000 deaths annually and could cause up to 10 million deaths by 2050.	Produces toxins, induces cytokines (TNF-α, IL-1, IL-6), immune evasion and endothelial damage	Culture positivity 12.1% (79,241 samples; 9,590 positive)	[63, 64, 80]
Pseudomonas aeruginosa	Efflux pumps, carbapenem resistance biofilm formation via three major exopolysaccharides Psl, Pel and alginate	32–42.8% in Europe and Asia	Two component system (TCS)-regulated response mechanisms	epithelial cells cultured at the air-liquid interface	[81, 82]
Acinetobacter baumannii	Biofilm using Csu pili and gene expression that build a defensive capsule in response to antibiotics i.e. the BfmRS TCS. Highly resistant to carbapenems, ciprofloxacin and trimethoprim–sulfamethoxazole	30–70% in Monterrey, Mexico and South India	Systemic inflammatory response, endothelial dysfunction, multi-organ effects	Cultured on sheep blood agar and tryptic soy agar	[83, 84]
Enterococcus spp.	Biofilm formation; intrinsic resistance; persistence in hospital environments	24–66% in Qatar, China and western interior of British Columbia, Canada	Mechanism involve two main surface proteins: (i) Esp, which helps form biofilms and causes UTIs (urinary tract infections), and *EfaA* and *Ace*, which lead to infective endocarditis and osteomyelitis.	Isolated from urine samples and wound exudate in a trauma patient. The pathogen was identified using using the Autof MS 1000 MALDI-TOF MS system.	[85–88]

molecular diagnostics, including real-time PCR and next-generation sequencing, have improved the detection of viral pathogens in bloodstream infections, allowing for earlier intervention and tailored antiviral therapy. Management of these infections requires prompt diagnosis, supportive care, and in some cases, targeted antiviral treatment, such as ganciclovir for CMV or antiretrovirals for HIV. Continuous monitoring and improved screening, especially in vulnerable populations, remain essential for reducing the morbidity and mortality associated with viral bloodstream infections. Table 2 showing the class, name, disease caused and pathogenesis by viral pathogens of BSIs.

Parasitic pathogens

Parasitic pathogens are significant contributors to bloodstream infections, particularly in tropical and subtropical regions where vector-borne diseases are prevalent. Such infections including malaria and trypanosomiasis, have been extensively studied due to their significant global health impact. *Plasmodium* spp. parasites undergo complex life cycles involving both mosquito vectors and human hosts, with the blood stage characterized by invasion and replication within red blood cells, leading to anemia, fever, and potentially severe organ damage [30]. Malaria remains a major public health challenge, causing high

Table 2 Showing major viral pathogens of bloodstream Infections, their resistance mechanism, regional mortality pathogenesis and diagnostic yield

Viral Pathogen	Resistance Mechanisms	Regional Mortality	Pathogenesis	Diagnostic Yield	Citation
Influenza A virus	(i) antigenic drift, via accumulation of mutations in hemagglutinin (HA) or neuraminidase (NA) surface glycoproteins (ii) antigenic shift, arising from genomic reassortment between phylogenetically distinct strains	Approximately 300 000 influenza-associated respiratory deaths occur worldwide each year. Most prominent in USA, sub-Saharan Africa, Southeast Asia, Indonesia Egypt	Severe epithelial injury, cytokine storm, endothelial dysfunction exacerbates chronic conditions such as coronary artery disease and chronic obstructive pulmonary disease	Conventional methods like viral culture and serology to modern molecular techniques, including CRISPR-based systems, next-generation sequencing (NGS), and biosensors.	[89–94]
Dengue virus	Resistance include the immune evasion pathways via three levels of innate, adaptive and effector mechanisms, including inhibition of interferon production, disruption of immunological signalling pathways, regulation of proliferation proteins and inhibition of effector cells. CD209 (DC-SIGN) is a well-known DENV receptor that facilitates viral attachment and entry. CLEC5A acts as a critical receptor that triggers the release of inflammatory cytokines upon DENV exposure, contributing to immunopathology.	In 2024, global dengue incidence reached approximately 14.1 million reported cases with 9,508 deaths, reflecting a major increase compared with previous years. Higher dengue-related mortality was significantly associated with countries in the Southern Hemisphere, warmer annual temperatures, and older population demographics.	It is known for complex interplay between virus, host genes and host immune response. Cytokines, immune dysregulation, endothelial dysfunction, and cytokine-induced plasma leakage, NS1 protein and anti-DENV NS1 are responsible for its pathogenesis.	Enzyme-Linked Immunosorbent assay is the conventional method but it is cost effective and time consuming. Immunochromatographic assays with gold nanoparticles and RT-PCR method is used to detect early infection at febrile stage but it also time-consuming with complicated procedure. These limitations necessitates the use of antigen detection of IgM and IgG. It can be diagnose with early days of infection.	[95–100]
Human Immunodeficiency Virus-1 (HIV-1)	The exact mechanism of how it contributes to the dramatic loss of CD4+T cells and the persistence of R5 and X4 strains during the AIDS status is still under exploration.	Mortality decreased by 39·7% (33·7–44·5), from 1·19 million (1·07–1·37) in 2010 to 718 000 (669 000–785 000) in 2021 in sub-Saharan Africa and south Asia.	CD4+T-cell depletion	Low-cost technologies such as Sanger sequencing, next-generation sequencing, point mutation assays, and genotype-free systems improve the diagnostic yield of HIV drug resistance detection. Combined with viral load monitoring and strengthened centralized laboratories, these approaches support timely treatment decisions, rational antiretroviral use, and reduced healthcare costs.	[101–107]
Cytomegalovirus (CMV)	Prolonged antiviral therapy in immunocompromised CMV patients can promote multidrug resistance through mutations in UL54, UL97, and UL56 genes, leading to resistance against ganciclovir, foscarnet, and letermovir.	Approximately 19,235 deaths globally in 2021	HCMV infects epithelial, endothelial, fibroblast, and immune cells, causing lytic or latent infection in hematopoietic progenitor cells. The virus evades immunity by inhibiting interferon signaling, antigen presentation, apoptosis, and NK/T-cell responses, while dysregulating PI3K/Akt/mTOR, JAK-STAT, and Wnt/β-catenin pathways to promote viral persistence, reactivation, inflammation, and cell transformation.	CMV diagnosis commonly uses pp65 antigenemia assays and quantitative nucleic acid testing (QNAT). However, viral load results vary with specimen type, plasma often showing ~ 10-fold higher values than whole blood, and lack of assay standardization limits universal comparison and monitoring.	[108–113]

Table 2 (continued)

Viral Pathogen	Resistance Mechanisms	Regional Mortality	Pathogenesis	Diagnostic Yield	Citation
Ebola Virus	Through mutations in the viral RNA-dependent RNA polymerase (L protein) and glycoprotein targets. A key remdesivir-resistance mutation, F548S in the EBOV polymerase, reduces viral susceptibility to the drug by altering nucleotide incorporation and delayed chain termination.	61.3% case fatality rate (CFR) in sub-Saharan Africa and 17,116 deaths from 34,527 cases Globally and 99.98% of the reported deaths from 99.96% cases in Africa.	It includes detrimental immune suppression and immune overactivation in different aspects of the immune response, disordered coagulation, tissue damage and organ failure.	Quantitative reverse transcriptase polymerase chain reaction (q-RT PCR) assay increases exponentially in blood.	[114–118]
Enterovirus A71	It is capable of developing antiviral resistance mainly through rapid selection of drug-resistant capsid variants during treatment with capsid-binding inhibitors such as pirodavir. Resistance emerges through mutations in viral capsid proteins and may also involve mutations in the viral 2 C protein, while combination therapy with protease (3 C) or RNA-dependent RNA polymerase inhibitors can delay resistance development.	22.22% mortality in children in Beijing, China. Chinese Center for Disease Control and Prevention identified 7,200,092 HFMD cases from 2008 to 2012, resulting in 2457 deaths.	Infection of specific cell types, such as neurons and pulmonary epithelial cells are critical to EV-A71 pathogenesis. These are promoted by Human nucleolin (hNCL), an interacting molecule for EV-A71, which facilitates the viral attachment and entry.	Diagnosis relies mainly on IgM/IgG serology to distinguish primary and secondary infections, but diagnostic yield is limited by poor genogroup specificity and low cerebrospinal fluid detection rates (2.5%) in neurological cases. glycoproteomic profiling is also helpful in identification of EV-A71-interacting proteins.	[119–125]

morbidity and mortality due to the parasite's ability to invade red blood cells and evade host immunity. Another notable parasitic bloodstream pathogen is *Trypanosoma* spp., responsible for African trypanosomiasis (sleeping sickness) and Chagas disease, which result in systemic infections affecting the blood and various organs [125]. *Trypanosoma* species, transmitted by tsetse flies in African trypanosomiasis and triatomine bugs in Chagas disease, also reside in the bloodstream and can subsequently invade other tissues, including the central nervous system [126]. Research efforts are directed towards understanding parasite-host interactions, developing new diagnostic tools, and identifying novel drug targets [127]. The diagnosis and treatment of parasitic bloodstream infections are complex due to their life cycles and immune evasion strategies. Recent advances in molecular diagnostics have improved detection sensitivity and specificity, facilitating timely therapeutic interventions. Additionally, climate change and urbanization are expanding the habitats of vectors such as mosquitoes and tsetse flies, increasing the risk of parasitic bloodstream infections in new geographic areas [128]. Continued surveillance, vector control, and development of novel therapeutics remain essential to control the burden of parasitic bloodstream infections worldwide.

Fungal pathogens

Fungal pathogens are increasingly recognized as major contributors to bloodstream infections (BSIs), especially in immunocompromised individuals. *Candida* species are the most frequent cause of fungemia, often originating from the gastrointestinal tract or indwelling devices [129]. Non-*albicans* species such as *C. glabrata*, *C. parapsilosis*, and *C. auris* have emerged as significant pathogens due to their antifungal resistance profiles and ability to cause nosocomial outbreaks. *C. auris*, in particular, has garnered global concern for its multidrug resistance and persistence in healthcare environments. *Aspergillus* species can also cause bloodstream infections, particularly in neutropenic patients. The pathogenesis of fungemia involves fungal adhesion to host tissues or devices, biofilm formation, and the release of virulence factors that can trigger inflammation and tissue damage. Research focuses on improving early diagnosis and developing more effective antifungal therapies, especially in the face of emerging antifungal resistance [130]. Invasive aspergillosis, primarily caused by *Aspergillus fumigatus*, is another serious fungal BSI, particularly in neutropenic or transplant patients, with bloodstream dissemination leading to multi-organ involvement. Diagnosis of fungal BSIs remains challenging due to nonspecific clinical features and limitations of blood cultures. However, advances in molecular diagnostics and fungal biomarkers, such as β-D-glucan and galactomannan, have improved early detection and management. The increasing incidence of fungal BSIs underscores the need for robust antifungal stewardship, enhanced infection control, and development of new therapeutic agents to address emerging resistance. The below table (Table 3) is showing the names of fungal pathogens, diseases caused by those and their pathogenesis.

Table 3 Showing major fungal pathogens of BSIs, their resistance mechanis, regional mortality, pathogenesis and diagnostic yield

Fungal Pathogen	Resistance Mechanism	Regional/Global Mortality	Pathogenesis	Diagnostic Yield	Citation
Candida glabrata	Resistance to antifungal drugs, notably to fluconazole and other azole derivatives. It develops through dense β−1,3-glucan biofilm matrices, efflux pump overexpression, resistance-associated gene activation, high cellular density, and CFEM-associated proteins enhancing iron regulation, adhesion, persistence, and virulence.	65% mortality in Hungary; 24.4% mortality in Yulin regions of China	It involves strong epithelial adhesion, biofilm formation, hydrolytic enzyme secretion, immune evasion, iron acquisition, macrophage survival, and persistent colonization of catheters and host tissues.	Diagnostic mainly depends on blood culture, although positivity is delayed and sensitivity remains moderate (21–71%). Advanced molecular tools such as T2Candida detect as low as 1 CFU/mL with high sensitivity and specificity. MALDI-TOF enables rapid species identification within minutes, while β-D-glucan assays, multiplex PCR, RAPD-PCR, and biosensors enhance early, accurate detection even during antifungal treatment.	[131–136]
Aspergillus fumigatus	Azole resistance mainly through CYP51A gene mutations and promoter tandem repeats (TR34/L98H, TR46/Y121F/T289A), causing altered 14-α sterol demethylase activity, reduced azole binding, impaired drug efficacy, and emergence of resistant environmental and clinical strains.	31% to 36% global mortality. 22% in US. 85.2% crude global mortality for invasive aspergillosis.	Through inhaled conidial germination, epithelial invasion, angioinvasion, and exaggerated Th2/Th17-mediated immune responses, leading to airway inflammation, eosinophilia, tissue destruction, allergic bronchopulmonary disease, and chronic pulmonary aspergillosis.	Diagnosis shows high yield using immunodiagnostic tests, mainly galactomannan detection and Aspergillus-specific IgG ImmunoCAP and ICT assays, combined serological testing improves specificity but prior antifungal or steroid therapy reduces diagnostic performance. Less common methods included cryptococcal antigen, MALDI-TOF.	[35, 137–142]
Candida albicans	It resists antifungals through biofilm formation, persister-cell development, reduced drug penetration, metabolic dormancy, activation of HOG-MAPK and stress-response pathways, upregulation of ERG and efflux pump genes, epigenetic remodeling, and adaptive metabolic changes causing multidrug tolerance and recurrent infections.	33.7% mortality in Zunyi, China. 33.7% mortality in London, UK. 63.6% mortality in USA.	It involves epithelial barrier disruption, yeast-to-hypha transition, adhesion, biofilm formation, and tissue invasion regulated by virulence genes including *EFG1*, *RBF1*, and *TUP1*, while secreted aspartyl protease genes facilitate endothelial penetration, immune evasion, macrophage escape, and bloodstream dissemination.	Diagnostic platforms have achieved rapid, sensitive, culture-independent detection through molecular assays, biosensors, Raman spectroscopy, PNA-FISH, and LC-MS/MS-based proteomics, enabling species identification, biofilm analysis, and antifungal-resistance profiling. However, limitations include high instrumentation costs, complex workflows, need for specialized expertise, matrix interference from clinical samples, incomplete clinical validation, low throughput in some methods, and reduced reproducibility in heterogeneous biological specimens.	[92, 143–147]
Cryptococcus neoformans	Fluconazole heteroresistance, capsule-mediated immune evasion. It develops through ergosterol biosynthesis alterations, efflux pump overexpression, genotype-specific azole tolerance, and prolonged antifungal exposure, especially in HIV/AIDS patients.	41%–61% global mortality. 34% mortality in Brisbane, Sydney, and Melbourne in a state-wide database of Australia. non-HIV-associated cryptococcal fungemia cohort reported approximately 41.7% mortality.	It establishes the infection after inhalation from environmental reservoirs. Key virulence factors include capsule formation, immune evasion, stress adaptation, and dissemination from lungs to bloodstream and CNS, causing cryptococcal meningitis and systemic infections.	The diagnosis has significantly improved through cryptococcal capsular antigen (CrAg) detection, particularly the CrAg lateral flow assay, which provides rapid, sensitive, point-of-care screening for cryptococcal disease and bloodstream dissemination. Additional diagnostic success has been achieved using molecular typing, antifungal susceptibility testing, and gene-based characterization of virulence factors, although limitations remain in resource-limited settings and advanced disseminated infections. Cryptococcal antigen detection and India ink staining are simple methods that can quickly assist in the diagnosis.	[148–153]

Table 3 (continued)

Fungal Pathogen	Resistance Mechanism	Regional/Global Mortality	Pathogenesis	Diagnostic Yield	Citation
Candida auris	It develops multidrug resistance through ERG11 and FKS1 mutations, efflux pump overexpression, biofilm formation, ergosterol pathway alterations, transcriptional reprogramming, and chromosomal aneuploidy, reducing susceptibility to azoles, echinocandins, and amphotericin B.	33% crude mortality in Pakistan. 50% mortality in Asia, the Far East, and US. 30%–60% mortality in Turkey. 31.8% mortality in Columbia. 30% to 72% global mortality in India, Brazil, Mexico, Pakistan, the United States and in European Countries.	Through biofilm-mediated persistence, skin colonization, immune evasion, mitochondrial adaptation, and survival in nutrient-limited hospital environments, facilitating dissemination and severe invasive disease in immunocompromised patients.	MALDI-TOF MS and species-specific PCR markedly improved identification accuracy because conventional biochemical systems frequently misidentified isolates	[76, 154–159]

The epidemiology of fungal bloodstream infections (BSIs) is characterized by substantial regional heterogeneity, which reflects not only differences in pathogen ecology but also variations in clinical practice, antifungal exposure, and healthcare infrastructure. Large longitudinal studies have consistently demonstrated that species distribution is not uniform across geographic settings, with *Candida albicans* remaining predominant globally but progressively declining relative to non-*albicans Candida* species [160, 161].

This shift is particularly pronounced in regions with extensive azole exposure, where selective pressure favors intrinsically less susceptible species such as *C. glabrata* and *C. krusei*. In contrast, tropical and resource-limited settings report higher proportions of *C. tropicalis* and *C. parapsilosis*, a pattern likely influenced by environmental reservoirs, higher device-associated transmission, and differences in infection control practices. Importantly, regional epidemiology is also shaped by patient demographics—such as higher rates of malignancy, intensive care utilization, and immunosuppressive therapy—which directly influence fungal colonization and invasion dynamics.

These geographic variations are not merely descriptive but have direct clinical consequences: studies emphasize that local epidemiological data are indispensable for guiding empiric antifungal therapy, as species distribution and resistance profiles differ significantly between institutions and regions. Thus, fungal BSI epidemiology must be interpreted within a regional and institutional context rather than generalized globally.

It has profound implications for empiric antifungal therapy, particularly in critically ill populations where delays in treatment are strongly associated with adverse outcomes. Contemporary evidence indicates that candidemia frequently occurs in patients with identifiable risk factors—including central venous catheters, broad-spectrum antibiotic exposure, and immunosuppression—highlighting the importance of early risk stratification in guiding empiric therapy [162]. Inappropriate or delayed antifungal treatment significantly increases the mortality. In a large propensity-adjusted analysis, untreated candidemia was associated with markedly higher mortality compared to treated cases, underscoring the necessity of timely therapeutic intervention [163]. Furthermore, emerging data from mixed Candida–bacterial bloodstream infections demonstrate even worse outcomes when initial antimicrobial therapy is inadequate, with mortality exceeding 60% in such cases [164].

Empiric antifungal therapy must be initiated early in high-risk patients and tailored to local resistance patterns. The increasing prevalence of non-*albicans Candida* species and antifungal resistance further complicates this decision-making process, necessitating the use of broad-spectrum agents initially, followed by de-escalation based on microbiological identification and susceptibility testing. Therefore, empiric therapy is no longer a standardized approach but a dynamic, epidemiology-driven strategy integrating patient risk, regional data, and pathogen-specific resistance trends. The overall mortality for BSIs typically ranges from 12% to 34% depending on etiology and clinical context [165], fungal BSIs consistently exceed these values. Recent studies report mortality rates ranging from approximately 27% to over 50% for fungal bloodstream infections, with some cohorts demonstrating 30-day mortality approaching 45–60% [161].

A multicenter ICU analysis comparing candidemia and bacteremia patients demonstrated significantly higher

in-hospital mortality in fungal infections (approximately 50% vs.~34%), along with longer ICU stay and increased need for organ support, indicating that excess mortality persists even after adjustment for illness severity rather than being solely attributable to host factors [166]. Similarly, retrospective cohort studies in high-risk populations such as cirrhotic and ICU-admitted patients consistently show markedly higher 30-day mortality in candidemia compared with bacterial bloodstream infections (e.g., ~65% vs.~38% in cirrhotic cohorts), reinforcing the reproducibility of this disparity across clinical settings [167, 168]. Global burden analyses further confirm the high lethality of candidemia, estimating over 995 000 deaths (63·6%) worldwide and persistent high case-fatality despite antifungal availability, particularly in low-resource and high-burden regions [169]. The mechanistic basis of this excess mortality is strongly supported by clinical evidence, including delayed diagnosis due to lower sensitivity and slower turnaround time of fungal cultures compared with bacterial pathogens, frequent occurrence in critically ill or immunocompromised hosts, and the role of biofilm formation on intravascular devices that reduces antifungal penetration and treatment efficacy. In contrast, viral bloodstream detection generally does not represent a primary sepsis-driving entity in immunocompetent patients, and mortality is therefore highly context-dependent, being largely restricted to immunosuppressed populations where viruses such as cytomegalovirus or Epstein–Barr virus act as opportunistic systemic pathogens rather than primary causes of septic shock physiology; thus, viral bloodstream involvement contributes comparatively lower direct attributable mortality at the population level. When integrated across ICU, oncology, transplant, and surveillance datasets, these findings consistently support a robust and reproducible mortality hierarchy—fungal bloodstream infections representing the highest lethality burden, bacterial infections occupying an intermediate but clinically significant position, and viral bloodstream involvement generally showing the lowest direct mortality contribution except in severely immunocompromised hosts—reflecting fundamental differences in diagnostic detectability, therapeutic responsiveness, and pathogen–host interaction dynamics.

The fungal BSIs are not simply an extension of general sepsis syndromes but represent a uniquely challenging category of infection defined by regional variability, evolving resistance, and high mortality. The integration of regional epidemiological surveillance with early diagnostic strategies and risk-adapted empiric antifungal therapy is essential to improve outcomes. Future research must focus on refining predictive models for early antifungal initiation and developing rapid diagnostic platforms capable of overcoming the current limitations of culture-based detection.

Diagnostic approaches for blood-related microbial diseases

The accurate and timely diagnosis of blood-related microbial diseases is critical for guiding appropriate treatment and improving patient outcomes. The literature highlights a range of diagnostic approaches, each with its own advantages and limitations. Diagnostic approaches for blood-related microbial diseases began with microscopic techniques like Giemsa-stained blood smears. Over time, advancements led to culture-based methods, serological assays, and now molecular diagnostics such as PCR, enabling rapid and specific pathogen detection [170].

Blood culture

Blood culture remains the cornerstone for diagnosing bloodstream infections (BSIs), particularly for bacterial and fungal pathogens. Traditional culture methods involve inoculating blood samples [171], into aerobic and anaerobic bottles, followed by incubation and periodic monitoring for microbial growth. While highly specific, blood culture can be time-consuming, and its sensitivity can be affected by factors such as prior antibiotic administration and intermittent bacteremia. Despite being the gold standard, these methods can be time-consuming, with detection taking 24–72 h depending on the organism [172]. Recent advancements have enhanced the sensitivity and specificity of blood culture systems. Automated blood culture instruments, such as the BACTEC and BacT/ALERT systems, continuously monitor samples for CO_2 production, indicating microbial metabolism and allowing for earlier detection.

Molecular diagnostic techniques

Molecular diagnostic techniques have significantly advanced the detection and identification of pathogens in bloodstream infections (BSIs), offering faster and more accurate results compared to traditional culture-based methods. Techniques such as polymerase chain reaction (PCR), multiplex PCR, and next-generation sequencing (NGS) allow for the direct detection of bacterial, viral, and fungal nucleic acids from blood samples, drastically reducing diagnostic turnaround time from several days to just a few hours [52, 173]. Complementary tools like matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) and automated susceptibility testing systems, including VITEK 2, further enhance diagnostic speed and accuracy following culture positivity [174].

Recent innovations in real-time PCR and multiplex assays enable simultaneous detection of multiple pathogens

and resistance genes, proving especially useful in cases with low-level bacteremia or fastidious organisms [47]. Moreover, NGS facilitates comprehensive microbial profiling, aiding in the diagnosis of rare or unexpected pathogens and improving outcomes in complex infections [175]. Digital PCR is emerging as a powerful tool for quantifying pathogen load and monitoring treatment responses with high precision [176].

Despite these advances, blood culture remains essential for antimicrobial susceptibility testing, which is critical for guiding therapy. Challenges include high costs, need for technical expertise, and difficulty distinguishing contaminants from true pathogens. Integration of molecular methods with clinical data and conventional diagnostics is vital for effective patient management. Research continues to focus on point-of-care assays and improved bioinformatics for broader global applicability [177].

Serological assays

Serological tests are helpful in diagnosing bloodstream infections (BSIs) by detecting pathogen-specific antibodies or antigens in patient sera. Examples include ELISA and rapid diagnostic tests for malaria and antibody tests for HIV and hepatitis. However, serological tests may have limitations in early infection or in immunocompromised individuals with impaired antibody responses. These assays are particularly useful for diagnosing viral and parasitic blood infections where direct detection of the pathogen in the bloodstream may be challenging or transient. Recent advancements have enhanced their sensitivity, specificity, and rapidity, facilitating timely and accurate identification of causative agents. For instance, Carvalho et al. [178]. introduced a magnetoelastic biosensor functionalized with SARS-CoV-2 nucleocapsid protein, demonstrating effective antibody detection in human plasma, thereby offering a promising tool for COVID-19 serodiagnosis. Additionally, Eryilmaz et al. [179]. developed a paper-based multiplexed vertical flow assay (xVFA) capable of detecting IgG and IgM antibodies against multiple SARS-CoV-2 proteins. This assay, combined with machine learning algorithms, achieved the 89.5% accuracy in classifying immunity status, highlighting the integration of computational tools in serodiagnostics. Furthermore, the application of machine learning models to routine blood test values has shown potential in differentiating between viral and bacterial infections, aiding in appropriate antibiotic administration [180]. These innovations underscore a trend towards rapid, cost-effective, and user-friendly serological diagnostics, crucial for effective patient management and antimicrobial stewardship. However, challenges such as cross-reactivity and variability in immune responses necessitate ongoing research to enhance assay reliability and applicability across diverse clinical scenarios.

Emerging diagnostic technologies

Ongoing research is exploring novel diagnostic technologies for blood-related infections, including biosensors, microfluidic devices, and metagenomic sequencing [181]. These technologies hold the promise of even faster, more sensitive, and more comprehensive detection of bloodstream pathogens, potentially leading to earlier and more targeted interventions [182]. Emerging diagnostic technologies are revolutionizing the detection and management of bloodstream infections (BSIs) by providing rapid and accurate pathogen identification. Metagenomic next-generation sequencing (mNGS) allows for comprehensive analysis of microbial DNA directly from patient samples, enabling the detection of diverse pathogens without prior culturing [183]. Microfluidic-based assays have also advanced, facilitating antimicrobial susceptibility testing directly from positive blood cultures. These devices utilize miniaturized fluidic channels to yield rapid and reliable resistance profiles, essential for initiating targeted antimicrobial therapy [184]. Moreover, CRISPR-based diagnostics are gaining traction for their high specificity and speed. Recent innovations like the CRISPR-Cascade system enable the detection of bloodstream pathogens in under an hour without nucleic acid amplification, simplifying workflows while maintaining accuracy [185]. Collectively, these innovations contribute to early diagnosis, reduce reliance on empirical therapy, and improve patient outcomes by tailoring treatment strategies based on precise pathogen identification and resistance patterns.

Treatment strategies and the challenge of antimicrobial resistance

The treatment of blood-related microbial diseases depends on the specific causative agent and the severity of the infection. Antimicrobial agents, including antibiotics, antivirals, antifungals, and antiparasitics, are the mainstay of therapy. However, the increasing prevalence of AMR poses a significant threat to the effective management of these infections. It poses a significant global health challenge, necessitating innovative treatment strategies to combat resistant pathogens effectively. Recent advancements have highlighted several promising approaches. Such approach involves:

1 **(i)** application of artificial intelligence (AI) in antibiotic discovery which enhances the efficiency and accuracy of drug discovery processes, offering a potential solution to the dwindling pipeline of effective antibiotics [186];

2 **(ii)** another emerging strategy is the utilization of antimicrobial peptides (AMPs). These are the naturally occurring molecules which exhibit a broad-spectrum activity against various pathogens and have shown efficacy in disrupting bacterial membranes, making them potent candidates in the fight against multidrug-resistant organisms. Recent studies on AMPs are ongoing, with efforts focused on optimizing their stability and reducing potential toxicity [187];
3 **(iii)** bacteriophage therapy also presents a targeted approach to combat the resistance to antimicrobials. This method employs viruses that specifically infect and lyse bacterial cells, offering a precision treatment that minimizes damage to the host's beneficial microbiota. Clinical trials are underway to assess the efficacy and safety of phage therapy in treating infections caused by drug-resistant bacteria [188]; and.
4 **(iv)** interrelationships of human, animal, and environmental health in addressing resistance patterns. This comprehensive strategy advocates for coordinated efforts across sectors to implement policies that promote responsible antibiotic use, enhance infection prevention measures, and foster the development of new therapeutics [189].

Collectively, these innovative strategies underscore the necessity for a multifaceted and collaborative approach to mitigate the escalating threat of antimicrobial resistance. These are discussed as follows:

Antimicrobial therapy

Effective management of bloodstream infections (BSIs) necessitates the prompt initiation of appropriate empiric antimicrobial therapy, as delays can significantly increase mortality rates [190]. The selection of appropriate antimicrobial therapy involves considering the likely pathogen, local resistance patterns, the patient's clinical status, and potential drug toxicities [191]. Empiric therapy, initiated before definitive identification of the pathogen, is often necessary in severe infections like sepsis. Once the causative organism and its susceptibility profile are known, therapy can be tailored accordingly [192]. Recent clinical trials indicate that shorter antibiotic courses, such as seven days, are non-inferior to traditional 14-day regimens in selected cases [193]. Additionally, early intravenous-to-oral switch strategies in stable patients with Gram-negative BSIs have proven effective and cost-saving [194, 195]. In pediatric populations, delayed administration of appropriate therapy correlates with an increased risk of organ dysfunction and adverse outcomes. Implementing individualized treatment plans that integrate local resistance data and rapid diagnostic technologies is essential for optimizing patient outcomes.

Antimicrobial resistance

The emergence and spread of antimicrobial-resistant microorganisms is a major global health concern, particularly in the context of bloodstream infections [196]. Resistance mechanisms can arise through genetic mutations or the acquisition of resistance genes, leading to treatment failure and increased mortality. The literature highlights the critical need for antimicrobial stewardship programs to optimize antibiotic use, prevent the development and spread of resistance, and promote the development of novel antimicrobial agents [197].

The overuse and misuse of antibiotics have accelerated the emergence of resistant pathogens, complicating therapeutic strategies. Notably, carbapenem-resistant Enterobacterales (CRE) have become prevalent, particularly in hospital settings, and are associated with higher mortality rates compared to community-onset infections [198]. In pediatric populations, multidrug-resistant organisms are implicated in approximately 10% of BSIs, highlighting the vulnerability of this group [199]. The Infectious Diseases Society of America (IDSA) has provided updated guidance on managing infections, emphasizing the importance of tailored antimicrobial stewardship programs [195]. Emerging therapies, such as the combination of aztreonam and avibactam, have shown efficacy against resistant Gram-negative bacteria, offering hope for more effective treatments [200]. Additionally, innovative approaches targeting bacterial porins have been identified as potential strategies to overcome drug resistance mechanisms [201].

Supportive care

In addition to antimicrobial therapy, effective supportive care is crucial in managing bloodstream infections, especially in critically ill patients. Preventing catheter-related bloodstream infections (CRBSIs) through strict adherence to insertion and maintenance protocols significantly reduces infection rates [202]. Early recognition of complications and prompt initiation of appropriate antimicrobial therapy improve patient outcomes [203]. Hemodynamic stabilization and organ support are critical in managing sepsis-related BSIs, often requiring multidisciplinary approaches to optimize care. Advances in rapid diagnostic techniques and personalized treatment plans also contribute to improved survival rates by enabling targeted therapy [204]. Collectively, combining rigorous infection control with individualized supportive care is essential for reducing morbidity and mortality associated with bloodstream infections.

Epidemiology and global burden

Blood-related microbial diseases, particularly bloodstream infections (BSIs), sepsis, and vector-borne parasitic infections, are major global health threats. BSIs are especially prevalent in low- and middle-income countries (LMICs), driven by poverty, malnutrition, poor sanitation, and limited healthcare infrastructure. These factors not only increase the incidence of infections but also worsen outcomes, including higher mortality rates. In LMICs, antibiotic-resistant bacteria contribute significantly to BSI cases, compounded by inadequate hospital facilities and insufficient infection control measures [205].

Socioeconomic determinants like poverty and malnutrition enhance susceptibility to infections, especially in populations lacking access to clean water and sanitation. Limited access to timely healthcare services further delays diagnosis and treatment. Globally, BSIs account for about 20 million cases annually with a mortality rate exceeding 15%, predominantly affecting LMICs [206]. A wide range of pathogens—including multidrug-resistant bacteria, fungi, and parasites like *Plasmodium* and *Trypanosoma* spp.—complicate the epidemiology of BSIs [53].

The challenge is intensified by rising antimicrobial resistance, which leads to increased morbidity, treatment failure, and healthcare costs [207]. In tropical regions, vector-borne infections such as malaria and trypanosomiasis remain endemic, inflicting heavy disease burdens and economic losses [208]. Hospital-acquired BSIs (HA-BSIs) are also increasing, particularly among immunocompromised patients and those using invasive devices, with surveillance data linking their rise to poor hospital hygiene and limited resources [209].

In developed countries, HA-BSIs also pose serious threats. For instance, HA Gram-negative BSIs in ICUs show an all-cause mortality rate of 44%, often associated with central venous catheters [210]. The emergence of drug-resistant strains such as carbapenem-resistant *Klebsiella pneumoniae* (38% resistance) underscores the urgency for new treatment strategies. Vector control and vaccination remain key to reducing infection rates. Effective programs have curbed the spread of diseases like dengue and malaria.

Furthermore, climate change and globalization are reshaping the epidemiology of blood-related diseases. Rising temperatures expand vector habitats, while international travel accelerates the global spread of infections [211]. Combating BSIs and HA-BSIs requires integrated strategies involving infection control, antimicrobial stewardship, vaccination, and environmental interventions.

Challenges in terms of diagnosis and treatment of BSIs

Critical challenges

Bloodstream infections (BSIs) remain a critical challenge in clinical medicine due to their rapid onset, severe systemic effects, and increasing resistance to antimicrobials. This review compiles findings from recent high-impact studies to present a consolidated understanding of key pathogens responsible for BSIs, their pathogenic mechanisms, associated mortality rates, and current treatment strategies, emphasizing the need for precision in diagnosis and targeted therapeutic approaches.

Gram-positive bacteria, particularly methicillin-resistant *Staphylococcus aureus* (MRSA), continue to be leading causes of hospital-acquired bacteremia. According to Pastagia et al. [212], MRSA bacteremia is associated with a high 90-day mortality rate exceeding 30%, particularly in patients with underlying comorbidities. The prompt initiation of empiric therapy using agents such as vancomycin or daptomycin, coupled with infectious disease consultation, significantly improves outcomes by ensuring timely source control and therapeutic optimization.

Fungal bloodstream infections, especially nosocomial *Candida* infections, are increasing in incidence and severity. In a 19-year retrospective analysis, Dai et al. [213] reported a 30-day mortality of 52.99% in candidemia patients, with mortality significantly influenced by species distribution and antifungal resistance. Echinocandins such as caspofungin and micafungin are recommended as first-line agents due to rising azole resistance among *Candida* species. Delayed diagnosis and lack of early catheter removal are major contributors to poor prognosis.

Gram-negative bacilli, notably *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*, are responsible for a large burden of community-acquired and healthcare-associated BSIs. These pathogens employ various virulence strategies such as immune evasion, iron sequestration, and epithelial translocation to establish bloodstream infections. Timely administration of broad-spectrum antibiotics like cefepime, piperacillin-tazobactam, or carbapenems is essential to reduce mortality, particularly in septic presentations.

Alarmingly, the emergence of multidrug-resistant (MDR) Gram-negative organisms further complicates therapeutic decisions. Tsachouridou et al. [214] demonstrated that in endemic regions, mortality from MDR Gram-negative bacteremia can exceed 50%, even with aggressive management. Therapeutic options often include colistin or tigecycline,

although their toxicity and limited efficacy warrant cautious use. Rapid diagnostics are critical in these cases to avoid inappropriate empirical therapy.

Invasive fungal infections, such as aspergillosis, are increasingly reported in immunosuppressed hosts. Fang et al. [215] highlight the diagnostic challenges and treatment complexities associated with these infections. Resistance to azole antifungals has driven the adoption of liposomal amphotericin B and isavuconazole as alternative agents. Delays in recognition often lead to dissemination and high case fatality rates.

Viral-associated bloodstream infections, although transient, present diagnostic and therapeutic dilemmas. Arboviruses such as dengue, chikungunya, and Zika have been associated with viremia during acute infection stages. Some studies reported that while direct antiviral treatment remains unavailable, supportive management is critical. Severe dengue, in particular, may progress to hemorrhagic manifestations with significant mortality [216, 217].

Moreover, emerging viral pathogens like the monkeypox virus may result in systemic spread and viremia, particularly in immunocompromised individuals. Alakunle et al. [218] suggested that while supportive care is adequate for most, severe cases may require antiviral agents such as tecovirimat.

The increasing resistance among bacterial and fungal pathogens highlights the urgent need for stewardship, rapid diagnostics, and new therapies. Early antibiotic use, such as vancomycin or daptomycin, improves outcomes, while resistant fungal infections, particularly from *Candida* spp., often require echinocandins. MDR gram-negative bacteria like *E. coli* and *K. pneumoniae* demand last-resort drugs like colistin. Invasive fungal infections, such as aspergillosis, threaten immunocompromised patients due to azole resistance. Viral bloodstream infections from dengue, chikungunya, and monkeypox further complicate care. While supportive treatment is key, antivirals like tecovirimat may help severe monkeypox. Timely, targeted therapy and close monitoring are vital for survival.

Bacterial bloodstream infections (bacteremia)

High prevalence of specific bacterial pathogens in bloodstream infections

Bacteremia are primarily caused by a defined group of bacteria that exhibit high prevalence in both community and healthcare settings. Their capacity to form biofilms on device surfaces significantly contributes to persistent infections and complicates treatment outcomes [219]. Coagulase-negative staphylococci, are also frequently isolated in nosocomial bloodstream infections, especially in immunocompromised patients and those with implanted devices. In community-acquired infections, *Streptococcus pneumoniae* remains a major causative agent of bacteremia, particularly in vulnerable populations such as the elderly, children, and individuals with underlying severe ilness. Despite advances in pneumococcal vaccination, this pathogen continues to cause significant morbidity and mortality worldwide.

Gram-negative bacilli have emerged as critical pathogens in BSIs, with *Escherichia coli* and *Klebsiella pneumoniae* being the most prevalent species implicated in both community and hospital settings [220]. These bacteria are notorious for their capacity to acquire and disseminate AMR genes, including extended-spectrum beta-lactamases (ESBLs) and carbapenemases, rendering many standard treatments ineffective. Other notable Gram-negative pathogens include *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, which are often associated with severe infections in critically ill patients and exhibit multidrug-resistant phenotypes [221]. The increasing prevalence of multidrug-resistant (MDR) strains (Fig. 2) within these species poses a substantial challenge to clinical management, highlighting the urgent need for effective infection control measures and novel therapeutic options.

The common routes of infections include breaches in skin integrity, contamination from surgical wounds, and the migration of pathogens from respiratory or urinary tracts (Fig. 3). One of the most frequent clinical sources is the use of central venous catheters (CVCs), which provide a direct pathway for microbes into the bloodstream, particularly in critically ill or immunocompromised individuals [223]. Infections associated with indwelling urinary catheters, known as catheter-associated urinary tract infections (CAUTIs), are also major contributors to secondary bloodstream infections due to bacterial translocation from the urogenital tract [224]. Likewise, lower respiratory tract infections such as ventilator-associated pneumonia can disseminate pathogens into circulation, especially in intensive care settings [225]. Once inside the bloodstream, pathogens utilize diverse virulence factors to survive and proliferate. These mechanisms include the production of protective capsules, secretion of toxins, and formation of biofilms—particularly on medical devices—which enhance resistance to both immune responses and antibiotic treatment [226, 227]. Additionally, some pathogens trigger excessive immune reactions by releasing endotoxins or exotoxins, potentially leading to septic shock. Understanding these entry points and survival strategies is essential for the development of effective interventions to reduce BSI incidence and associated mortality.

Contemporary bacterial bloodstream infections are increasingly defined not only by pathogen identity but by the emergence and global dissemination of antimicrobial

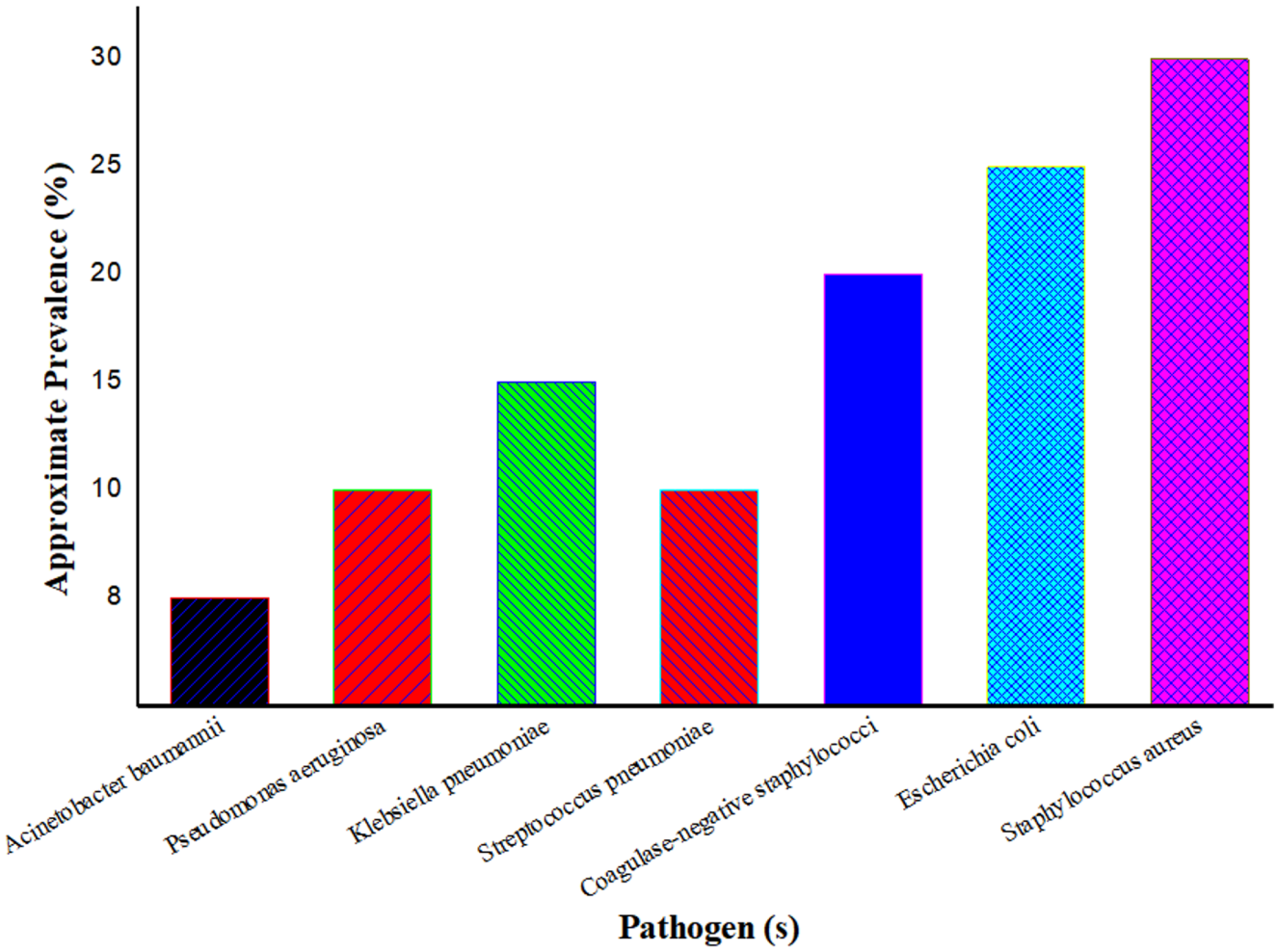

Fig. 2 A bar graph illustrating the relative prevalence of the top 5 bacterial species isolated from bloodstream infections in a pooled analysis of multiple studies [38, 75, 213, 215, 217, 218, 222]

resistance (AMR), which has become a dominant determinant of clinical outcome. Surveillance data from the WHO Global Antimicrobial Resistance and Use Surveillance System (GLASS) consistently demonstrate rising prevalence of resistant Gram-negative organisms, particularly carbapenem-resistant Enterobacterales (CRE), and methicillin-resistant *Staphylococcus aureus* (MRSA), across multiple regions including South Asia, sub-Saharan Africa, and parts of Europe and the Americas, highlighting the global and non-uniform nature of resistance evolution [228]. Within CRE, resistance is primarily mediated by three clinically dominant carbapenemase families: KPC (*Klebsiella pneumoniae* carbapenemase), NDM (New Delhi metallo-β-lactamase 1), and OXA-48–like enzymes, which differ in geographic distribution but collectively contribute to treatment failure in bloodstream infections. KPC remains highly prevalent in North America and parts of Europe, NDM predominates in South Asia, and OXA-48-like enzymes are widely distributed across the Mediterranean region and increasingly globally disseminated through hospital networks, reflecting plasmid-mediated horizontal gene transfer and clonal expansion dynamics documented in multicenter genomic surveillance studies [229]. These resistance mechanisms are clinically significant because they restrict the effectiveness of first-line β-lactams and are strongly associated with delayed initiation of active therapy, which is a consistently validated predictor of mortality in CRE bloodstream infections [82].

Outcome-based comparative evidence further demonstrates that antimicrobial resistance significantly modifies mortality within bacterial bloodstream infections. In *Staphylococcus aureus* bacteremia, a large pooled meta-meta-analysis including 38,159 patients has shown that MRSA bloodstream infection is associated with approximately two-fold higher mortality risk compared with MSSA bacteremia, reflecting both intrinsic resistance and delays in effective antimicrobial therapy initiation [230]. This mortality difference remains consistent across multiple independent systematic reviews and is attributed primarily to delayed administration

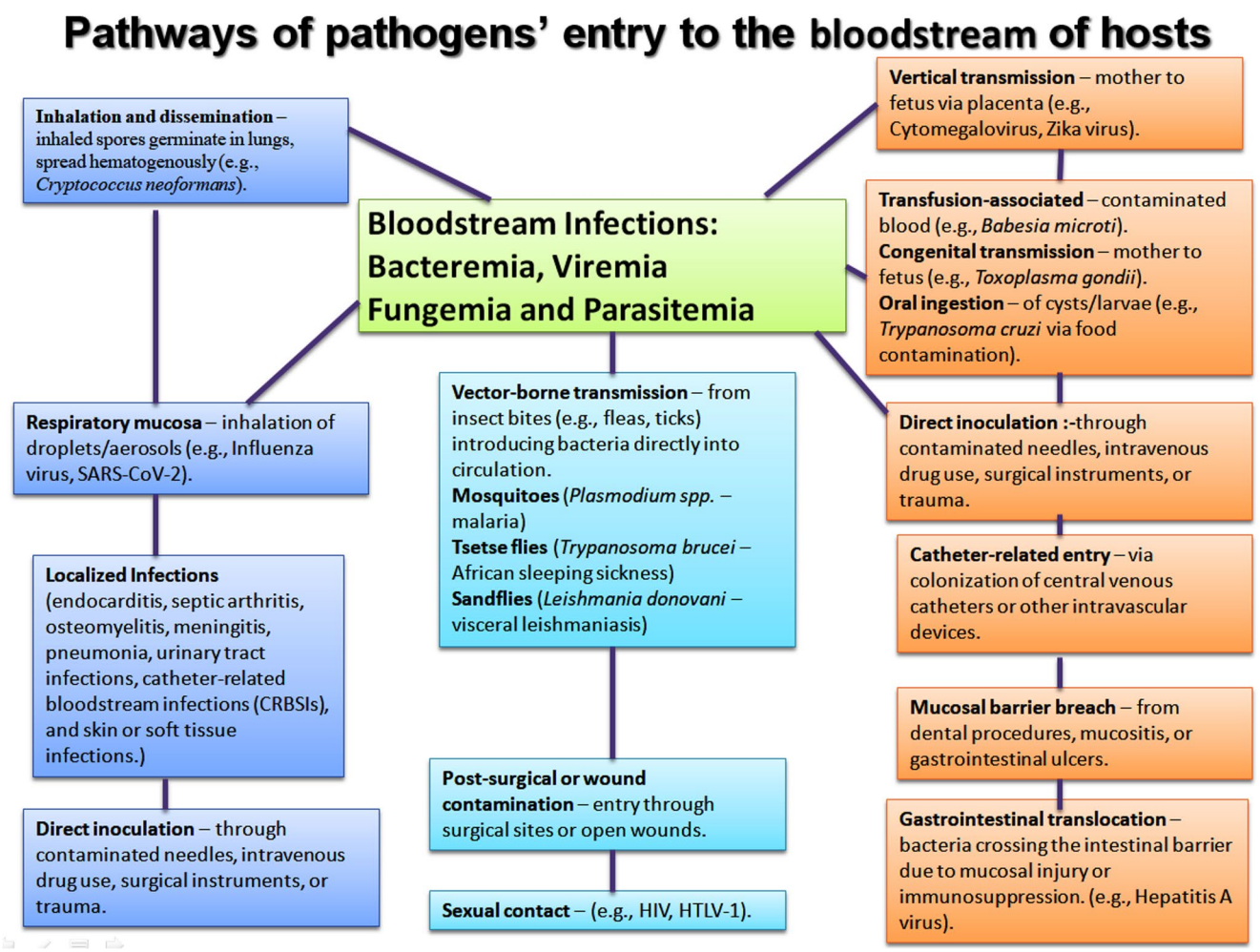

Fig. 3 Flowchart representation depicting the common pathways of pathogens entry into the bloodstream, starting from ihalation and localized infections or invasive procedures and culminating in systemic dissemination

of effective anti-staphylococcal therapy and limited empiric coverage for resistant strains. Similarly, in Enterobacterales BSIs, ESBL-producing organisms demonstrate consistently worse outcomes than non-ESBL strains, with meta-analytic evidence indicating increased mortality risk driven by delayed carbapenem or β-lactam/β-lactamase inhibitor therapy and higher rates of septic shock at presentation [231].

In carbapenem-resistant Enterobacterales bloodstream infections, multicenter ICU studies show high crude mortality rates, often exceeding 25–40% at 30 days, with outcomes strongly influenced by severity of illness and timing of effective antimicrobial therapy rather than carbapenemase type alone in some cohorts [232]. Notably, septic shock and delayed active therapy are repeatedly identified as independent predictors of death, underscoring that resistance acts synergistically with host severity rather than in isolation [82]. CDC surveillance similarly identifies MRSA and carbapenem-resistant Enterobacterales as urgent threats due to their consistent association with increased mortality, prolonged hospitalization, and increased healthcare burden compared with susceptible counterparts [37]. In contrast, methicillin-susceptible *S. aureus* (MSSA) and non-ESBL Enterobacterales infections demonstrate comparatively lower mortality when appropriate early therapy is administered, reinforcing the central role of resistance phenotype in outcome determination.

These integrated surveillance and outcome datasets establish a robust hierarchy within bacterial BSIs, in which MRSA and carbapenem-resistant Gram-negative organisms (KPC, NDM, OXA-48 producers) are consistently associated with the highest mortality risk, ESBL-producing organisms occupy an intermediate risk category, and fully susceptible organisms such as MSSA and non-ESBL Enterobacterales demonstrate comparatively better outcomes. This stratification is not merely microbiological but clinically operational, as it directly determines empiric antibiotic adequacy, timing of effective therapy, and ultimately survival in bloodstream infection management.

Mortality trends associated with antimicrobial resistant bacteria from 2010 to 2024 and 2025 to mid 2026

Antibiotic-resistant bloodstream infections (BSIs) continue to pose a critical threat to global health, contributing significantly to mortality. These infections, particularly those caused by multidrug-resistant (MDR) organisms, are associated with poorer clinical outcomes and higher fatality rates. During 2010–2012, carbapenem-resistant *Klebsiella pneumoniae* (CRKP), MRSA, and multidrug-resistant *Pseudomonas aeruginosa* emerged as dominant causes of severe healthcare-associated BSIs (Fig. 4). Qureshi et al. [233] reported approximately 42% 30-day mortality among patients with KPC-producing *K. pneumoniae* bacteremia, whereas Nguyen et al. [234] documented 58.3% in-hospital mortality and 41.7% 14-day mortality, particularly among ICU and transplant patients receiving delayed effective therapy. These findings demonstrated the early devastating impact of carbapenem resistance on bloodstream infection outcomes.

Between 2013 and 2015, mortality remained critically high because of widespread dissemination of carbapenemase-producing *K. pneumoniae* (KPC/VIM), ESBL-producing *Escherichia coli*, multidrug-resistant *Acinetobacter baumannii*, and resistant *Pseudomonas aeruginosa*. Daikos et al. [235] evaluated 205 patients with carbapenemase-producing *K. pneumoniae* BSIs in Greece and observed nearly 40% 28-day mortality. Importantly, mortality reached 44.4% in patients receiving monotherapy but decreased to 27.2% with combination therapy. Similarly, Tumbarello et al. [236] reported mortality exceeding 40% among Italian patients with KPC-producing *K. pneumoniae* bloodstream infections, emphasizing the increasing therapeutic limitations associated with pan-resistant Gram-negative pathogens.

During 2016–2018, mortality further escalated because of the rapid dissemination of NDM-producing Enterobacterales in China, India, and Southern Europe. Xu et al. [236] and Zhang et al. [237] reported mortality rates ranging from 33.5% to over 42% among CRKP bloodstream infections, while several ICU-based investigations documented

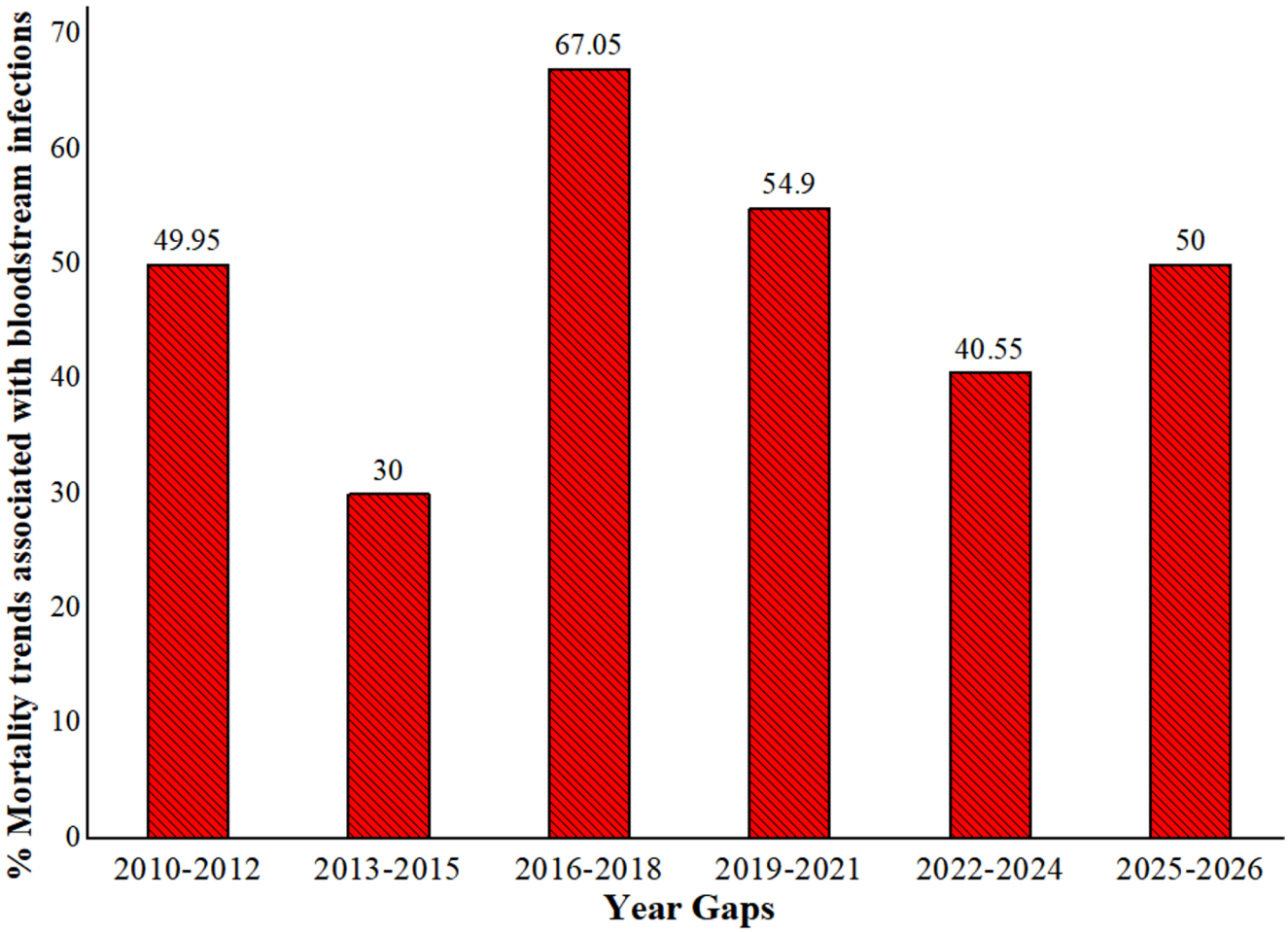

Fig. 4 Showing the mortality trends associated with bloodstream infections caused by antibiotic-resistant bacteria over successive three-year intervals (2010–2024) and 2025 to mid 2026

mortality exceeding 50% in critically ill patients. Russo et al. [238] further demonstrated that delayed active antimicrobial therapy substantially increased mortality risk in CRKP bacteremia. These findings indicated that increasing carbapenem resistance and ICU-associated outbreaks significantly worsened patient survival.

From 2019 to 2021, antimicrobial resistance became a major global cause of death (Fig. 4). The Global Burden of Disease (GBD) and GRAM analyses estimated approximately 4.95 million deaths associated with bacterial antimicrobial resistance and 1.27 million deaths directly attributable to AMR in 2019 [36]. Resistant BSIs caused by MRSA, carbapenem-resistant *A. baumannii* (CRAB), and CRKP were among the leading contributors to sepsis-related mortality worldwide [239]. The highest mortality burden occurred in western sub-Saharan Africa, where death rates reached approximately 27.3 deaths per 100,000 population. Ikuta et al. (2022) [38] and Maraolo et al. [236] additionally highlighted the increasing frequency of ICU outbreaks, prolonged hospitalization, and limited therapeutic options associated with resistant Gram-negative BSIs.

During 2022–2024, mortality remained alarmingly high despite advances in antimicrobial stewardship and newer β-lactam/β-lactamase inhibitor therapies. Updated GBD analyses estimated approximately 4.71 million AMR-associated deaths and 1.14 million directly attributable deaths globally in 2021 [207]. Methicillin-resistant *Staphylococcus aureus* alone accounted for nearly 550,000 associated deaths worldwide. Simultaneously, carbapenem resistance among Gram-negative pathogens increased substantially between 1990 and 2021, especially in South Asia, Latin America, and sub-Saharan Africa. Boral et al. [240] and Gupta et al. [241] reported increasing incidence of NDM-producing Enterobacterales BSIs with mortality ranging from 26% to 57.1%, particularly among elderly ICU patients and individuals with delayed effective therapy.

By 2025–mid-2026, mortality trends showed a further increase because of the emergence of near pan-resistant Gram-negative bacilli, colistin-resistant *Klebsiella pneumoniae*, and NDM-producing carbapenem-resistant Enterobacterales (NDM-CRE). Studies from China reported 52.8% in-hospital mortality and 25.7% 30-day mortality among ICU patients with NDM-CRE BSIs [242]. Similarly, Perez-Lazo et al. [243] suggested approximately 33–40% 30-day mortality in Peru, whereas de Araujo et al. [244] observed mortality rates exceeding 30% in Brazil. Reports from Saudi Arabia also demonstrated mortality ranging from 30 to 70% among critically ill patients infected with carbapenemase-producing Enterobacterales [245]. Collectively, these findings indicate that although improved stewardship and novel antimicrobial combinations have modestly improved outcomes in some regions, the global mortality burden associated with antimicrobial-resistant BSIs has generally increased over time because of the continued emergence and dissemination of highly resistant pathogens with limited therapeutic options. Table 4 summarizes the mortality rates, predominant resistant pathogens, their geographical distribution, and clinical implications.

Globally, the trajectory of AMR suggests a worsening scenario. Projections indicate that by 2050, approximately 1.91 million deaths per year could be attributed to AMR, a nearly 70% increase from 2022 levels [207, 253]. This anticipated rise reflects not only the biological challenges of resistance but also the insufficient pace of new antibiotic development. In the European context, Hassoun-Kheir et al. [254]. report that infections with drug-resistant pathogens such as carbapenem-resistant *Klebsiella pneumoniae* result in significantly elevated mortality risks—up to 3.44 times higher than susceptible strains—further substantiate the threat of resistance to public health systems. Beyond clinical outcomes, such resistances impose a profound economic burden; often necessitating extended hospital stays, the use of more toxic and costly last-resort drugs, and increased demands on intensive care resources. These factors underscore the urgent need for global antimicrobial stewardship, enhanced surveillance systems, and accelerated research into novel therapeutic strategies (Fig. 4).

Viral bloodstream infections (viremia)

It represents a critical phase in the pathogenesis of many systemic viral infections. This stage facilitates the dissemination of viruses from their primary entry site to various organs and tissues, often resulting in systemic involvement and severe clinical manifestations. The occurrence and magnitude of viremia serve as key indicators of disease progression and severity. For many viruses, including flaviviruses, herpes viruses, and corona viruses, the initial replication occurs locally before viral particles gain access to the circulatory system—a process termed primary viremia. Subsequent replication in systemic tissues may then lead to a more intense secondary viremia, which can amplify tissue damage and immune dysregulation [255]. Table 5 represents a summary of different viremic viruses responsible for infections of humans via different routs viz., skin, genital tract, or eye and their primary target organs and associated clinical manifestations. A summary of different viremic viruses that initiate infection of Humans via different routs including Skin, Genital Tract, or Eye and their primary target organs and associated clinical manifestations is given in Table 5.

In recent studies on SARS-CoV-2, viremia has been directly associated with adverse clinical outcomes. Elevated levels of viral RNA in plasma were strongly correlated with

Table 4 Estimated mortality trends associated with bloodstream infections caused by antibiotic-resistant bacteria over successive three-year intervals (2010–2024 and 2025–2026). This table summarizes the mortality rates, predominant resistant pathogens, geographical distribution, and clinical implications. Data extracted from published researches [233–247]

Time Period intervals	Predominant resistant pathogens in BSIs	Major resistance mechanisms	Regional mortality	Major geographical distribution	Clinical implications	Citations
2010–2012	Carbapenem-resistant *Klebsiella pneumoniae* (CRKP), MRSA, multidrug-resistant *Pseudomonas aeruginosa*	KPC carbapenemases, VIM metallo-β-lactamases, altered penicillin-binding proteins (mecA), porin loss combined with efflux mechanisms	42% 30-day mortality among patients with KPC-producing *K. pneumoniae* bacteremia. 58.3% in-hospital mortality and 41.7% 14-day mortality in CRKP bloodstream infections. Mortality was particularly high in ICU patients and in those receiving delayed effective therapy.	United States, Greece, Italy, tertiary-care ICUs and transplant units	Rapid progression to septic shock, failure of carbapenem monotherapy, increased ICU stay, emergence of healthcare-associated outbreaks	[233, 246, 247]
2013–2015	Carbapenemase-producing *K. pneumoniae* (KPC/VIM), ESBL-producing *Escherichia coli*, multidrug-resistant *Acinetobacter baumannii and P. aeruginosa* and	KPC, VIM and OXA carbapenemases; CTX-M ESBLs; aminoglycoside-modifying enzymes; biofilm-associated resistance	0% to 60% global mortality. Daikos et al. evaluated 205 patients with carbapenemase-producing *K. pneumoniae* BSIs in Greece and reported 40% 28-day mortality. Mortality reached 44.4% with monotherapy but decreased to 27.2% with combination therapy. Pan-resistant isolates were also documented. Tumbarello et al. similarly reported mortality exceeding 40% in KPC-producing *K. pneumoniae* BSIs in Italy.	Greece, Italy, Mediterranean Europe, hospital endemic regions	Increased dependence on colistin and tigecycline combinations, rising pan-resistant Gram-negative strains, prolonged hospitalization and recurrent nosocomial transmission	[234, 235, 248]
2016–2018	CRKP, ESBL-producing *E. coli*, multidrug-resistant *P. aeruginosa*, MRSA	Carbapenemase production (KPC, NDM), CTX-M ESBLs, fluoroquinolone target mutations, efflux-mediated multidrug resistance	61.2% to 73% global mortality. 42.14% among CRKP infections and mortality exceeding 50% in CRKP bloodstream infections. Studies from China and Southern Europe reported increasing prevalence of NDM-positive Enterobacterales and ICU-associated outbreaks with mortality rate of 33.5%- 42.14%.	China, India, Southern Europe, Asia-Pacific ICUs	Increased empirical therapy failure, delayed active treatment associated with higher mortality, increased antimicrobial stewardship burden	[236–238, 249, 250, 251]
2019–2021	MRSA, third-generation cephalosporin-resistant *E. coli*, carbapenem-resistant *A. baumannii* (CRAB), carbapenem-resistant *K. pneumoniae* (CRKP)	mecA-mediated methicillin resistance in MRSA; ESBLs (CTX-M) in *E. coli*; OXA-type carbapenemases in *A. baumannii*; KPC, NDM, and OXA-48 carbapenemases in *K. pneumoniae*	52·9%−56·9% Global mortality. Global AMR caused 1.27 million attributable deaths and 4.95 million associated deaths in 2019; highest mortality occurred in western sub-Saharan Africa (27.3 deaths/100,000 population). MRSA and resistant Gram-negative BSIs were major contributors to sepsis mortality.	Highest burden in sub-Saharan Africa, South Asia, and healthcare-associated settings worldwide	Increased BSI-associated mortality, prolonged hospitalization, limited treatment options, ICU outbreaks, and rapid dissemination of multidrug-resistant clones	[38, 238, 239, 251, 252]
2022–2024	NDM-producing Enterobacterales, CRE, MRSA, drug-resistant *A. baumannii*	NDM metallo-β-lactamases, OXA carbapenemases, plasmid-mediated resistance transfer, multidrug efflux systems, colistin heteroresistance	26% – 57.1% global mortality. Updated GBD AMR analyses estimated 4.71 million deaths associated with bacterial AMR in 2021 including 1.14 million directly attributable deaths. MRSA alone caused approximately 550,000 associated deaths globally in 2021. Carbapenem resistance among Gram-negative bacteria increased markedly between 1990 and 2021. Multiple regional surveillance programs documented rising incidence of NDM-positive BSIs in India, Pakistan, Latin America and the United States.	South Asia, Latin America, North America, sub-Saharan Africa	Expansion of pan-resistant Gram-negative pathogens, rising geriatric mortality, increasing failure of empirical sepsis therapy, urgent need for novel β-lactam/β-lactamase inhibitor combinations	[209, 240, 241, 253, 254]

Table 4 (continued)

Time Period intervals	Predominant resistant pathogens in BSIs	Major resistance mechanisms	Regional mortality	Major geographical distribution	Clinical implications	Citations
2025–2026	NDM-producing carbapenem-resistant Enterobacterales (NDM-CRE), carbapenemase-producing Enterobacterales (CPE), colistin-resistant *Klebsiella pneumoniae*, pan-resistant Gram-negative bacilli	**bla**<sub> NDM dissemination, carbapenemase production, porin-loss with β-lactamase activity, plasmid-mediated horizontal transfer, emerging polymyxin resistance	30–70% pooled mortality. **China**: high mortality, including 52.8% in-hospital and 25.7% 30-day mortality in ICU cohorts. **Peru**: approximately 33%–40% 30-day mortality. **Brazil**: Mortality rates exceeding 30%. **Saudi Arabia**: Mortality ranging from 30–70%.	China, Peru, Brazil, Saudi Arabia, global ICU and tertiary-care hospital networks	Near-total therapeutic failure in severe Gram-negative BSIs, dependence on cefiderocol- and aztreonam-based salvage regimens, prolonged hospitalization, ICU outbreaks, and major infection-control burden	[243, 244, 244, 245]

inflammatory biomarkers and multi-organ dysfunction, indicating a poor prognosis in COVID-19 patients [256]. This systemic spread has been linked to immune dysregulation, coagulopathies, and fibrotic pathways, emphasizing the importance of controlling viremia early in infection [257]. Moreover, the presence of viral genetic material in the blood—termed DNAemia or RNAemia depending on the virus—has been reported in pediatric sepsis, with higher viral loads correlating with increased risk of mortality, regardless of bacterial co-infection [258].

Viremia also lays a diagnostic role. In pediatric febrile illnesses with unclear etiology, the detection of viral nucleic acids in blood has helped differentiate between viral and bacterial infections, thus preventing unnecessary antibiotic usage [259]. Additionally, phenomena such as antibody-dependent enhancement (ADE) observed in dengue infection underscore how viremia can be exacerbated by immune mechanisms, leading to more severe secondary infections [260].

Overall, viremia is not merely a byproduct of viral replication but a central component of systemic disease progression. Its presence signals potential for increased disease severity, supports diagnostic precision, and provides insight into immune evasion strategies employed by viruses. Continued research into the molecular and immunological mechanisms governing viremia will be instrumental in guiding future antiviral therapies and clinical management strategies.

Neurotropic viruses such as Japanese encephalitis virus (JEV) and chikungunya virus (CHIKV) often result in encephalitis or meningoencephalitis due to their ability to invade the central nervous system (CNS). Elevated cytokines like IL-6 and TNF-α in cerebrospinal fluid during infection have been correlated with CNS inflammation and neuronal injury [261]. In contrast, hepatotropic viruses such as hepatitis C virus (HCV) preferentially infect liver cells, initiating hepatic inflammation and fibrosis. The innate immune response, particularly through Toll-like receptor and RIG-I signaling, plays a crucial role in detecting viral RNA and mounting antiviral defenses, though viruses like HCV can suppress these responses to establish the severity [262]. Additionally, systemic immune responses influence disease outcomes across various viruses. In SARS-CoV-2 infection, delayed interferon signaling is associated with enhanced viral dissemination and severe disease, as shown by Carrau et al. [263]. Excessive immune activation, or cytokine storms, further exacerbates tissue damage in multiple viral infections. Understanding these dynamics is vital for designing targeted antiviral therapies.

Diverse clinical manifestations dependent on viral tropism

The epidemiology and clinical significance of viral bloodstream infections (BSIs) have evolved considerably over the past decade. Unlike bacterial BSIs, which are typically characterized by active microbial proliferation in the bloodstream, viral BSIs are often identified through the detection of viral DNA or RNA in blood, commonly referred to as DNAemia or viremia. The presence of viral nucleic acids in blood is increasingly recognized as an indicator of systemic dissemination, impaired immune control, and disease severity. As summarized in Table 6, the dominant viral pathogens, underlying immune-evasion mechanisms, clinical outcomes, and diagnostic approaches have changed substantially from 2010 to mid-2026.

During 2010–2012, viral bloodstream infections were predominantly reported in hematopoietic stem cell transplantation (HSCT) and solid-organ transplantation settings. Cytomegalovirus (CMV), Epstein–Barr virus (EBV), and adenovirus were the principal pathogens detected in blood. These viruses exploit latency and immune-evasion strategies, including inhibition of antigen presentation, downregulation of major histocompatibility complex class I (MHC-I) molecules, and reactivation during profound immunosuppression. CMV DNAemia was strongly associated with increased transplant-related mortality and heightened

Table 5 Summary of different viremic viruses that initiate infection of Humans via the Skin, Genital Tract, or Eye and their primary target organs and associated clinical manifestations

Virus	Virus Family	Route of Infection	Primary Target Organs	Major Clinical Manifestations
Dengue virus	Flaviviridae	Skin (mosquito bite)	Endothelial cells, liver, spleen, blood vessels	Fever, rash, myalgia, hemorrhagic fever, shock
Zika virus	Flaviviridae	Skin (mosquito bite), sexual transmission, conjunctiva, maternal-fetal	Brain, nervous tissue, placenta	Fever, rash, conjunctivitis, microcephaly in neonates
HIV	Retroviridae	Genital tract, blood (injection, transfusion), vertical transmission	CD4+T cells, lymphoid tissue, CNS	Immunodeficiency (AIDS), opportunistic infections
Hepatitis B	Hepadnaviridae	Blood, genital tract (sexual), perinatal, injection	Liver	Hepatitis, jaundice, cirrhosis, hepatocellular carcinoma
Rabies virus	Rhabdoviridae	Animal bite (saliva), injection	CNS, salivary glands	Encephalitis, hydrophobia, coma, death
Ebola virus	Filoviridae	Broken skin, mucous membranes, injection, direct contact	Liver, spleen, endothelial cells	Hemorrhagic fever, multiorgan failure, shock
West Nile virus	Flaviviridae	Skin (mosquito bite)	CNS (brain, spinal cord)	Fever, encephalitis, meningitis
Chikungunya virus	Togaviridae	Skin (mosquito bite)	Joints, muscles, skin, blood	Fever, arthralgia, rash
Yellow Fever virus	Flaviviridae	Skin (mosquito bite)	Liver, heart, kidney	Fever, jaundice, bleeding, organ failure
Herpes Simplex Virus (HSV)	Herpesviridae	Genital tract, oral mucosa, conjunctiva, eye	Mucocutaneous tissues, CNS (in some cases)	Vesicular lesions, encephalitis (HSV-1), genital ulcers (HSV-2)

susceptibility to secondary bacterial and fungal infections. EBV DNAemia emerged as a major risk factor for post-transplant lymphoproliferative disorder (PTLD), a severe complication associated with mortality rates exceeding 30–50% in the absence of timely intervention. Disseminated adenovirus infection was particularly devastating in pediatric HSCT recipients, where mortality frequently ranged from 20% to 50% and exceeded 50% in patients with persistent high-level viremia. During this period, routine quantitative PCR surveillance became increasingly integrated into transplant programs, establishing viral load monitoring as an essential component of patient management [264–267].

Between 2013 and 2015, the clinical burden of CMV, EBV, adenovirus, and BK polyomavirus remained substantial, but increasing attention was directed toward antiviral resistance and immune reconstitution. CMV infections exhibiting UL97 and UL54 resistance mutations were increasingly reported among HSCT recipients, complicating treatment outcomes. Adenoviral viremia continued to be associated with poor prognosis, with mortality rates ranging from approximately 26% to 50%, while severe disseminated disease occasionally exceeded 80% mortality. EBV-associated PTLD remained a significant contributor to post-transplant mortality. This period also witnessed major advances in molecular diagnostics, including widespread implementation of quantitative PCR surveillance, resistance genotyping, and the early development of adoptive virus-specific T-cell therapies. Consequently, viral management shifted from simple pathogen detection toward individualized immune-guided monitoring and intervention [280–285].

The period from 2016 to 2018 marked an important transition in the understanding of viral bloodstream infections. Although CMV, EBV, adenovirus, BK virus, and Parvovirus B19 continued to dominate among transplant recipients, viral reactivation was increasingly recognized in critically ill immunocompetent individuals. CMV reactivation emerged as an important prognostic marker in intensive care units (ICUs), where it was associated with prolonged mechanical ventilation, longer hospital stays, increased nosocomial infections, and elevated mortality. Meta-analytical evidence indicated approximately a two-fold increase in overall mortality and a 2.5-fold increase in ICU mortality among patients experiencing CMV reactivation. These findings broadened the concept of clinically relevant viral DNAemia beyond traditional transplant populations and stimulated interest in viral-load-guided management, antiviral prophylaxis, and immune-based therapeutic approaches [268–270, 286, 287].

A major paradigm shift occurred during 2019–2021 with the emergence of the COVID-19 pandemic. SARS-CoV-2 became the dominant bloodstream viral pathogen, and the detection of viral RNA in blood (RNAemia) gained considerable clinical importance. SARS-CoV-2 RNAemia was consistently associated with severe disease, intensive care admission, mechanical ventilation, multiorgan dysfunction, and mortality. Meta-analyses demonstrated significantly higher odds of ICU admission and death among

Table 6 Estimated mortality trends associated with bloodstream infections caused by viruses over successive three-year intervals (2010–2024) and 2025 to mid 2026. This table summarizes the mortality rates, predominant viral pathogens, geographical distribution, and clinical implications. Data synthesized from peer-reviewed sources [17, 192184−]

Time Period Intervals	Predominant Viral Pathogens	Major Viral Persistence/ Evasion Mechanisms	Reported Mortality Findings	Geographical Distribution	Clinical Implications	Citations
2010–2012	CMV, EBV and Adenovirus	Latency in leukocytes and tissues (CMV, EBV, HHV-6); inhibition of antigen presentation; downregulation of MHC-I; viral homologs of cytokines; immune exhaustion; reactivation during T-cell depletion and immunosuppression; persistence in renal and lymphoid reservoirs (BKV)	CMV DNAemia was strongly associated with increased transplant-related mortality and secondary bacterial/ fungal infections. EBV DNAemia predisposed to PTLD with mortality often exceeding 30–50% if not treated early. Disseminated adenovirus infection in pediatric HSCT recipients frequently resulted in mortality of 20–50%, and mortality exceeded 50% in patients with persistent high-level viremia. HHV-6 reactivation was associated with encephalitis, GVHD, delayed engraftment, and increased mortality. In one pediatric SCT cohort, viral complications (CMV, EBV, AdV) accounted for 21% of all deaths.	North America, Western Europe, Scandinavia, Japan; most reports originated from HSCT and solid-organ transplant centers	Routine quantitative PCR monitoring of CMV, EBV, and AdV became standard practice in many transplant programs; recognition of viral DNAemia as a major contributor to transplant-related morbidity and mortality; emergence of pre-emptive antiviral therapy and immune monitoring strategies	[264–267]
2013–2015	CMV, EBV, Adenovirus, BK virus	CMV latency with emergence of **UL97 and UL54 drug-resistance mutations**; EBV latency in B lymphocytes causing PTLD; adenoviral persistence with impaired T-cell immunity; BKV persistence in renal epithelium and urothelium; HHV-6 chromosomal integration and latency; immune escape through T-cell dysfunction and delayed immune reconstitution	CMV remained a major contributor to transplant-related mortality despite pre-emptive therapy. Drug-resistant CMV infections were increasingly reported in HSCT recipients. Adenoviral viremia and disseminated disease continued to show mortality rates of approximately 26–50%, exceeding 80% in severe disseminated disease. EBV-associated PTLD remained a life-threatening complication with substantial mortality in untreated cases. Viral infections collectively remained a major cause of morbidity and mortality after allo-HSCT.	Europe, North America, East Asia (particularly transplant centers in Germany, Sweden, Japan, China, and the United States)	Expansion of quantitative PCR-based viral surveillance; routine CMV, EBV, and AdV monitoring; increasing use of pre-emptive antiviral therapy; recognition of antiviral resistance testing (UL97/UL54 genotyping); development of adoptive virus-specific T-cell therapies and immune-monitoring approaches	[270–273, 284,]
2016–2018	CMV, EBV, Adenovirus, BK virus, Parvovirus B19	Lifelong latency and reactivation (CMV, EBV, HHV-6); CMV immune evasion through MHC-I/II downregulation, NK-cell inhibition, and latency in myeloid progenitors; EBV persistence in memory B cells; adenoviral persistence in lymphoid tissue; BKV persistence in renal epithelium; Parvovirus B19 persistence in bone marrow and endothelial tissues during immune dysfunction.	CMV reactivation was increasingly associated with prolonged ICU stay, longer mechanical ventilation, higher nosocomial infection rates, and increased mortality among critically ill patients. Meta-analyses demonstrated approximately a 2-fold increase in overall mortality and a 2.5-fold increase in ICU mortality among patients with CMV reactivation. Viral DNAemia remained a major cause of morbidity and mortality after HSCT and solid-organ transplantation.	Europe, North America, China, Japan, South Korea	Recognition of viral reactivation in immunocompetent critically ill patients; widespread adoption of quantitative PCR surveillance; increasing use of viral-load-guided management; expansion of virus-specific T-cell therapies for refractory CMV, EBV, and adenovirus infections; growing interest in antiviral prophylaxis beyond transplant settings.	[267–271]

Table 6 (continued)

Time Period Intervals	Predominant Viral Pathogens	Major Viral Persistence/ Evasion Mechanisms	Reported Mortality Findings	Geographical Distribution	Clinical Implications	Citations
2019–2021	SARS-CoV-2, CMV, EBV, HSV-1/2, HHV-6	SARS-CoV-2 interferon antagonism (ORF6, ORF8 and related immune-evasion pathways), lymphocyte depletion, cytokine dysregulation, endothelial injury, viral dissemination into blood (RNAemia); CMV, EBV, HSV and HHV-6 reactivation driven by immune exhaustion and critical illness-associated immunosuppression	SARS-CoV-2 RNAemia was consistently associated with severe disease, ICU admission, mechanical ventilation, multiorgan dysfunction, and increased mortality. Meta-analyses showed significantly higher odds of ICU admission (OR ≈ 4.3) and all-cause mortality (OR ≈ 11) among RNAemic patients. ICU studies demonstrated higher 28-day mortality among patients with detectable SARS-CoV-2 RNA in blood. CMV and HSV reactivation were increasingly recognized as contributors to prolonged ICU stay and secondary complications in severe COVID-19.	Worldwide (Europe, North America, South America, China, East Asia, Middle East, Africa)	Viral infection became a major focus of critical-care research; blood viral-load measurement emerged as a prognostic biomarker; widespread implementation of plasma PCR and molecular surveillance; recognition of COVID-19 as a systemic vascular and immunological disease rather than solely a respiratory infection; increased investigation of herpesvirus reactivation in ICU patients.	[22, 271–274]
2022–2024	SARS-CoV-2, CMV, EBV, HSV-1/2, Adenovirus	Persistent viral reservoirs, immune exhaustion, T-cell dysfunction, interferon-response impairment, herpesvirus reactivation during critical illness, endothelial injury and systemic inflammation	Systematic reviews confirmed that viremia is consistently associated with severe disease, organ dysfunction, ICU admission, and increased mortality across several viral infections. SARS-CoV-2 RNAemia remained a strong predictor of poor outcome, while CMV and HSV reactivation were linked to prolonged critical illness and secondary complications.	Global transplant centers and ICUs (North America, Europe, Asia-Pacific, Latin America, Africa)	Viral sepsis increasingly recognized as an underdiagnosed cause of critical illness; blood viral-load monitoring gained value for risk stratification; emphasis shifted toward precision medicine, immune profiling, and early identification of viral-induced organ dysfunction.	[275–277]
2025–2026	CMV, EBV, Adenovirus, HSV-1/2, SARS-CoV-2 variants	Lifelong latency, viral immune escape, impaired T-cell surveillance, antiviral resistance, persistent low-level replication, immune exhaustion in transplant and ICU patients	Viremia remained a strong predictor of severe disease and poor prognosis. In adult allo-HSCT recipients, adenovirus-related mortality was 16.7% overall, 11.5% among patients with viremia, **and increased to** 24.0% in high-level viremia (> 1000 copies/mL). CMV reactivation continued to contribute substantially to transplant-related morbidity and mortality despite prophylactic strategies.	Global transplant centers and critical-care units (North America, Europe, Asia-Pacific, Latin America)	Expansion of metagenomic next-generation sequencing (mNGS), blood virome profiling, cell-free DNA diagnostics, precision monitoring of viral reactivation, and integration of molecular surveillance into transplant and ICU management	[275, 278, 279]

patients with detectable viral RNA in blood. Mechanistically, SARS-CoV-2 employed multiple immune-evasion strategies, including interferon antagonism, lymphocyte depletion, endothelial injury, and cytokine dysregulation, facilitating systemic dissemination. Concurrently, reactivation of latent herpesviruses such as CMV, EBV, HSV, and HHV-6 became increasingly recognized in severe COVID-19 cases, highlighting the contribution of immune exhaustion and critical illness-associated immunosuppression to disease progression. These observations transformed viral load measurement from a niche transplant tool into a broadly applicable prognostic biomarker in critical-care medicine [22, 271–274].

From 2022 to 2024, growing evidence established viremia as a universal marker of disease severity across multiple viral infections. SARS-CoV-2 continued to dominate the literature, while CMV, EBV, HSV, and adenovirus remained clinically important causes of viral DNAemia in transplant and critically ill populations. Persistent viral reservoirs, immune exhaustion, T-cell dysfunction, impaired interferon signaling, and systemic inflammation were recognized as major drivers of adverse outcomes. Systematic reviews confirmed strong associations between viremia, organ dysfunction, ICU admission, and mortality. During this period, the concept of viral sepsis gained increasing acceptance, emphasizing that viral pathogens can induce systemic inflammatory and organ-failure syndromes comparable to those traditionally attributed to bacterial infections. Consequently, blood viral-load monitoring, immune profiling, and early recognition of viral-induced organ dysfunction

became increasingly important components of precision medicine approaches in critical care and transplantation [275–277].

The most recent period, spanning 2025 to mid-2026, is characterized by the integration of advanced molecular technologies into the management of viral bloodstream infections. CMV, EBV, adenovirus, HSV, and circulating SARS-CoV-2 variants remain the predominant viruses detected in blood, particularly among transplant recipients and critically ill patients. Viral persistence is facilitated by latency, immune escape, impaired T-cell surveillance, antiviral resistance, and chronic immune dysfunction. Recent evidence indicates that viremia remains a robust predictor of poor clinical outcome. A systematic review and meta-analysis of adult allogeneic HSCT recipients reported adenovirus-associated mortality rates of 16.7% overall, 11.5% among viremic patients, and 24.0% in individuals with high-level viremia exceeding 1000 copies/mL. Despite advances in prophylactic strategies, CMV reactivation continues to contribute significantly to transplant-related morbidity and mortality. Simultaneously, metagenomic next-generation sequencing (mNGS), blood virome profiling, and cell-free DNA diagnostics are increasingly being incorporated into clinical practice, enabling earlier pathogen detection and more precise monitoring of viral reactivation. These developments reflect a transition from conventional pathogen-specific surveillance toward comprehensive molecular characterization of the blood virome and individualized patient management [275, 278, 279].

The period from 2010 to 2026 illustrates a progressive shift in the understanding of viral bloodstream infections—from complications primarily confined to transplant recipients to broadly recognized indicators of systemic disease severity, immune dysregulation, and adverse clinical outcomes. Advances in molecular diagnostics, viral load monitoring, immune profiling, and metagenomic technologies have substantially improved the detection and management of viral BSIs, while ongoing research continues to refine their prognostic and therapeutic significance across diverse patient populations.

Impact of antiviral therapy on viral load and disease progression

Antiviral therapy plays a critical role in controlling viral infections by reducing viral replication, lowering viral load, and preventing the progression of disease. It has been found that, the efficacy of antiviral therapies in reducing viral load (the quantity of virus in the bloodstream) and altering the course of viremic infections like HIV and Hepatitis C [288, 289]. Early initiation of antiviral treatment is often associated with better clinical outcomes and reduced transmission rates. In COVID-19 patients, early administration of antivirals such as nirmatrelvir/ritonavir (Paxlovid) significantly shortens the duration of viral shedding and mitigates symptom severity, especially in high-risk groups. A recent study by Colaneri et al. [290]. found that patients treated within five days of symptom onset had a significantly reduced viral clearance time compared to untreated individuals. In hepatitis B virus (HBV) infection, nucleoside analogues effectively suppress HBV DNA levels, which correlates with improved liver functions and delayed disease progression. Ma et al. [291]. observed that antiviral therapy led to a consistent decline in HBV DNA within four weeks, continuing up to 48 weeks, particularly in patients with high baseline viral loads. Similarly, in hepatitis C virus (HCV) infection, direct-acting antivirals (DAAs) have revolutionized treatment by achieving sustained virologic response (SVR) in over 95% of cases. Shailja et al. [292]. reported complete viral clearance at 12 weeks post-treatment, maintained at one-year follow-up (Fig. 5), regardless of liver disease stage. In the context of HIV, addressing viral co-infections such as cytomegalovirus (CMV) has therapeutic relevance. Weibel et al. [293]. demonstrated that letermovir, an anti-CMV drug, reduced systemic inflammation and improved immune markers in individuals with HIV on stable antiretroviral therapy. These findings underscore the importance of targeted antiviral strategies in managing viral load and improving long-term clinical outcomes across diverse viral infections.

Fungal bloodstream infections (fungemia) with special emphasis on predominance of *Candida* species

Fungemia, or fungal bloodstream infection, is a critical medical condition where fungi, especially *Candida* species, invade the bloodstream. It commonly affects individuals with weakened immune systems, those undergoing invasive medical procedures, or patients with indwelling medical devices like central venous catheters. This infection can lead to severe complications, including sepsis and multi-organ failure, if not identified and treated promptly. Due to increasing antifungal resistance and the rise of non-*albicans Candida* species, there is growing concern about treatment challenges and the need for improved therapeutic strategies.

Recent surveillance data show a marked shift in the epidemiology of candidemia, with non-*albicans Candida* (NAC) species increasingly dominating bloodstream infections (Fig. 6). While *Candida albicans* remains common, multiple studies report that species such as *C. parapsilosis*, *C. tropicalis*, and *C. glabrata* are becoming more prevalent in clinical settings. A nine-year study across hospitals in Western China found *C. tropicalis* accounted for 37.4% of

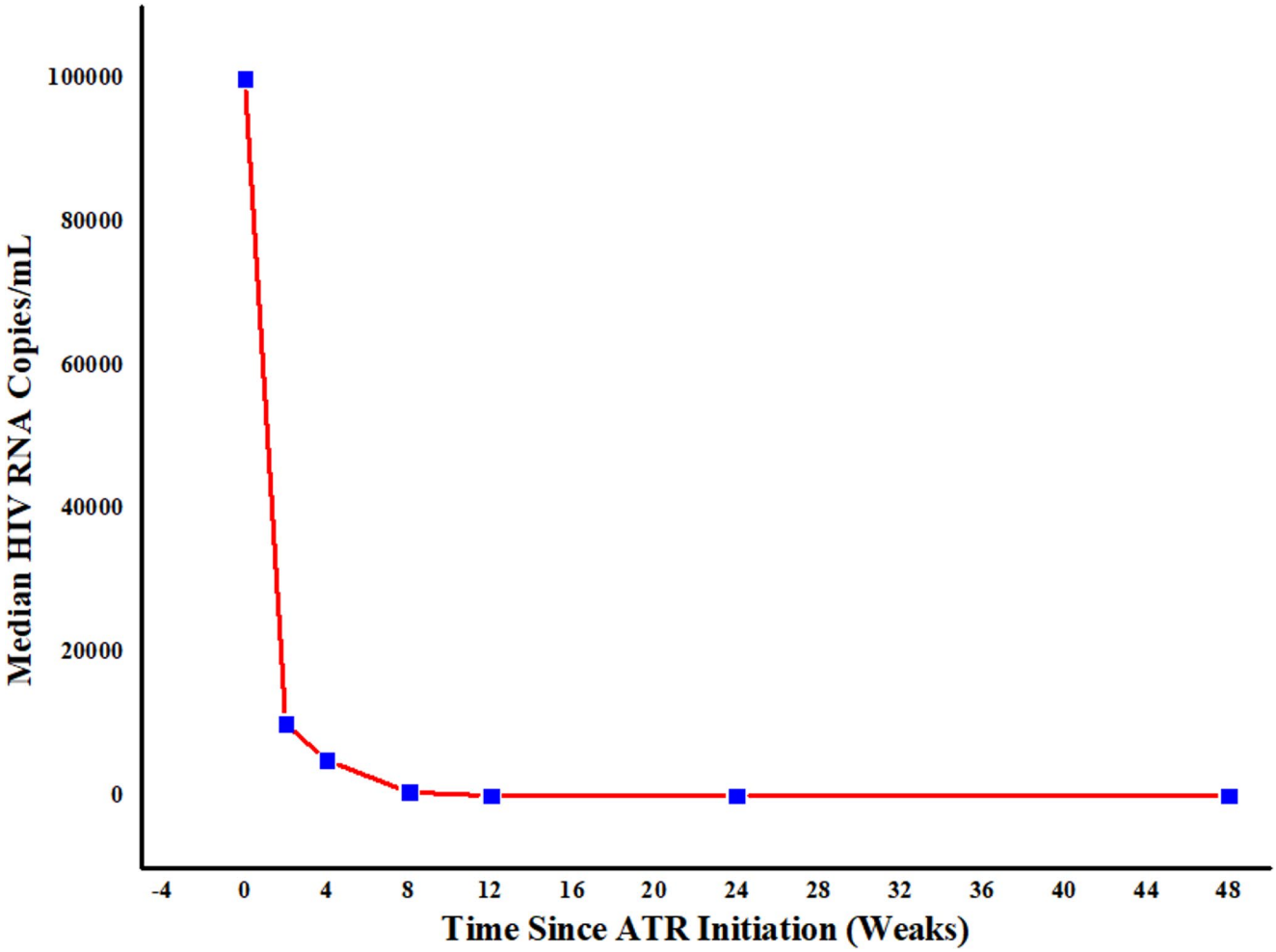

Fig. 5 A line graph showing the typical decrease in viral load (e.g., HIV RNA copies/mL) over time in a patient undergoing effective antiviral therapy. Data synthesized from global surveillance studies and peer-reviewed sources [292–294]

isolates, surpassing *C. albicans* (32.4%) [295]. Similarly, a retrospective analysis in a Chinese tertiary hospital showed *C. albicans* remained the leading cause (46.3%), but NAC species collectively constituted over 50% of cases [296]. Notably, *C. parapsilosis* has emerged as the dominant species in some regions, accounting for 59.6% of bloodstream isolates in a 2020 Greek hospital cohort [297].

This shift carries clinical implications, as NAC species often exhibit differing antifungal susceptibility profiles. For instance, rising fluconazole resistance among *C. parapsilosis* isolates has been documented, with non-susceptibility rates escalating from 6.8% in 2015 to 62.7% by 2022 [297]. Moreover, the emergence of multidrug-resistant *Candida auris*—reported in 15.6% of candidemia cases in a 2023 Greek study—has heightened concerns over treatment options [299]. These trends underscore the importance of local epidemiological monitoring and species-specific antifungal stewardship to ensure effective patient management. Table 7 represents the estimated mortality trends associated with fungal bloodstream infections (BSIs) over in the recent years along with fungal pathogens, pathogenesis, geographical distribution, and clinical implications.

Data represented in Fig. 6 is derived from the multicenter surveillance study by Tan et al., which included 25 hospitals and a total of 1,910 non-duplicate bloodstream *Candida* isolates, demonstrate that a limited number of species account for the vast majority of candidemia cases. *Candida albicans* was the predominant species overall, representing 41.3% of isolates, followed by *C. tropicalis* (25.4%), *C. glabrata* (13.9%), and *C. parapsilosis* (12.1%). Collectively, these four species contributed to approximately 92.9% of all bloodstream infections caused by *Candida*. However, the dominance of *C. albicans* was not uniform across institutions; in 12 out of the 25 hospitals, its proportion remained below 40%, with substantial inter-hospital variability (median 41.9%, range 5.56–58.3%), indicating localized epidemiological differences rather than a consistent global pattern.

Geographical variation was particularly evident in the distribution of non-*albicans Candida* species. In tropical

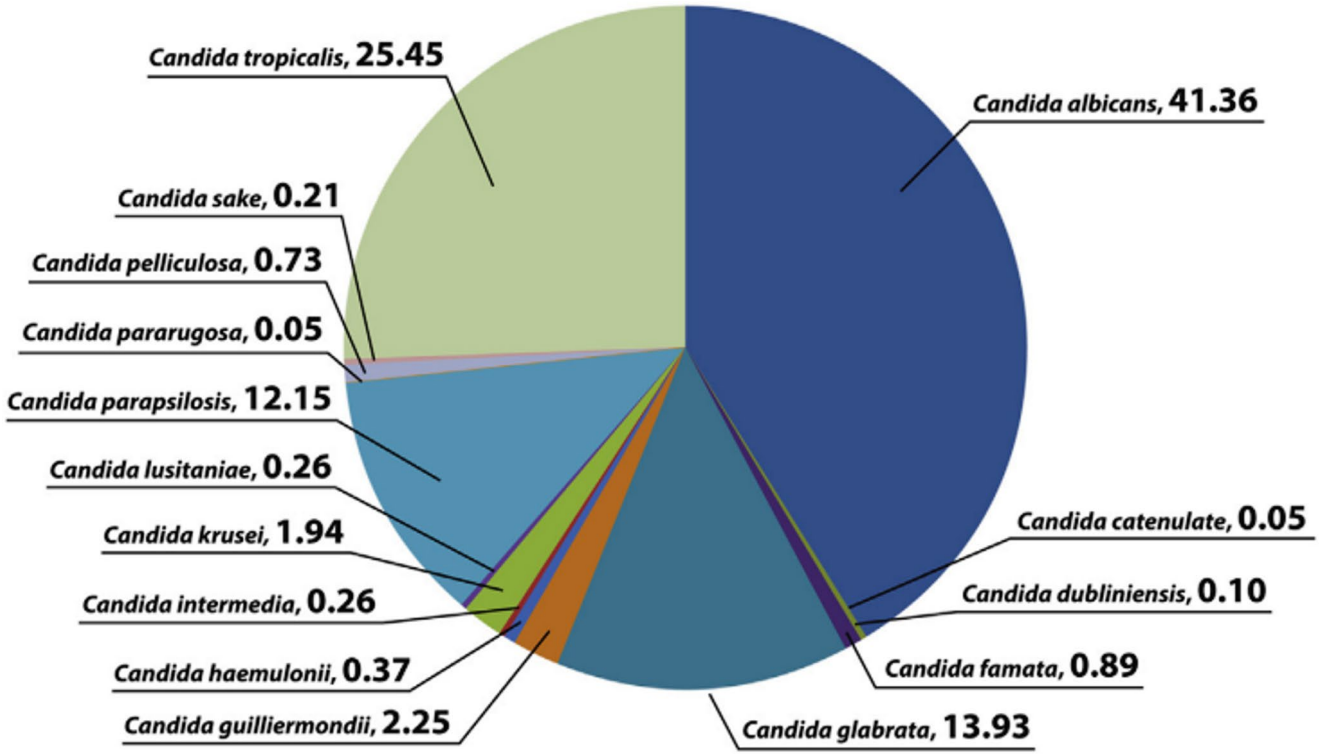

Fig. 6 A pie chart illustrating the distribution of different *Candida* species isolated from bloodstream infections based on pooled data from multiple studies (number denotes %). Each section in the pie diagram represents a different *Candida* species, and the size of the section corresponds to its proportion in fungemia cases [298]

regions such as India, Thailand, and Singapore, *C. tropicalis* constituted a significantly higher proportion of bloodstream isolates compared with non-tropical settings (46.2% vs. 18.9%), suggesting environmental and host-related factors influencing species prevalence. *C. glabrata* emerged as the leading non-*albicans* species in a subset of hospitals, particularly in China and Taiwan, where it accounted for up to 26% of candidemia cases in certain centers. Similarly, *C. parapsilosis* showed marked institutional predominance, contributing to approximately one-third of cases in one Indian hospital and substantial proportions in hospitals in China and Taiwan, reflecting its association with healthcare-related transmission and device use. Although *C. krusei* was infrequently isolated overall, it demonstrated localized epidemiological relevance, accounting for 12.2% of bloodstream isolates in a single center.

Association with indwelling medical devices and immunocompromised states

The rising prevalence of fungemia in clinical settings is strongly associated with the use of indwelling medical devices and the presence of immunocompromised conditions. Central venous catheters (CVCs), urinary catheters, and implanted medical devices act as ideal surfaces for fungal colonization and biofilm formation, particularly by *Candida* species such as *C. albicans* and *C. parapsilosis* [310]. These biofilms enhance microbial resistance to antifungal agents and protect pathogens from host immune responses, thereby contributing to persistent bloodstream infections. Immunocompromised individuals—such as those undergoing hematopoietic stem cell transplantation, chemotherapy, or immunosuppressive therapy—are particularly vulnerable due to impaired innate immunity [311].

Recent studies have emphasized the critical role of prompt catheter removal in managing catheter-associated candidemia, as antifungal lock therapy alone is often insufficient for complete eradication of biofilm-associated infections [311]. Preventive strategies are equally important, including the use of aseptic insertion techniques, minimizing the duration of catheterization, and developing biofilm-resistant materials like auranofin-coated catheters, which have shown efficacy in preventing fungal and bacterial colonization [312]. Additionally, proactive surveillance and prophylactic antifungal use in high-risk patients may reduce infection incidence. As fungemia continues to cause high morbidity and mortality, especially in compromised hosts, a multidisciplinary approach that combines device innovation, clinical vigilance, and targeted antifungal strategies remains essential.

Table 7 Estimated mortality trends associated with fungal BSIs over in the recent years along with fungal pathogens, pathogenesis, geographical distribution, and clinical implications. Data synthesized from global surveillance studies and peer-reviewed sources

Fungal Pathogen	Disease Name	Pathogenesis	Global Mortality Rate	Geographical Distribution	Clinical Implications	References
Candida albicans	Candidemia	Opportunistic infections; biofilm formation on medical devices.	Approximately 19–40%.	Worldwide.	Leading cause of invasive candidiasis; associated with use of catheters and broad-spectrum antibiotics.	[300]
Candida glabrata	Candidemia	Reduced susceptibility to azoles; often seen in patients with prior antifungal exposure.	Data not specified.	Worldwide.	Increasing prevalence in bloodstream infections; challenges in treatment due to antifungal resistance.	[301]
Candida auris	Candidemia	Emerging multidrug-resistant yeast; associated with healthcare outbreaks.	Approximately 30–60%.	Global, notably in the USA.	Difficult to identify with standard laboratory methods; high mortality and resistance rates necessitate stringent infection control measures.	[302]
Candida parapsilosis	Candidemia	Biofilm formation on catheters; common in neonatal intensive care units.	5–45%	Worldwide.	Significant cause of fungemia in critically ill patients; requires careful management of intravascular devices.	[301, 303]
Candida tropicalis	Candidemia	Noted for virulence in neutropenic patients; capable of biofilm formation.	63.6%	High prevalence in South Asia, Brazil, USA, Europe.	Common in hematological malignancies; necessitates prompt antifungal therapy.	[304]
Candida krusei	Candidemia	Intrinsically resistant to fluconazole; often seen in patients with prior azole exposure.	71.4–100%	Worldwide.	Limited treatment options; requires use of alternative antifungals like echinocandins.	[305]
Cryptococcus neoformans	Cryptococcosis	Inhalation of spores leading to pulmonary infection; can disseminate to CNS causing meningitis.	Approximately 12% in the USA.	Worldwide; prevalent in sub-Saharan Africa.	Major cause of meningitis in HIV/AIDS patients; requires prolonged antifungal treatment.	[306]
Aspergillus fumigatus	Aspergillosis	Inhalation of conidia leading to respiratory infections; can disseminate in immunocompromised hosts.	Up to 85% in invasive cases.	Worldwide; expanding due to climate change.	Causes invasive pulmonary aspergillosis; significant risk in neutropenic patients.	[141]
Histoplasma capsulatum	Histoplasmosis	Inhalation of spores from contaminated soil; primarily affects the lungs.	Around 53% in critically ill patients.	Americas, Africa, Asia; notably in the Mississippi and Ohio River valleys.	Can disseminate in immunocompromised individuals; requires antifungal therapy.	[149, 307]
Fusarium spp.	Fusariosis	Opportunistic infections; can cause disseminated disease in immunocompromised individuals.	High mortality in disseminated cases.	Worldwide.	Resistant to many antifungal agents; requires combination therapy and management of underlying conditions.	[308]
Trichosporon spp.	Trichosporonosis	Opportunistic pathogen; affects immunocompromised patients, especially with hematologic malignancies.	60–70%	Worldwide.	Causes invasive infections; resistant to echinocandins; requires alternative antifungal therapy.	[309]

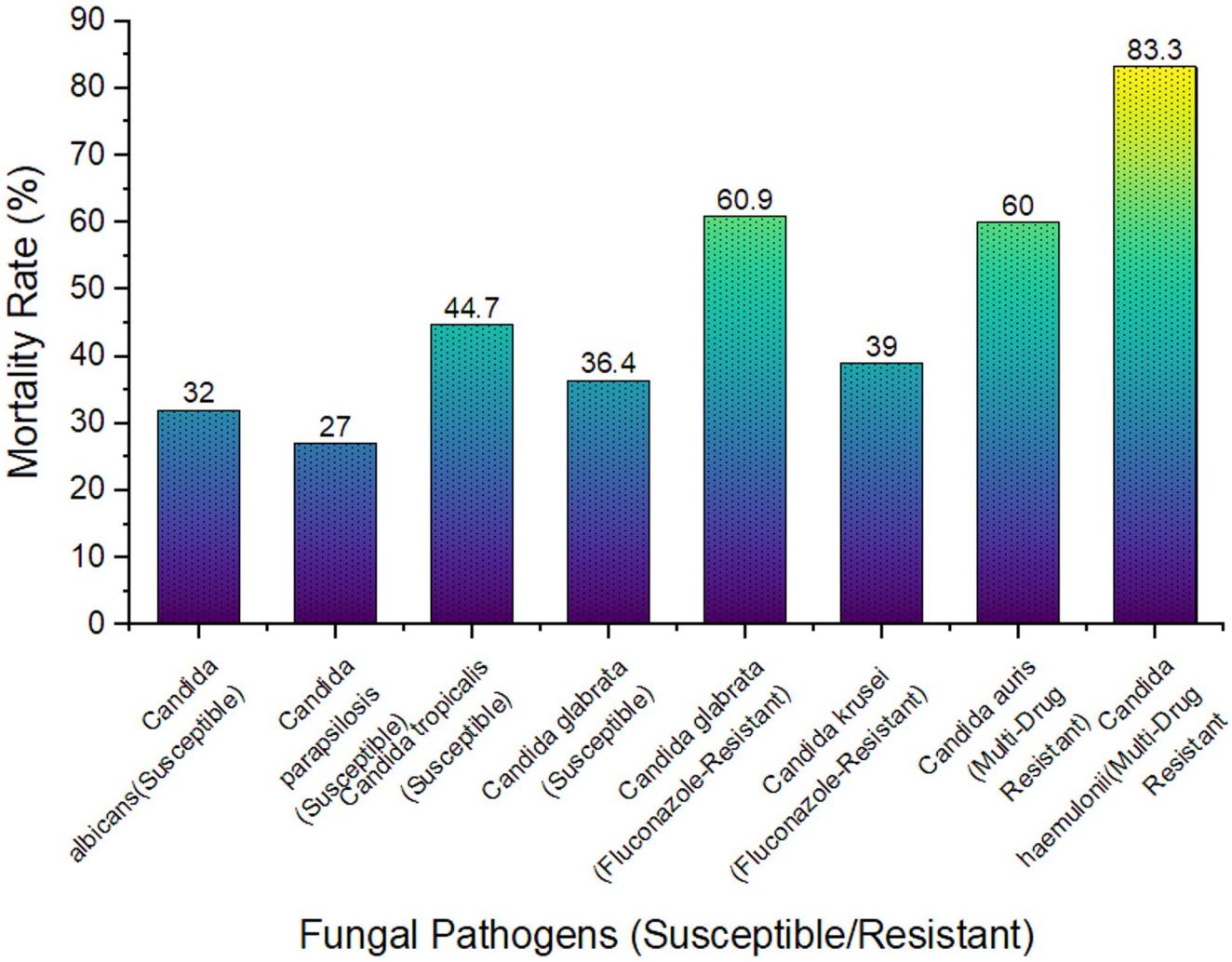

Fig. 7 A bar graph comparing the mortality rates of patients with bloodstream infections caused by susceptible versus antifungal-resistant *Candida* species [312, 316–323]

High mortality rates and challenges in treatment due to resistance in fungemia

Fungemia, particularly invasive candidiasis, remains a critical concern in healthcare due to its high mortality rates and growing antifungal resistance. Despite advancements in antifungal therapy and intensive care, mortality rates still range between 40% and 60%, particularly in critically ill and immunocompromised patients [313]. A major contributor to this challenge is the emergence of multidrug-resistant *Candida* species, especially *Candida auris*, which demonstrates resistance to azoles, polyenes, and echinocandins, complicating empirical therapy [314].

The epidemiology of candidemia has shifted from *C. albicans* to non-*albicans* species such as *C. glabrata*, *C. tropicalis*, and *C. parapsilosis*, which often exhibit reduced susceptibility to standard antifungals [315]. For example, recent surveillance data show that over 55% of *C. tropicalis* isolates in certain Asian regions are resistant to fluconazole, marking a worrying trend [316]. This shift in species distribution demands reevaluation of treatment guidelines and localized antifungal resistance mapping. Figure 7 showed a clear comparison in the mortality rates of patients with bloodstream infections caused by susceptible versus antifungal-resistant *Candida* species.

Delayed administration of effective antifungal agents, especially within the first 24 h of bloodstream infection onset, is associated with significantly higher mortality [317]. Compounding the issue, challenges in timely removal of indwelling devices and source control, particularly in ICU settings, further reduce treatment success. Resource-limited settings face additional burdens, including lack of rapid diagnostic tools, limited antifungal availability, and absence of stewardship protocols, exacerbating resistance trends [324]. Addressing fungemia requires integrated strategies involving prompt diagnosis, resistance surveillance,

stewardship programs, and development of new antifungal agents to curb mortality and improve global outcomes.

General observations across the microbial types

BSIs represent a critical health concern involving a wide array of pathogens, including bacteria, fungi, and viruses. Bacterial agents are the most prevalent and often lead to acute and severe clinical outcomes. Fungal pathogens, particularly *Candida* species, are increasingly recognized in immunocompromised and critically ill patients, with rising antifungal resistance complicating treatment. Although less common, viral BSIs—such as those caused by cytomegalovirus or Epstein-Barr virus—can lead to significant morbidity, especially in transplant recipients. A common challenge across these pathogen types is antimicrobial resistance, which contributes to increased mortality and healthcare burden, highlighting the need for early, accurate diagnostics and pathogen-specific interventions. Delayed diagnosis and pathogen-specific challenges often result in suboptimal outcomes. These trends underscore the urgent need for improved diagnostic tools, targeted therapies, and comprehensive surveillance in managing BSIs.

Importance of early diagnosis for improved outcomes

Early and accurate diagnosis of BSIs is crucial for improving patient outcomes and reducing mortality rates. Recent advancements in rapid diagnostic technologies have significantly decreased the time to identify pathogens and determine antimicrobial susceptibilities. For instance, a study by Bandy et al. [325]. demonstrated that implementing molecular rapid diagnostic tests led to a 1.8-fold faster optimization of therapy and a 67% reduction in 30-day in-hospital mortality among patients with vancomycin-resistant *Enterococcus* BSIs. Similarly, a systematic review by Peri et al. [326]. found that combining rapid diagnostic tests with antimicrobial stewardship programs notably reduced mortality and shortened hospital stays. Furthermore, integrating artificial intelligence with blood tests has shown promise in early sepsis detection, potentially enhancing risk stratification and timely intervention. These findings underscore the importance of adopting rapid diagnostic tools and interdisciplinary approaches to promptly identify BSIs, tailor antimicrobial therapy, and ultimately improve patient survival rates.

Impact of host factors on susceptibility and severity

Variety of hosts plays a pivotal role in determining both the susceptibility to and severity of bloodstream infections (BSIs). Age is a key determinant, with individuals over 55 years showing an increased risk of infection due to immune senescence and comorbidities. Chronic diseases such as liver and renal dysfunction further compromise host defenses, facilitating pathogen entry into the bloodstream. In critically ill patients, especially those admitted to intensive care units (ICUs) with COVID-19, prolonged mechanical ventilation, extended hospitalization, prior antibiotic exposure, and elevated inflammatory markers like C-reactive protein (CRP) have all been associated with a higher incidence of BSIs and poorer outcomes [327]. Additionally, recent studies have highlighted the influence of gut microbiota composition on infection risk. Disruptions in the microbial balance of the gut may impair mucosal barrier function, enabling microbial translocation and increasing the likelihood of bloodstream invasion. These insights emphasize the importance of evaluating host factors—such as age, preexisting conditions, and microbiome health—when assessing BSI risk. A patient-centered approach that accounts for these variables can lead to earlier interventions and more effective infection control.

The growing threat of antimicrobial resistance across all microbial types

Antimicrobial resistance (AMR) has become one of the principal determinants of adverse outcomes in BSIs, contributing to delayed effective therapy, prolonged hospitalization, increased healthcare costs, and excess mortality across bacterial, fungal, and viral pathogens [37, 328]. The burden of AMR is particularly pronounced among Gram-negative pathogens, where resistance is increasingly mediated by the combined effects of antibiotic-inactivating enzymes, reduced membrane permeability, active efflux systems, target modification, and biofilm-associated tolerance mechanisms [195, 329]. Resistant strains such as carbapenem-resistant bacterial species emerged as significant contributors to hospital-acquired BSIs, often resulting in limited treatment options and increased mortality [51]. In Europe, vancomycin-resistant *Enterococcus faecium* has shown fluctuating but persistently high incidence rates, with associated bloodstream infections posing major treatment challenges [330]. While resistance in viral pathogens is less frequently reported in BSIs, antiviral-resistant strains in immunocompromised individuals, such as ganciclovir-resistant cytomegalovirus, pose a growing concern. These patterns underscore the need for global surveillance, stringent antimicrobial stewardship, and urgent investment in novel antimicrobial agents and diagnostics to mitigate the growing burden of AMR in BSIs.

Among Enterobacterales, carbapenem resistance represents one of the most serious therapeutic challenges because carbapenems are frequently used as last-line agents for

severe sepsis and bacteremia [195]. Carbapenem resistance is primarily mediated by carbapenemases belonging to Ambler classes A, B, and D. Class A enzymes include Klebsiella pneumoniae carbapenemases (KPCs), class B enzymes include metallo-β-lactamases such as New Delhi metallo-β-lactamase (NDM), Verona integron-encoded metallo-β-lactamase (VIM), and imipenemase (IMP), whereas class D enzymes are represented mainly by OXA-48-like carbapenemases [330]. However, carbapenemase production alone often does not explain high-level resistance. Loss or alteration of outer membrane porins, particularly OmpK35 and OmpK36 in Klebsiella pneumoniae, reduces antibiotic penetration into the bacterial cell, while overexpression of multidrug efflux systems such as AcrAB-TolC further decreases intracellular antimicrobial concentrations [320, 329, 331]. The coexistence of carbapenemases, porin deficiency, and efflux-pump activation frequently generates extensively drug-resistant phenotypes associated with therapeutic failure and increased mortality [328].

The epidemiology of carbapenem-resistant Enterobacterales (CRE) demonstrates substantial geographical variation. KPC-producing strains predominate in North America and several European countries, whereas NDM-producing Enterobacterales are highly prevalent across South Asia and have disseminated globally through international travel and healthcare-associated transmission [328, 332]. According to recent EARS-Net surveillance data, carbapenem-resistant Klebsiella pneumoniae bloodstream infections continue to pose a major public-health challenge in southern and eastern Europe despite improvements in antimicrobial stewardship programs [333]. In contrast, the Indian subcontinent remains a major reservoir of NDM-producing Enterobacterales, contributing significantly to the global spread of carbapenem resistance [36].

The clinical consequences of resistance are reflected in current treatment recommendations. Recent IDSA guidance recommends ceftazidime-avibactam, meropenem-vaborbactam, or imipenem-cilastatin-relebactam as preferred therapies for bloodstream infections caused by KPC-producing Enterobacterales because these agents have demonstrated superior clinical outcomes compared with polymyxin-based regimens [328]. However, treatment of NDM-producing isolates remains considerably more difficult because currently available β-lactamase inhibitors do not inhibit metallo-β-lactamases. Consequently, ceftazidime-avibactam plus aztreonam or cefiderocol-based therapy is frequently required.

Among non-fermenting Gram-negative pathogens, carbapenem-resistant Acinetobacter baumannii (CRAB) has emerged as one of the most lethal causes of healthcare-associated bloodstream infection. Resistance in CRAB is mediated by OXA-type carbapenemases, permeability defects, AdeABC-family efflux pumps, biofilm formation, and stress-response mechanisms that facilitate long-term persistence in hospital environments [327, 334]. Clinical studies consistently report 30-day mortality rates exceeding 40–50% in patients with CRAB bacteremia, particularly among critically ill individuals with septic shock [327, 335]. Because of limited therapeutic options, recent IDSA guidance recommends sulbactam-containing combination regimens whenever susceptibility data and drug availability permit.

Resistance among Gram-positive bloodstream pathogens remains equally concerning. Vancomycin-resistant Enterococcus faecium (VREfm) has become a major cause of healthcare-associated bacteremia worldwide. Resistance is primarily mediated by acquisition of the vanA or vanB operons, which replace the D-Ala-D-Ala terminus of peptidoglycan precursors with D-Ala-D-Lac, reducing vancomycin binding affinity by approximately 1000-fold [336]. European surveillance studies have demonstrated increasing incidence of VRE bloodstream infections during the last decade, accompanied by shifts in dominant vanA- and vanB-containing lineages [336, 337]. These developments are clinically significant because treatment options are largely restricted to linezolid and high-dose daptomycin-based regimens, while emerging daptomycin resistance increasingly threatens therapeutic success.

Fungal antimicrobial resistance has also become a major concern because of the emergence of multidrug-resistant Candida auris. Fluconazole resistance in C. auris is commonly associated with mutations in ERG11 and overexpression of ATP-binding cassette transporters, whereas echinocandin resistance is linked to mutations in hotspot regions of the FKS1 gene [338, 339]. These mechanisms significantly reduce susceptibility to first-line antifungal agents and complicate the management of candidemia and invasive fungal BSIs [338]. Furthermore, the ability of C. auris to persist on environmental surfaces and spread within healthcare facilities has facilitated numerous hospital outbreaks worldwide.

Although less common than antibacterial resistance, antiviral resistance is increasingly recognized in immunocompromised patients with viral bloodstream infections. Cytomegalovirus (CMV) provides a notable example. Resistance to ganciclovir most frequently arises through mutations in the UL97 kinase gene, which impair intracellular drug activation, whereas mutations in the UL54 DNA polymerase gene may confer cross-resistance to ganciclovir, cidofovir, and foscarnet [278]. These resistant variants are encountered primarily in hematopoietic stem-cell and solid-organ transplant recipients and are associated with persistent viremia, prolonged hospitalization, graft dysfunction, and adverse clinical outcomes.

Current EUCAST and IDSA recommendations increasingly emphasize rapid molecular diagnostics, resistance-gene detection, and mechanism-guided therapy rather than prolonged empirical broad-spectrum antimicrobial use [328, 340]. The integration of whole-genome sequencing, metagenomic diagnostics, and resistance-marker surveillance into routine clinical practice is expected to improve early identification of resistant pathogens and facilitate precision antimicrobial therapy. Future reductions in BSI-associated mortality will therefore depend not only on the development of novel antimicrobial agents but also on the implementation of coordinated antimicrobial stewardship, genomic surveillance, and individualized treatment strategies [328, 329].

Despite the challenges, treatment outcomes for bloodstream infections have improved due to better antimicrobial and antiviral drugs, enhanced supportive care, and stronger infection control practices. Collaboration among healthcare providers specializing in infectious diseases, microbiology, and critical care helps optimize patient management. Programs promoting responsible use of antibiotics also help slow the development of resistance. However, continuous vigilance and innovation are necessary to address the evolving threat of resistant pathogens and to manage infections in increasingly complex patient populations.

Future aspects of diagnostic and treatment strategies for BSIs

Rapid diagnostics and targeted therapeutics are revolutionizing the management of bloodstream infections—such as fungemia, parasitemia, viremia, and bacteremia—with increasing precision and speed. Automated blood-culture systems coupled with advanced molecular platforms like dd-PCR, FilmArray, and GeneXpert can now deliver pathogen and resistance profiling within 3–4 h, enabling clinicians to tailor treatments more rapidly [341]. Moreover, metagenomic next-generation sequencing (mNGS) is emerging as a powerful tool for identifying elusive or mixed infections—especially in immunocompromised patients with negative culture results. On the therapeutic front, precision dosing guided by therapeutic drug monitoring (TDM) is becoming standard in intensive care settings to ensure optimal antibiotic and antifungal exposure, thereby improving outcomes and reducing the risk of resistance [341]. Complementing these advances, deep learning applied to digital imaging of Gram-stained smears has shown promising accuracy—up to 96%—in rapidly identifying bacterial and fungal pathogens directly from blood, which can enable immediate, data-driven treatment decisions [342].

Recent advances in bloodstream infection diagnostics are driven by parallel development of multiplex PCR platforms and metagenomic next-generation sequencing (mNGS), but current evidence shows that these technologies occupy fundamentally different positions in the diagnostic workflow rather than functioning as direct substitutes. Recent comparative clinical studies (2024–2025) demonstrate that multiplex PCR systems remain superior in time-to-result efficiency and standardized clinical interpretation, with turnaround times typically within 1–4 h after a positive blood culture signal, making them highly suitable for acute sepsis management where early targeted therapy is critical [343]. Their diagnostic strength lies in the use of predefined panels that ensure reproducible detection of clinically common bloodstream pathogens, including major bacterial and fungal agents, which allows direct linkage to antimicrobial stewardship decisions in real time.

In contrast, recent clinical evaluations of mNGS confirm that it provides a significantly broader diagnostic spectrum by enabling culture-independent detection of bacteria, fungi, viruses, and parasites within a single assay, including fastidious and unexpected organisms that are frequently missed by conventional culture or targeted PCR methods [344]. A recent multicenter clinical study demonstrated that mNGS can increase pathogen detection rates in complex infections and guide antimicrobial adjustment in more than half of evaluated cases, particularly in polymicrobial and culture-negative bloodstream infections [345]. However, comparative evaluations of metagenomic and targeted sequencing platforms provide a more nuanced understanding of their diagnostic trade-offs. While mNGS provides the broadest pathogen coverage, detecting the highest number of species, its clinical utility is constrained by higher cost and longer turnaround time. In contrast, capture-based targeted NGS demonstrates superior overall diagnostic accuracy and very high sensitivity when evaluated against composite clinical diagnosis, making it more suitable for routine use. However, its relatively lower specificity for certain viral detections indicates a risk of overdiagnosis. Amplification-based targeted NGS offers advantages in speed and resource efficiency but shows reduced sensitivity, particularly for bacterial pathogens, which may limit its reliability as a standalone diagnostic tool. Notably, targeted sequencing platforms also enable concurrent identification of antimicrobial resistance genes and virulence factors, enhancing their clinical relevance. Overall, mNGS is best reserved for complex or atypical infections, whereas capture-based targeted NGS represents a more practical option for routine diagnostics, with amplification-based methods serving as alternatives in resource-limited or time-sensitive settings. The increased sensitivity is accompanied by important

limitations, including longer turnaround time (20 h), higher cost, and variability in diagnostic interpretation depending on sequencing depth and bioinformatic pipelines [346]. Therefore, current evidence supports mNGS as a second-line or problem-solving diagnostic tool, particularly valuable in immunocompromised patients or unexplained BSIs, rather than a first-line replacement for PCR-based systems.

A critical issue emerged from the recent research is that mNGS and multiplex PCR differ not only in technical design but also in clinical decision latency. While mNGS expands pathogen discovery space, multiplex PCR provides faster and more standardized actionable output, which is crucial because delays in effective therapy remain one of the strongest predictors of mortality in bloodstream infections. Recent 2025 comparative diagnostic frameworks emphasize that optimal clinical performance is achieved when PCR is used for rapid stabilization of empiric therapy, while mNGS is reserved for diagnostic escalation in unresolved or atypical infections rather than immediate emergency decision-making contexts [341].

Recent systematic analyses as well as diagnostic comparison studies consistently demonstrate that mNGS is significantly more expensive than multiplex PCR due to sequencing infrastructure, computational requirements, and bioinformatics interpretation needs, limiting its routine use in low- and middle-income countries where bloodstream infection burden is highest [346]. Even multiplex PCR, although less expensive than mNGS, still requires cartridge-based consumables and automated platforms, which restrict scalability in district-level hospitals. WHO surveillance reports continue to emphasize that such disparities create a global diagnostic imbalance, where advanced molecular diagnostics are concentrated in tertiary centers while the majority of patients still depend on blood culture systems with delayed turnaround and reduced sensitivity [342, 343, 347].

Artificial intelligence–based Gram-stain interpretation represents a third emerging layer of diagnostic acceleration, but recent evidence clarifies that reported high accuracies (often ~ 90–96%) are derived mainly from retrospective or internally validated datasets rather than real-world prospective clinical deployment. Recent clinical validation studies show that deep learning models perform well in controlled laboratory conditions for differentiating Gram-positive vs. Gram-negative organisms and for preliminary morphological classification; however, performance decreases when applied across heterogeneous hospital workflows due to variability in smear quality, staining protocols, and imaging systems [344].Therefore, AI-based Gram-stain interpretation should be interpreted as a decision-support augmentation tool rather than an autonomous diagnostic system, and its clinical utility depends on integration with microbiologist validation and molecular confirmation rather than standalone use [347, 348].

Evidences based on recent advancements indicate that the future of BSIs diagnostics will not be determined by a single dominant technology but by a tiered diagnostic architecture, in which multiplex PCR provides rapid frontline identification, mNGS serves as an expanded diagnostic escalation platform for unresolved infections, and AI-assisted microscopy functions as an early interpretive accelerator. The clinical challenge is therefore not technological capability alone, but optimizing integration across cost, turnaround time, interpretability, and healthcare system accessibility.

Conclusion

Bloodstream infections (BSIs) remain a major global health concern and are associated with significant morbidity, mortality, prolonged hospital stays, and increased healthcare costs. The development and severity of BSIs depend on multiple factors, such as pathogen virulence, host immune status, underlying medical conditions, healthcare exposure, and environmental influences. Their pathogenesis typically involves the evasion of host immune defenses, and initiation of systemic inflammatory responses that can progress to life-threatening sepsis. Therefore, effective management requires a comprehensive understanding of the interactions between pathogens, hosts, and their surrounding environment. The epidemiology of BSIs continues to evolve due to changes in healthcare practices, population demographics, and microbial adaptation. Although bacterial pathogens remain the leading cause of bloodstream infections worldwide, the growing recognition of fungal and viral bloodstream infections, as well as polymicrobial infections, has broadened the clinical spectrum of disease. In addition, considerable regional differences exist in pathogen prevalence, antimicrobial susceptibility patterns, and healthcare-associated risk factors. These variations highlight the importance of continuous surveillance and the development of region-specific prevention and treatment strategies.

One of the greatest challenges in the management of BSIs is the increasing prevalence of antimicrobial resistance (AMR). The emergence of multidrug-resistant and extensively drug-resistant organisms has reduced the effectiveness of many commonly used antimicrobial agents. Pathogens have developed various resistance mechanisms, including drug inactivation, target modification, reduced permeability, active efflux systems, and biofilm formation. As a result, treatment options are becoming increasingly limited, leading to poorer clinical outcomes and higher

healthcare burdens. Addressing AMR requires coordinated efforts involving antimicrobial stewardship, infection prevention measures, surveillance programs, and the development of new therapeutic agents.

Rapid and accurate diagnosis remains essential for improving patient outcomes. While blood culture remains the gold standard for diagnosing BSIs, its limitations, including delayed results and reduced sensitivity after antibiotic exposure, can hinder timely treatment. The diagnostic and treatment landscape is evolving toward rapid, precise, and patient-centered solutions. Advanced molecular methods, including multiplex PCR systems, targeted next-generation sequencing (tNGS), and metagenomic approaches, can provide same-day pathogen identification and resistance profiling. Artificial intelligence–driven image analysis of blood smears, along with predictive machine-learning models, shows strong potential for early recognition of BSIs before culture results are available. Coupled with precision dosing through therapeutic drug monitoring, these innovations can significantly improve clinical outcomes while reducing inappropriate antimicrobial use. However, widespread implementation faces challenges related to cost, accessibility, and integration into routine workflows, especially in resource-limited settings. BSIs continue to pose a significant and evolving challenge to global healthcare. Addressing these barriers—while continuing to advance point-of-care technologies, AI-enhanced diagnostics, and targeted therapeutics—will be essential. A multidisciplinary approach that unites rapid diagnostics, personalized treatment strategies, and robust antimicrobial stewardship offers the most promising path to reducing the global burden of bloodstream infections. Future progress will depend on advances in diagnostic technologies, improved understanding of host–pathogen interactions, effective antimicrobial stewardship, and strong surveillance systems. Continued research and international collaboration are essential to reduce the burden of bloodstream infections, improve patient outcomes, and combat the growing threat of antimicrobial resistance.

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Declarations

Ethical approval There are no ethical issues in this manuscript. This article is a review paper and does not involve studies or experiments on human or animals.

Consent to participate All authors whose names appear on the submission: 1) made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data; or the creation of new software used in the work; 2) drafted the work or revised it critically for important intellectual content; 3) approved the final version to be published; and 4) agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Consent to the journal All the authors affirm that the content of the manuscript is original, has not been published elsewhere, and is not currently under consideration by any other journal. Proper citations have been duly provided where applicable. A figure (figure 6) was taken from a recently published research paper with the permission of Journal's Editor-in-Chief and the publishing company. Proper citation was given in the diagram as well as in the reference section.

Competing interests The authors declare no competing interests.

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