Candida Bloodstream Infections: Changes in Epidemiology and Increase in Drug Resistance

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ABSTRACT: The literature on bloodstream infections (BSIs) have predominantly been biased towards bacteria, given their superior clinical significance in comparison with the other types of microorganisms. Fungal pathogens have epidemiologically received relatively less attention, although they constitute an important proportion of BSI aetiologies. In this review, the authors discuss the clinical relevance of fungal BSIs in the context of *Candida* species, as well as treatment options for the infections, emphasizing the compelling need to develop newer antifungals and strengthen antimicrobial stewardship programmes in the wake of the rapid spread of antifungal resistance.

KEYWORDS: Bloodstream infections, fungal pathogens, *Candida* species, antifungal resistance

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Introduction

Bloodstream infections (BSIs) refer to the occurrence of microorganisms – viruses, parasites, bacteria and fungi – in the otherwise sterile blood.[1,2] These microorganisms could be present in an inexhaustive variety of combinations, giving rise to descriptions of BSIs as monomicrobial (involving one microbial aetiology) or polymicrobial (involving a mixture of microbial aetiologies), among many others. BSIs, as a composite, pose a threat to public health globally. Data emanating from an amalgam of North American and European countries suggest BSIs as part of the seven topmost causes of death, with an annual occurrence of more than two million episodes, coupled with 250 000 deaths and a 13% to 20% case-fatality rate.[3]

The literature on BSIs have primarily focused on bacteria, as they constitute the predominant aetiologies in comparison to the other types of microorganisms.[4] Fungal pathogens, despite constituting an important proportion of BSI aetiologies, have epidemiologically received relatively less attention, probably owing to difficulties in their detection in clinical specimens.[5-7] Even so, mortality rates of up to 71%[8-10] and healthcare costs of about 563 million Australian dollars[11] have been reported in connection with some of the BSIs they cause.

In this review, the authors discuss fungal BSIs caused by *Candida* species, demonstrating their clinical relevance, possible epidemiological shifts in their aetiologies, as well as their treatment options, highlighting the urgency with which newer antifungals are needed in light of rapidly spreading drug-resistant candidaemic pathogens, particularly, the clinically-significant, multidrug-resistant non-*albicans Candida* species – *Candida auris*.

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Clinical Significance of, and Possible Aetiological Shift in, Candida BSIs

Candida-caused BSIs account for more than 90% of fungal BSIs.[12] They have been ranked fourth in the United States of America and seventh in Europe among BSIs recorded in these regions, as well as third among late-onset sepsis aetiologies in neonates.[13-15] Among patients on hospital admission especially, organisms of the *Candida* genus are the most frequently isolated fungal BSI pathogens.[16] Studies conducted in hospital settings have reported the incidence of *Candida* BSIs per 1000 admissions to range between 0.3 and 5 globally.[17] It is important to note that *Candida* BSIs could also serve as prequels to invasive, deep-seated infections of the eyes, heart valves, spleen, liver and other organs of the body.[18] Invasive forms of *Candida* BSIs have been associated with significant costs (about $160 000 per patient) and healthcare use.[19,20] They are also associated with high mortalities, which reportedly range between 35% and 71%,[8,21-25] and could be exacerbated when empirical antifungal therapy is delayed.[26-28]

Individuals at risk of developing candidaemia include burns patients,[29] immunocompromised persons with comorbidities like malignancies and haematological aberrations,[30,31] persons in whom central venous catheters have been placed,[32] and those in intensive care.[31,33-35] Furthermore, factors such as colonization with *Candida* species, glucocorticoid use, haemodialysis, total parenteral nutrition, broad-spectrum antimicrobial use, being a preterm infant, being a neonate with low birth weight, solid organ transplantation, presence of acute necrotizing pancreatitis and having abdominal surgery have also been reported to predispose to invasive forms of *Candida* BSIs.[36-38]

Candida albicans has for long been the most clinically-significant BSI aetiology of the *Candida* genus.[8,23,39-42] For instance, according to hospital-based data collected by Pfaller et al[43] from January 1, 1997, through December 31, 2000, from Canada and the United States, as well as European and Latin American participating countries of the SENTRY Antifungal Surveillance Programme, *Candida albicans* accounted for 54% of the 2047 *Candida* BSIs recorded. The distribution for the other species was: *C. glabrata* (16%), *C. parapsilosis* (15%), *C. tropicalis* (10%), *C. krusei* (2%), *C. guilliermondii* (1%) and *C. lusitaniae* (1%). Similarly, in another study conducted by Dogan et al[44] in Turkey during the period January 2015 to November 2018, the predominant organism isolated from 342 candidaemic patients was *C. albicans* (47.4%); the rates reported for the other candidaemic organisms were: *C. parapsilosis* (26.6%), *C. tropicalis* (9.6%) and *C. glabrata* (7.6%).

Increased proportions of cases of *Candida* BSI due to species other than *C. albicans* have, however, been reported in several studies, including recent ones.[45-50] To illustrate, in a five-year study conducted by Yang et al[51] on *Candida* BSI epidemiology, the distribution of non-*C. albicans* species was: *C. glabrata* (7.4%), *C. parapsilosis* (19.8%), *C. tropicalis* (14.9%), *C. krusei* (4.1%), *C. sake* (5%), *C. guilliermondii* (5.8%), *C. haemulonii* (0.8%), *C. theae, C. intermedia* and *C. lusitaniae* (1.7% each), making up a collective proportion of 62.8% in comparison to the 37.2% observed for *C. albicans*. In a similar study involving hospital-based data on *Candida* BSI for the period 2010 to 2014,[52] the distribution of non-*C. albicans* species was: *C. glabrata* (9%), *C. parapsilosis* (23%), *C. tropicalis* (10%), *C. krusei* (0.8%), *C. guilliermondii* (2%), and *C. utilis, C. pelliculosa*, and *C. lusitaniae* (0.4% each). Although the proportion of *C. albicans* BSI was 68% at the early part of the time series, it later decreased significantly to 48% ($p = .040$), whereas that of *C. parapsilosis* increased from 8% to 30% ($p = .036$). Likewise, in a retrospective cohort study spanning between January 2006 and December 2017, the distribution of non-*C. albicans* species was *C. glabrata* (30.1%), *C. parapsilosis* (19.4%), *C. tropicalis* (17.9%), *C. krusei* (3.1%), *C. famata* (2.3%), *C. trichosporon asahii, C. dubliniensis, C. kefyr* and *C. lusitaniae* (0.5% each), other non-*C. albicans* (1.5%), with the remaining 23.5% accounted for by *C. albicans*.[53] A comparable trend was reported by Al-Musawi et al[54] in a seven-year *Candida* BSI surveillance study. Additionally, in a four-year study that compared *Candida* BSI species distribution pre- and post-echinocandin and -fluconazole era, although the proportion of *C. albicans* BSIs reduced marginally (from 61% to 60%), that of *C. glabrata* increased from 0% to 16% after the inception of use of the cited antifungal agents.[55]

Diekema et al.'s[55] study highlights, to some extent, the contributory effects of wide usage of antifungal agents to the phenomenon of *Candida* BSI aetiologic shift. Reports that have implicated the use of echinocandins and fluconazole in *C. parapsilosis* and *C. glabrata* emergence[36,56] further buttress this assertion. Geographical disparities have also been implicated in this aetiologic shift,[57,58] as well as other factors like being a neonate, having a haematologic transplant history, use of central venous catheter for extended periods, being of female gender and artificial surgical implant use.[48,59,60] The risk factors seem to overlap with what have been reported for *C. albicans* BSIs, and hence could blur tailored public health interventions for selectively combating these two groups of *Candida* BSIs. Probably, any interventions to be implemented in a given setting would need to be done holistically if successful *Candida* BSI control is to be expected.

Treatment Options for *Candida* BSIs and the Need for Newer Antifungals

The major treatment options for *Candida* BSIs belong to the classes polyenes, echinocandins, azoles and flucytosine.[61] Polyenes bind and extract ergosterol in the fungal cell wall, consequently undermining its structural integrity, resulting in leakage of ions and other components of the cell.[62] Echinocandins have as their target glucan synthase, which catalyzes the biosynthesis of the fungal cell wall.[63] As regards the azoles, their mechanism of action involves inhibiting lanosterol 14-α-sterol demethylase, which is responsible for converting lanosterol to ergosterol, and subsequently altering fungal cell membrane structure and function.[64-67] With reference to flucytosine, it is a cytosine analogue, and hence disrupts DNA and protein synthesis in fungi – it serves as a precursor for forming a non-competitive inhibitor of thymidylate synthetase (5-fluorodeoxyuridylic acid monophosphate) following deamination to 5-fluorouracil.[68]

Initially, the polyene amphotericin B was frequently used in treating *Candida* BSIs, but was largely substituted for the echinocandin caspofungin and the azoles voriconazole and fluconazole following published reports of the markedly lower toxicity demonstrated by the latter, whose efficacy were comparable to the former.[69-71] Further impetus for rendering amphotericin B use obsolete was provided in subsequent studies in which similar comparable efficacies to that of amphotericin B and caspofungin were reported for another echinocandin – micafungin,[72,73] thus widening treatment options for candidaemia and other fungal BSIs. Hence in modern times, it is in resource-poor settings that amphotericin B use is usually encountered.[74]

Since the relegation of amphotericin B, fluconazole has generally been used more – it has been an effective systemic antifungal agent for treatment of *Candida* BSIs, and appears to be beneficial to patients when administered early on in treatment, especially, when the source of infection is concurrently controlled.[28,75-78] However, the 2016 Infectious Disease Society of America (IDSA) treatment guidelines favour the use of an echinocandin for primary therapy of candidaemia in people who are moderately ill to severely ill.[12] This is understandable, as relatively more positive results have been observed for

echinocandins in recent reports.[44,76,79,80] In the report by Reboli et al,[79] which was on a randomized controlled trial involving a comparison between yet another echinocandin – anidulafungin – and fluconazole in treating *Candida* BSIs, anidulafungin was demonstrated to have higher success rates. Furthermore, the report of Cui et al,[80] based on retrospective cohort analysis, noted that initial treatment with an echinocandin was superior to fluconazole in reducing hospital mortality. These reports were corroborated by a more recent observational study conducted by Dogan et al[44] involving 10 healthcare centres in Turkey. Besides these, superior health outcomes have been reported in connection with echinocandins compared to polyenes and triazoles.[76]

Regardless, establishment of the superiority of echinocandins relative to azoles has not been unequivocal, and future randomized controlled trials involving large populations would need to be relied upon to achieve that. Of more primary concern, however, is the rising trend of resistance in candidaemic and other fungal isolates, in response to wide usage of these agents and other antifungals.[81] To illustrate, in a survey conducted in Denmark to compare year groups – 2004 to 2007, 2008 to 2011 and 2012 to 2015 – with regard to azole susceptibility, the researchers reported susceptibility rates of 68.5%, 65.2% and 60.6% for the respective year groups.[82] Similarly, in the ARTEMIS Antifungal Surveillance Programme, 14% of *C. glabrata* BSI isolates were reported to be resistant to fluconazole for the period 2001 to 2007, which was a marked increase over the 9% rate recorded for the period 1992 to 2001.[83] Besides these, 11.6% and 11.9% respectively of *C. tropicalis* and *C. glabrata* clinical isolates emanating from 31 countries were reported to be resistant to fluconazole.[84] With regard to resistance to echinocandins, in a study conducted over a 10-year period, *C. glabrata* resistance to echinocandins increased to greater than 13% for the period 2009 to 2010 in comparison with the between 2% and 3% recorded at the early stages of the time series.[85] Similarly, the SENTRY Antifungal Surveillance Programme reported rates ranging from 8% to 9.3% for *C. glabrata* BSI based on data spanning from 2006 to 2010.[86]

Three mechanisms that underlie resistance of *Candida* species to azoles have been reported.[64,67,87] One involves upregulation of, or mutations in, genes whose encoded products are the drug targets, such as *ERG11* which encodes ergosterol, thus yielding high levels of the gene products or altering the drug binding sites on the target enzymes.[64,67] Another means of resistance involves pumping out the drugs through multidrug efflux pump introduction in fungal cell walls via upregulation of mutant genes, such as *CDR1/2* and *MDR/1*.[64,67,87] The other mechanism is developing mutations that specify alternative cell wall and cell membrane integrity-maintaining pathways that are not affected by azoles.[64] As regards resistance to echinocandins, mutants of *FSK1* and *FSK2* genes have been implicated.[87,88]

The most significant phenomenon of antifungal resistance in candidaemic isolates nonetheless seems to be the emerging, rapidly-spreading, biofilm-forming, multidrug-resistant non-*albicans Candida* species – *Candida auris* – which is listed as part of the 10 most-feared fungi globally.[89-92] In one India-based antifungal resistance surveillance study involving 350 *C. auris* isolates, the resistance rates were 2% for each of micafungin and anidulafungin, 8% for amphotericin B and 90% for fluconazole.[93] A similar trend of resistance has been reported for *C. auris* in the United States – echinocandins (5%), amphotericin B (30%) and fluconazole (90%)[94] – as well as in a collection of *C. auris* from South America, Asia and Africa (7%, 35% and 93% respectively).[95]

Evidently, the markedly higher rates of fluconazole resistance recorded in *C. auris* relative to echinocandin resistance stems from the wider spatial and temporal coverage of the former. As noted earlier, echinocandins seem to be fast replacing the azoles, specifically, fluconazole, in clinical practice and hence appear to be the immediate prominent future of antifungal therapy. Therefore, it is only a matter of time before the inception and sustenance of significant increases in echinocandin resistance occurs. Extrapolating from the exponential spread of antibiotic resistance in both pathogenic and commensal bacteria under similar circumstances, the time for this phenomenon may not be far away. Certainly, then, there is an urgent need to step up the development of new antifungals in synchrony with fortification of stewardship programmes for antifungals and other antimicrobials.

Conclusions and Future Perspectives

Candida species are important aetiologies of clinically-significant BSIs. Wide usage of antifungals, in association with other factors, appears to be causing a shift in these aetiologies from *C. albicans* to species with higher propensity for developing resistance, such as the multidrug resistant species *C. auris* that is fast spreading globally. This underscores the need to intensify the development of newer antifungals, while concurrently bracing up antimicrobial stewardship programmes in order to keep up pace with the fast spreading antifungal resistance menace. Moreover, several studies on *C. auris* and its infections could be carried out to improve insights on its epidemiology.

Author Contributions

Conceptualization and design, FCNK and ESD; writing – original draft preparation, FCNK, NTKDD, PBT-Q and ESD; writing – review and editing, FCNK, NTKDD, PBT-Q and ESD.

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