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Mini Review

Device-Associated Fungal Bloodstream Infections and Central Nervous System Invasion: Mechanisms, Immunopathogenesis and Stewardship Strategies

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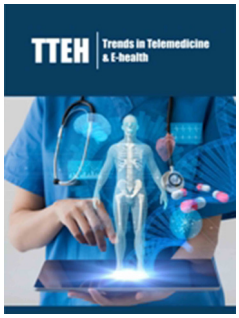
ISSN: 2689-2707



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Submission: March 20, 2026
Published: April 06, 2026

Volume 6 - Issue 4

How to cite this article: Gargee Anand and Rijhul Lahariya*. Device-Associated Fungal Bloodstream Infections and Central Nervous System Invasion: Mechanisms, Immunopathogenesis and Stewardship Strategies. 6(4). TTEH. 000643. 2026.
DOI: 10.31031/TTEH.2026.06.000643

Abstract

Healthcare-Associated Infections (HAIs), particularly device-associated infections, remain a major cause of morbidity and mortality in hospitalized patients. Among these, Central Line-Associated Blood-Stream Infections (CLABSIs) are well recognized; however, the contribution of fungal pathogens has gained increasing clinical importance. *Candida* species, including *Candida albicans, Candida parapsilosis* and the emerging multidrug-resistant *Candida auris*, are primary etiological agents capable of colonizing indwelling medical devices and forming resilient biofilms. These biofilms facilitate persistent bloodstream infections and enable hematogenous dissemination. In rare but severe cases, fungal pathogens can invade the Central Nervous System (CNS), resulting in meningoencephalitis. Mechanistically, CNS invasion occurs through multiple pathways, including direct endothelial invasion, paracellular traversal and the "Trojan horse" mechanism via infected phagocytes. Neurotropic fungi such as *Cryptococcus neoformans* demonstrate a high propensity for blood-brain barrier penetration, whereas device-associated fungi may access the CNS through colonized neurosurgical hardware such as ventricular drains and shunts. Host immune responses, including innate defenses and adaptive T-cell-mediated immunity, play a critical role in controlling infection but may also contribute to neuroinflammation. Clinical outcomes are often poor, with high mortality rates, particularly in immune-compromised individuals. Complications such as hydrocephalus and cerebral abscesses further worsen prognosis. Antifungal stewardship is therefore essential, emphasizing early diagnosis, targeted therapy and therapeutic drug monitoring. A comprehensive understanding of fungal pathogenesis, host-pathogen interactions and optimized stewardship strategies is crucial to improving outcomes in these life-threatening infections..

Keywords: Device-associated infections; Fungal bloodstream infections; *Candida* species; Meningoencephalitis; Antifungal stewardship

Introduction

Healthcare Associated Infections (HAIs) are defined as infections acquired during medical care that were neither present nor incubating at the time of admission, and they are linked to increased morbidity, mortality, prolonged hospitalization and higher healthcare costs [1]. Device-associated infections significantly contribute to ICU morbidity, with hundreds of cases reported in large cohorts of patients with invasive devices [2,3]. Central Line-Associated Blood-Stream Infections (CLABSIs) are among the most significant HAIs globally and are strongly associated with adverse outcomes in hospitalized patients [4,5]. While bacterial pathogens remain the predominant cause of device-related bloodstream infections, fungal pathogens, particularly *Candida* spp., have gained increasing clinical importance, accounting

for approximately 20% of bloodstream infections in ICU patients and strongly associated with invasive devices such as central venous catheters [6,7]. Fungal pathogens, particularly Candida spp., are recognized causes of BSIs associated with intravascular devices, with rising incidence in hospital settings [8-10]. Fungal BSIs frequently involve *Candida* species, which can colonize indwelling devices such as central venous catheters, ventricular assist devices and Cerebro-Spinal Fluid (CSF) shunts [11]. These infections can disseminate hematogenously, occasionally crossing the Blood Brain Barrier (BBB) to cause severe meningoencephalitis [12]. Neurotropic fungi such as *Cryptococcus neoformans* classically invade via the bloodstream, whereas device associated fungi such as *Candida* spp. may use colonized CSF shunts or drains as conduits for CNS entry [6,13]. The clinical consequences are profound: Delayed diagnosis, therapeutic complexity and high morbidity and mortality, particularly in immunocompromised hosts [1]. Fungal neuroinfections, although relatively rare, are life-threatening, with cryptococcal meningitis alone causing ~220,000 cases and 180,000 deaths annually worldwide, highlighting the need for rapid diagnosis and targeted antifungal therapy [14-16].

Recent increases in device utilization have expanded opportunities for fungal biofilm-mediated infections, with *Candida* spp. responsible for ~5.4-16% of catheter-related bloodstream infections, where biofilm formation on devices facilitates immune evasion, persistent fungemia and dissemination to deep organs including the CNS [17-19]. The ability of fungi to adhere to foreign surfaces, form resilient biofilms and resist antifungal agents compounds the risk of invasive disease progression and complicates management [1]. This narrative review aims to synthesize current knowledge on mechanisms of fungal dissemination in device associated settings, the profile of organisms implicated, host immune responses, clinical prognosis and the critical role of antimicrobial stewardship in optimizing outcomes.

Mechanism of BSI Causing Meningoencephalitis

Device colonization and biofilm formation

The initiation of a device associated fungal infection typically involves colonization of abiotic surfaces by fungal cells [20]. Species such as *Candida albicans, Candida parapsilosis* and the emerging multidrug resistant *Candida auris* exhibit strong adhesive properties and the capacity to form structured biofilms on device surfaces [20,21]. Biofilms protect fungi from host immune defenses and enhance tolerance to antifungal agents, creating a persistent reservoir for bloodstream seeding [22]. Species such as *Candida albicans, Candida parapsilosis* and the emerging multidrug-resistant *Candida auris* exhibit substantial biofilm-forming capacity, with reported rates of approximately 30-50% in C. *albicans*, 66-82% in C. parapsilosis, and up to 60-90% in C. auris isolates, of which nearly 25-30% are strong biofilm producers [23,24]. In addition, non-*albicans Candida* species collectively demonstrate biofilm formation in up to 80-90% of clinical isolates, reflecting their increasing role in device-associated infections [21]. Other opportunistic fungi, including *Aspergillus* spp., also form structurally complex biofilms in a majority of isolates, further contributing to device colonization [25]. These biofilms provide a protective extracellular matrix that limits antifungal penetration and shields fungal cells from host immune responses, leading to significantly increased antifungal tolerance and persistent infection. Consequently, indwelling medical devices act as reservoirs for sustained fungal shedding into the bloodstream, promoting candidemia and other invasive fungal infections. Once fungi gain access to the bloodstream, they may disseminate hematogenously. Although rare, this systemic spread can lead to seeding of the CNS, especially in immunocompromised individuals or patients with breaches in meninges or neurosurgical hardware [20,26].

Hematogenous dissemination and blood-brain barrier penetration

Once established in the bloodstream, fungal pathogens such as *Candida* and *Cryptococcus* species can disseminate systemically [27]. Mechanisms of dissemination include direct invasion of endothelial barriers, survival within phagocytes (the "Trojan horse" model), and paracellular traversal of endothelial tight junctions [12]. Cryptococcal species are particularly adept at crossing the blood brain barrier, often within macrophages, leading to meningitis or meningoencephalitis [12]. Postbiotics, particularly short-chain fatty acids derived from gut microbiota, modulate the gut-brain axis by regulating systemic immune responses and neuroinflammatory pathways, which may influence host susceptibility and inflammatory response to hematogenous fungal dissemination in device-associated BSIs [28,29].

Device associated CNS infections

Indwelling CNS devices such as External Ventricular Drains (EVDs), Ventriculo-Peritoneal (VP) shunts and Ommaya reservoirs provide direct access to the CNS and can be focal points for fungal colonization and infection [6]. Infections may begin at the device interface and then propagate along catheter tracks into CSF spaces, leading to meningeal inflammation and brain parenchymal involvement [6]. Case reports highlight the rare but clinically significant role of fungi in device-associated CNS infections, with *Candida parapsilosis* identified as a cause of VP shunt and EVD infections, including recent reports emphasizing its occurrence in neurosurgical patients despite its rarity, while emerging data on *Candida auris* document multidrug-resistant meningitis secondary to infected shunt systems, with only a limited number of cases reported globally, underscoring its evolving neuroinvasive potential [30-33]. Table 1 depicts various fungal BSI causing organisms leading to CNS infections.

Table 1: Key pathogens in device-associated fungal BSIs with CNS involvement.

Organism	Device Association	Neuroinvasive Potential	Evidence
Candida albicans	CVC, shunts	Moderate	Well, described in CNS candidiasis, especially post neurosurgery (36)
Candida parapsilosis	CVC, Shunts, EVD	Moderate	Reported in device associated CNS infections (6)
Candida auris	CVC	Emerging	Increasing BSI cases; rare but documented CNS involvement (37)
Cryptococcus neoformans	Hematogenous	High	Classical neurotropic fungal pathogen (13)
Aspergillus spp.	Rare	Variable	Documented in hematogenous CNS invasion (11)

Action of the Immune System in Fungal Device BSI and CNS Infection

Innate immune defenses

The innate immune system represents the first line of defense against fungal invasion [34]. Neutrophils, macrophages, and dendritic cells recognize fungal pathogen associated molecular patterns via pattern recognition receptors such as Toll like receptors and C type lectin receptors [35]. Neutrophils can phagocytose yeast cells and release reactive oxygen species and neutrophil extracellular traps to limit fungal spread [27]. Trained immunity, a form of innate immune memory mediated through epigenetic and metabolic reprogramming of monocytes and macrophages, enhances antifungal host responses following prior exposure to fungal components such as β-glucan [36-38]. However, in device associated infections, biofilms can shield fungal cells from phagocytosis, enabling persistent bloodstream infection [22].

Adaptive immune responses

CD4+ T cells and Th1 responses are critical for controlling systemic fungal infections. Interferon γ and other pro inflammatory cytokines enhance macrophage fungicidal activity [39,40]. Clinical and translational studies demonstrate that restoration of $CD4^+$ T cell responses reduce fungal burden, but paradoxically, approximately 10-30% of patients with cryptococcal meningitis develop Immune Reconstitution Inflammatory Syndrome (IRIS) following immune recovery, reflecting excessive Th1-driven inflammation [41]. Meta-analytic data further indicate that cryptococcal IRIS carries a mortality of ~20.8%, compared to ~4.5% across all IRIS forms, underscoring its severity [42]. Mechanistically, Th1 polarization with interferon-γ production promotes macrophage fungicidal activity but also drives recruitment of inflammatory myeloid cells and cytokine-mediated tissue injury within the central nervous system [43]. In CNS fungal disease, immune responses can be a double-edged sword: While necessary for pathogen clearance, they can contribute to inflammation of the meninges and cerebral tissue, exacerbating clinical severity [44].

Immunocompromised hosts

Patients with neutropenia, HIV/AIDS, immunosuppressive therapies, or critical illness have impaired innate and adaptive responses [45,46]. Cohort data indicate that in HIV-associated cryptococcal disease, median CD4 counts are often <50 cells/mm^3, reflecting profound immunosuppression, while mortality remains high at ~30% despite treatment [47]. This immunosuppression facilitates fungal BSI establishment, persistence, and dissemination to deep organs including the CNS [48]. Mechanistically, fungal pathogens exploit impaired immune surveillance to cross the blood–brain barrier via transcellular migration, paracellular entry, or "Trojan horse" transport within infected phagocytes [49]. Consequently, these vulnerabilities enable the development of meningoencephalitis, particularly in patients with severe immune deficits or disrupted host barriers [50].

Prognosis

Clinical outcomes

Fungal BSIs carry high mortality, particularly when associated with invasive devices and underlying critical illness. *Candida* BSI alone has been associated with mortality rates ranging from 30-60%, a figure that increases dramatically with CNS involvement or delayed treatment [9]. Device associated fungal infection of Ventricular Assist Devices (VADs) also carries significant mortality and morbidity, and the presence of *Candida* species can lead to endocarditis and reduced long term survival in VAD recipients [51]. Hence early detection and prompt initiation of appropriate therapy in bloodstream infections are critical to limit hematogenous dissemination and reduce the risk of metastatic complications, including central nervous system involvement [52,53].

Complications

Complications of fungal meningoencephalitis are common and clinically significant, with studies reporting hydrocephalus in approximately 9-63% of patients with cryptococcal meningitis, reflecting one of the most frequent and life-threatening sequelae requiring cerebrospinal fluid diversion [54-57]. In cohort analyses of CNS cryptococcosis, cerebral abscesses (cryptococcomas) occur in ~12% of cases, while hydrocephalus and raised intracranial pressure remain dominant contributors to morbidity [58]. Long-term outcomes are also substantial, with systematic review data showing that neurological impairment persists in 19-70% of survivors, highlighting the burden of chronic deficits [59]. These conditions often require prolonged antifungal therapy and sometimes surgical intervention such as device removal or debridement [56,60].

Importance of antimicrobial stewardship

Antimicrobial Stewardship Programs (ASP) have traditionally focused on bacterial pathogens; however, the rise of invasive fungal infections underscores the need for robust antifungal stewardship [61]. Appropriate antifungal stewardship involves optimizing diagnosis, prescribing targeted antifungal agents, minimizing inappropriate use, and monitoring therapeutic drug levels to avoid toxicity [62].

Benefits of stewardship

i. Improved diagnosis: Utilization of biomarkers (e.g., βD glucan), molecular diagnostics, and rapid species identification to confirm fungal infection and species susceptibility [63].

ii. Rational use of antifungals: Tailoring therapy based on susceptibility patterns to avoid unnecessary broad-spectrum antifungals that drive resistance [62].

iii. Therapeutic drug monitoring: Ensuring appropriate serum drug levels for agents like amphotericin B or triazoles to maximize efficacy while minimizing toxicity [64].

iv. Outcome improvement: Stewardship interventions have been shown to increase appropriate antifungal use and reduce inappropriate prescriptions, a key component in invasive infection management [65]. Importantly, timely and targeted therapy may limit hematogenous dissemination and reduce secondary complications, including central nervous system involvement. Emerging evidence suggests that preservation of blood-brain barrier integrity and Neuro-Vascular Unit (NVU) function is a critical determinant of CNS susceptibility, further underscoring the importance of early, optimized intervention.

Conclusion

Device-associated fungal bloodstream infections represent a complex interplay between pathogen virulence, device-related biofilm biology, and host immune status. This review highlights that *Candida* species, particularly C. *albicans*, C. parapsilosis and the emerging C. auris, along with other opportunistic fungi, possess strong biofilm-forming capacity that facilitates persistence on indwelling devices and sustained bloodstream seeding. Hematogenous dissemination, aided by mechanisms such as endothelial invasion and "Trojan horse" transport, enables these pathogens to breach the blood-brain barrier and establish meningoencephalitis, particularly in immunocompromised hosts. While innate and adaptive immune responses are essential for fungal clearance, dysregulated inflammation, such as IRIS, can exacerbate CNS injury, underscoring the dual role of host immunity. Clinically, these infections are associated with high mortality, frequent complications including hydrocephalus and long-term neurological deficits, and often require prolonged antifungal therapy alongside surgical interventions. Importantly, this review underscores the growing clinical significance of fungal pathogens in device-associated infections and the need for integrated antifungal stewardship strategies to enable early diagnosis, targeted therapy and improved outcomes. As device use and high-risk patient populations continue to expand, addressing these infections will require coordinated advances in diagnostics, therapeutics and infection control practices.

Statements and Declarations

Competing interests

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Funding

No funding was received.

Authors contribution

Rijhul Lahariya and Gargee Anand contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Gargee Anand and Rijhul Lahariya. The first draft of the manuscript was written by Rijhul Lahariya and Gargee Anand. Rijhul Lahariya and Gargee Anand both contributed equally to the work*. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Acknowledgement

None

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