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Review article

Candida and candidemia in Korea

Yong Jun Kwon, Jong Hee Shin
Department of Laboratory Medicine, Chonnam National University Medical School, Gwangju, Korea

Abstract

Purpose: Candidemia is a common cause of nosocomial bloodstream infections associated with high mortality rates. Its incidence varies significantly across countries and hospitals, and its epidemiology is a subject of continuous investigation. This review aims to provide a comprehensive analysis of candidemia in Korea, addressing its changing epidemiology, species distribution, antifungal resistance, and clinical implications.

Current content: In Korea, *Candida albicans* remains the most common isolate in blood cultures; however, infections caused by non-*albicans Candida* species are increasing. The 30-day mortality rates for patients with candidemia vary considerably across different *Candida* species, with *Candida tropicalis* at 47.0%, *C. albicans* at 36.4%, *Candida glabrata* at 34.7%, and *Candida parapsilosis* at 22.5%. Recent Korean studies have highlighted the clonal spread of bloodstream infections caused by *C. parapsilosis* with the Erg11p Y132F mutation, and certain isolates are becoming endemic to specific healthcare settings. *C. glabrata* poses a significant threat; this species is increasingly resistant to antifungal medications and multidrug-resistant isolates are emerging. Whole-genome sequencing analysis elucidates the transmission dynamics of clonal bloodstream isolates of *C. glabrata* among patients receiving antifungal therapy. This analysis demonstrates varying degrees of fluconazole susceptibility and distinct Pdr1p mutation profiles, identifying the molecular mechanisms underlying multidrug resistance. Furthermore, the first nosocomial outbreak of *Candida auris* underscores the importance of multicenter surveillance for identifying and managing *C. auris* outbreaks.

Conclusion: The changing epidemiology of candidemia, along with the continued emergence of antifungal resistance among bloodstream isolates of non-*albicans Candida* species warrants continuous monitoring of candidemia in Korea. By integrating clinical, microbiological, and public health perspectives, healthcare systems can develop robust strategies to optimize therapeutic approaches, prevent nosocomial transmission, and ultimately reduce morbidity and mortality associated with these life-threatening infections.

Keywords: Antifungal drug resistance, *Candida*, *Candida auris, Candida glabrata, Candida parapsilosis,* Candidemia

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Corresponding author
Jong Hee Shin
E-mail: shinjh@chonnam.ac.kr

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Introduction

Background

The worldwide prevalence of fungal diseases has significantly increased in recent years. Data from more than 120 countries collected between 2010 and 2023 revealed that there are approximately 6.5 million life-threatening fungal infections annually, with 2.5 million fatalities, which is a disease burden similar to that of tuberculosis, the world's leading infectious disease [1]. Many fungi cause clinical diseases, *Candida* and *Aspergillus* species being the most life threatening [1,2]. Globally, approximately 1,565,000 individuals are affected by candidemia or invasive candidiasis each year, with 995,000 deaths (63.6%) [1]. Candidemia affects at least 600,000 individuals annually, with mortality rates ranging from 30% to 40%, even in high-income countries [2]. Although candidemia is the most common form of invasive candidiasis, culture-negative deep-tissue infections after hematogenous seeding have also been reported [3]. Of the 10,758 Korea Global Antimicrobial Resistance Surveillance System (Kor-GLASS) bloodstream infection (BSI) pathogens identified in 2020–2021, *Candida* species ranked fourth among all BSI pathogens, followed by *Escherichia coli*, *Klebsiella pneumoniae*, and *Staphylococcus aureus*. Furthermore, among hospital-origin pathogens, *Candida* species ranked second, following *E. coli*. These findings highlight the significant contribution of *Candida* species in regard to nosocomial BSIs in South Korea [4].

The epidemiology of candidemia has changed over the past few decades. *Candida albicans* remains the most common isolate in blood cultures; however, infections caused by non-*albicans Candida* (NAC) species are increasing. The emergence of azole-resistant *Candida parapsilosis*, multidrug-resistant (MDR) *Candida glabrata* and *Candida auris* poses significant global public health challenges [5,6]. In October 2022, the World Health Organization released an initial fungal priority pathogen list that classified 19 fungal species into critical, high, and medium categories, suggesting research priorities [2]. *C. auris* and *C. albicans* are of critical concern, while *C. glabrata, Candida tropicalis,* and *C. parapsilosis* are of high concern [2]. *Candida* species differ in their virulence, antifungal susceptibility, and clinical profiles, which must be thoroughly understood if the disease is to be effectively managed [4,7,8].

Objectives

This review presents an overview of the current epidemiology, antifungal resistance, and clinical implications of *Candida* species as the primary agents responsible for candidemia. It thoroughly examines recent research conducted in Korea to clarify the reasons for the rising incidence of antifungal drug-resistant pathogens contributing to candidemia in hospitals nationwide. It aims to comprehensively analyze the molecular mechanisms and clinical implications of antifungal resistance in *Candida* bloodstream isolates, considering the evolving epidemiology of candidemia. We focus on species distribution, antifungal resistance patterns, and clinical outcomes, especially in intensive care units, to identify mechanisms that could improve therapeutic and preventive strategies.

Species distribution and candidemia mortality

Over 90% of all global candidemia episodes are caused by *C. albicans*, *C. glabrata*, *C. tropicalis*, and *C. parapsilosis* [4,8,9]. *C. albicans* is predominant species responsible for candidemia worldwide; however, significant variations exist in the incidence of cases attributed to NAC [4,7,8]. *C. glabrata* infections are common in both Northern Europe and the United States. In Spain and Brazil, *C. parapsilosis* infections are more frequent [7]. Early multicenter investigations in South Korea identified *C. parapsilosis* as the NAC most frequently isolated from candidemia patients [10-12]. However, from 2020 to 2021, *C. tropicalis* (17.6%) and *C. glabrata* (17.4%) will be the most common NACs in South Korea [4,8,10-14] (Fig. 1). Similar shifts in the species distribution have been reported in other Korean report [8]. A recent Korean report found that 87.6% of *Candida* BSI isolates were of hospital origin, and 41.3% were from patients in intensive care units (ICUs) [4]. Adults aged > 60 years accounted for 75.7% of all cases [4]. Candidemia predominantly affects those aged > 60 years; *C. glabrata* BSIs are most common in the elderly (> 70 years) and *C. parapsilosis* candidemia is more common in males [4]. The factors driving the evolving epidemiology of NAC in South Korea remain unclear, although certain antifungal medications, infection control measures, and risk profiles of hospitalized patients may play a role [8,9].

A Korean multicenter study evaluated 807 cases of candidemia reported by 11 hospitals in 2017 and 2018. The overall crude 30-day mortality rate was 36.4%. The 30-day mortality rates of patients with candidemia due to *C. tropicalis, C. albicans, C. glabrata*, and *C. parapsilosis* were found to be 47.0%, 36.4%, 34.7%, and 22.5%, respectively. Notably, the 30-day mortality rate of ICU-acquired candidemia (ICUAC) was significantly higher than that of non-ICUAC patients (49.5% vs. 25.4 %) for all species (*C. albicans*, 47.6% vs. 27.7%; *C. tropicalis*, 57.8% vs. 33.3%; *C. glabrata*, 50.0% vs. 24.7%; *C. parapsilosis*, 36.7% vs. 11.3%) [8]. ICU admission was an independent predictor of mortality associated with *C. glabrata* [odds ratio (OR), 2.07–2.48] and *C. parapsilosis* (OR, 6.06–11.54) candidemia. Fluconazole resistance predicted *C. glabrata*-associated mortality (OR, 2.80–5.14). An antifungal therapy delay of > 3 days was the strongest predictor of 7-day mortality which was attributable to ICUAC caused by *C. albicans* (OR, 18.33), *C. tropicalis* (OR, 10.52), and *C. glabrata* (OR, 21.30) but was less strongly linked to 30- and 90-day mortality rates (OR, 2.72–6.90). Mortality attributable to *C. glabrata* ICUAC was found to be more strongly correlated with the absence of antifungal therapy (55.2%) than that attributed to ICUAC caused by other species (30.6%–36.7%). As ICUAC mortality rates and predictors of mortality differ significantly from those in patients with non-ICUAC [8], continuous epidemiological surveillance is essential to detect any shift in species distribution and antifungal resistance among *Candida* BSIs in ICU patients.

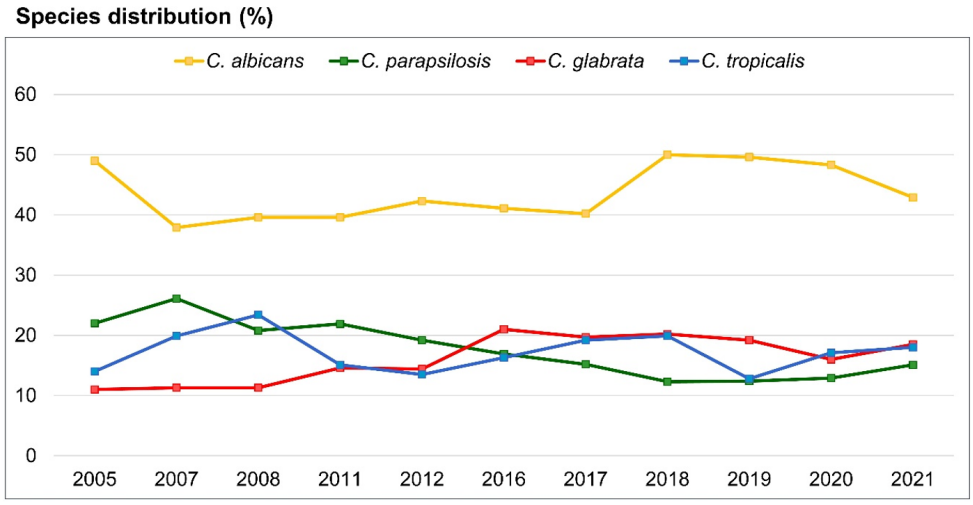

Fig. 1. Species distribution of the *Candida* bloodstream infection isolates from Korean hospitals.

Antifungal resistance

The global rise in antifungal-resistant *Candida* species is particularly concerning, but the rates of resistance to both azoles and echinocandins vary by geographic region, hospital, and ICU. According to the 1997–2016 SENTRY Antimicrobial Surveillance Program, fluconazole resistance in *C. glabrata* is the highest in North America (10.6%), whereas resistance in *C. tropicalis* is the highest in the Asia-Pacific region (9.2%) [9]. The prevalence and fluconazole resistance of *C. glabrata* have increased steadily over the past 20 years in the United States. The echinocandin resistance rates ranged from 3.5% for *C. glabrata* to 0.1% for *C. albicans* and *C. parapsilosis* [9]. The 2019–2020 SENTRY Antimicrobial Surveillance Program reported that 0.5%, 4.5%, 10.5%, and 1.2% of all *C. albicans, C. glabrata, C. parapsilosis,* and *C. tropicalis*, respectively, were fluconazole-resistant [15]; among the NAC species, azole resistance was found to be increasing. All *C. albicans, C. tropicalis,* and *Candida krusei* isolates, and most *C. glabrata* (96.2%–97.9%) and *C. parapsilosis* (86.2%–100%) isolates were susceptible to echinocandins [15]. Antifungal resistance rates in bloodstream isolates of the four *Candida* species from 2005 to 2021 in Korea showed relatively higher fluconazole resistance rates in *C. glabrata* and *C. parapsilosis* without consistent trends, whereas echinocandin-resistant isolates were rarely observed (Fig. 2). [4,8,10-14]. The *Candida* data of Kor-GLASS obtained from nine sentinel hospitals between 2020 and 2021 revealed that 21.1%, 4.0%, 0.1%, 0.0%, and 0.1% of all *Candida* isolates in BSIs were not susceptible to fluconazole, voriconazole, caspofungin, micafungin, and anidulafungin, respectively [4]. Fluconazole resistance was apparent in 0% (0/348), 2.2% (3/135), 5.3% (7/133), and 5.6% (6/108) of the *C. albicans, C. tropicalis, C. glabrata,* and *C. parapsilosis* BSIs, respectively [4]. The mechanisms of azole antifungal resistance in major *Candida* species, as identified in Korean multicenter studies, vary among the species (Table 1) [16-20]. Erg11p and Tac1p amino acid substitutions (AASs) may play significant roles in regard to the development of antifungal resistance in *C. albicans* strains infecting the bloodstream. Most fluconazole-non-susceptible (FNS) infections are not linked

to prior azole exposure [16]. In contrast, most FNS *C. tropicalis* isolates overexpress *CDR1*, *MDR1*, and *ERG11*, and fungemia typically follows azole treatment in immunocompromised patients [17].

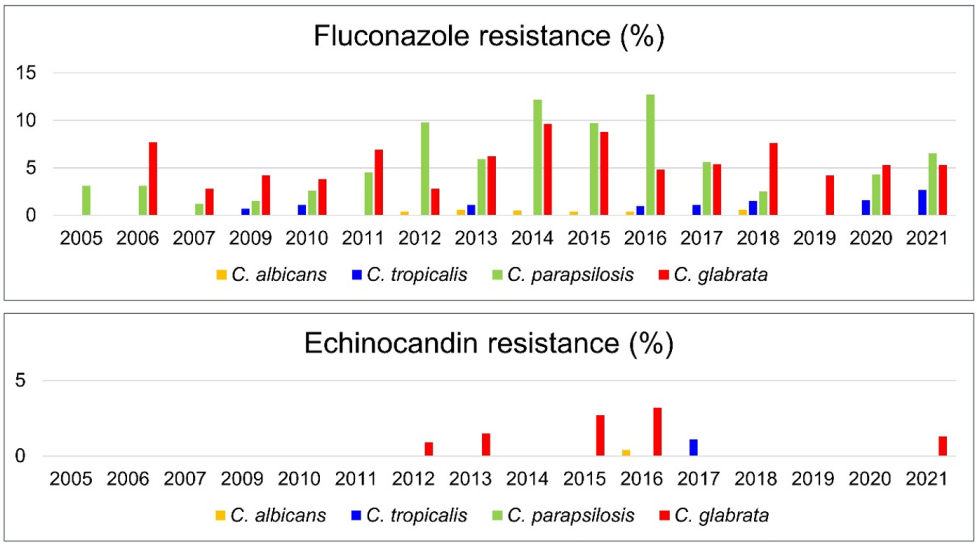

Fig. 2. Antifungal resistance of the *Candida* bloodstream infection isolates from Korean hospitals using new clinical breakpoints (CLSI M60-ED2:2020) [36].

Table 1. Studies describing the azole antifungal resistance mechanisms in the *Candida* isolates collected from Korean multicenter studies.

Candida species	*C. albicans*	*C. tropicalis*	*C. parapsilosis*	*C. glabrata*	*C. auris*
Collection period of isolates	2006–2021	2003–2013	2005–2016	2008–2018	1996–2022
Number of hospitals	10	8	8	19	13
Number of isolates	26 BSI (14 FNS and 12 FS) isolates	9 FNS, 12 FS (MIC, 1–2 μg/ml), and 14 control (MIC, 0.125–0.5 μg/ml) isolates	67 BSI (47 FR and 20 FS) isolates	278 BSI (66 FR and 212 F-SDD) isolates	104 (96 clade II and 8 clade I) isolates
Genes studied	Sequencing of *ERG11*, *TAC1*, *MRR1*, and *UPC2*	Quantitation of *CDR1*, *MDR1*, and *ERG11* expression, and sequencing of the *ERG11* and *UPC2* genes	Sequencing of *ERG11*, *TAC1*, *MRR1*, and *UPC2*	Sequencing of pleiotropic drug resistance transcription factor (*PDR1*)	Sequencing of *ERG11*, *TAC1A*, and *TAC1B*
Results	Erg11p and Tac1p AASs are likely to contribute to FR in *C. albicans* BSI isolates in Korea	The majority of FNS *C. tropicalis* isolates show overexpression of *CDR1*, *MDR1*, and *ERG11* genes	Majority (63.8%) of the *C. parapsilosis* FR isolates exhibit the Y132F substitution in Erg11p	Most FR BSI isolates of *C. glabrata* in Korea harbor FR-specific Pdr1p AAS	Tac1Bp AASs may be the predominant fluconazole resistance mechanism in clade II Korean isolates of *C. auris*
Year of publication	2023	2016	2018	2021	2023
References	[16]	[17]	[18]	[19]	[20]

Abbreviations: BSI, bloodstream infection; FNS, fluconazole non-susceptible; FS, fluconazole susceptible; F-SDD, fluconazole susceptible dose-dependent; FR, fluconazole resistant; MIC, minimal inhibitory concentration; AAS, amino acid substitution.

Pathophysiology

Candida species, predominantly *C. albicans* and *C. tropicalis* (with lower proportions of *C. parapsilosis* and *C. glabrata*), are integral components of the normal gastrointestinal microbiome [21]. Most candidemia cases are endogenous infections, *C. albicans* (which constitutes 70%–80% of commensal *Candida*) is the most common causative agent [22]. The main mechanism of candidemia is thought to be the leakage of *Candida* through the intestinal mucosa following mucosal insults [23], such as those caused by abdominal surgery, anastomotic leaks, antibiotic use, and pancreatitis. In addition, *Candida* often gains bloodstream access via intravenous catheters, particularly in central venous lines. In patients receiving total parenteral nutrition (TPN), lipid emulsions enhance *Candida* biofilm formation, potentially increasing its virulence. Altered gut function in TPN recipients may also be conducive for *Candida* translocation [24]. Many molecular typing studies have shown that small clusters of candidemia attributable to isogenic isolates are frequent within hospitals, *Candida* can spread nosocomially [18,25,26] via the hands of healthcare personnel or contamination of intravenous saline used to flush central venous catheters (CVCs) shared among patients. In addition, person-to-person transmission among hospitalized patients may have occurred more frequently than previously thought. The clonal spread of *C. albicans* causing candidemia is common in hospitals [25,26]. Outbreaks of *C. albicans* often occur over a short period and simultaneously involve multiple patients. In contrast, *C. parapsilosis* is more persistent in healthcare settings, with clusters of infected patients developing over time [27], likely due to its frequent presence on the hands of healthy individuals and healthcare workers [6]. Strict adherence to routine hand hygiene and the appropriate management of CVCs are of utmost importance [6]. "Catheter care bundles," which are standardized interventions that prevent catheter-associated BSIs, significantly decrease the incidence of candidemia [6].

Epidemiology, antifungal resistance and clinical significance of the most concerning *Candida* species

1) *Candida parapsilosis*

C. parapsilosis is the second most common cause of *Candida* BSIs in Latin America, Asia, and Southern Europe, and the third most common global BSI cause [5,28]. *C. parapsilosis* candidemia is frequently attributed to external fungal acquisition; *C. parapsilosis* tends to colonize hospital settings and equipment, particularly CVCs and other medical devices [29]. One Korean study explored whether biofilm formation was associated with clinical features [30]. The proportion of blood NAC isolates that formed biofilms was significantly higher than that of NAC isolates from other locations (79% vs. 52%). Specifically, bloodstream isolates of *C. parapsilosis* demonstrated a significantly higher likelihood of being biofilm positive than those obtained from other sites (86% vs. 47%). All NAC species, including *C. parapsilosis*, were more likely to form biofilms when isolated from patients with CVC-related candidemia associated with TPN than from other patients. The ability of *in vitro* biofilm formation in *C. parapsilosis* when grown in glucose-containing

Sabouraud dextrose broth is an important virulence factor that causes CVC-related fungemia in patients treated with TPN [30].

Although *C. parapsilosis* is usually susceptible to azole antifungals, *C. parapsilosis* BSIs caused by FNS isolates have become increasingly common worldwide [5,26]. The global prevalence of fluconazole resistance ranges from 0% to 100%, and the pooled resistance rate may reach 15.2% [31]. Recent reports indicated that 60.7%-63.8% FNS *C. parapsilosis* isolates harbored a Y132F substitution in the *ERG11* gene ("Y132F isolates"), and most were clonally related. BSI outbreaks caused by Y132F isolates have been reported in multiple countries across four continents, and some clonal isolates have become endemic over several years in affected hospitals [18,32]. An early multicenter Korean report found that among 1,009 non-duplicated BSIs of *C. parapsilosis* obtained from 20 hospitals between 2005 and 2016, 47 (4.7%) from eight university hospitals were fluconazole resistant and 64% (30/47) harbored the same Y132F mutation in Erg11p [18].

A recent Korean study found that long-term clonal transmission of *C. parapsilosis* BSI Y132F isolates in Korean hospitals was associated with a "sinking" (not a "floating") phenotype [33]. In contrast to floating phenotypes, sinking phenotypes are presented as a smaller, button-like appearance in the plate well of Clinical and Laboratory Standards Institute broth microdilution antifungal susceptibility test; all cells sank in U-shaped, round-bottom wells. The sinking phenotype was detected in 86.7% of the FNS BSI isolates, and 92.9% of the Y132F BSI isolates of *C. parapsilosis*. As azole breakthrough fungemia, ICU admission, and urinary catheter use were independent risk factors for fungemia caused by Y132F sinking phenotype isolates, strain with a sinking phenotype may be prone to having an *ERG11* Y132F substitution after azole exposure, may be more enriched, and may persist for a long time in the ICU environment, where they may cause BSI in vulnerable patients with indwelling catheters or azole exposure [33]. Microsatellite typing revealed that these isolates exhibited greater clonal transmission than other fluconazole-resistant isolates and persisted in hospitals for several years. The evolution of fluconazole resistance in Y132F clonal *C. parapsilosis* isolates from a South Korean hospital has been studied [34]. Increased fluconazole resistance has been associated with the acquisition of *MRR1* mutations. Thus, continuous surveillance of fluconazole resistance rates, resistance mechanism(s), and clonality of hospital *C. parapsilosis* isolates is essential [33,34].

2) *Candida glabrata*

C. glabrata is one of the most concerning *Candida* species of nosocomial importance; its antifungal drug resistance rate is increasing, and MDR isolates are emerging [4,9,35]. *C. glabrata* is innately relatively resistant to azoles, especially fluconazole, and can rapidly develop fluconazole resistance during treatment, probably because its haploid genome is mutable. *C. glabrata* isolates are no longer considered fluconazole-susceptible but rather fluconazole-susceptible dose-dependent (F-SDD) or fluconazole-resistant [35,36]. Although the incidences of echinocandin-resistant and MDR *C. glabrata* BSIs are low, fluconazole-resistant *C. glabrata* BSIs have been increasingly reported worldwide, typically at a rate of 2.6%–10.6% but increasing up to 17% [9].

Gain-of-function (GOF) mutations in the transcription factor pleiotropic drug resistance protein 1 (encoded by *PDR1*) mediate *C. glabrata* azole resistance by controlling the expression of genes encoding efflux pumps [*CDR1, CDR2* (*PDH1*), and *SNQ2*], although other mechanisms may also be involved [37]. A Korean multicenter study found that 98.5% of fluconazole-resistant *C. glabrata* BSIs and 0.9% of *C. glabrata* F-SDD BSIs exhibited one or two AASs in the Pdr1p protein, excluding five genotype-specific AASs [19]. Of the 49 Pdr1p AASs, 33 were found to be new; most fluconazole-resistant BSIs harbored fluconazole resistance-specific Pdr1p AASs. More importantly, patients infected with fluconazole-resistant *C. glabrata* BSIs harboring Pdr1p mutations exhibited high mortality; the 30-day rate for 64 patients was 60.9%, and the 90-day rate was 78.2%, which was significantly higher than that for patients with F-SDD BSIs (30-day rate, 36.4%; 90-day rate, 43.8%) [19].

The echinocandin resistance rate of *C. glabrata* ranged from 1.7% to 3.5% and resistance did not increase over time [9,38]. However, at the institutional level, the prevalence of echinocandin resistance varies significantly, and sometimes exceeds 13% [9,38]. A recent Korean study used whole-genome sequencing (WGS) in order to explore the molecular mechanisms of MDR in 10 serial *C. glabrata* isolates from a patient with BSI experiencing breakthrough fungemia during extended amphotericin B (AMB)/echinocandin therapy [39]. *ERG3* and *ERG6* may be involved in AMB resistance, and Fks2p mutations outside the high-susceptibility regions contribute to low echinocandin resistance [39]. The minimal inhibitory concentration (MIC) of fluconazole for *C. glabrata* isolates with the same Pdr1p GOF mutation was reduced in AMB-resistant isolates with Erg6p mutations, indicating a complex relationship between AMB and azole resistance. Changes in the ergosterol biosynthesis pathway may explain the azole resistance in some *C. glabrata* strains [39].

Although *C. glabrata* transmission within hospitals is less common than that of other *Candida* species, some transmission has been observed [40,41]. The prevalence of antifungal-resistant BSIs caused by *C. glabrata* is increasing worldwide [5,9,19], but the transmission of such resistant strains within hospitals has rarely been reported. However, the Centers for Disease Control and Prevention's Emerging Infections Program in USA found an exceptionally high proportion of echinocandin-resistant *C. glabrata* with the *FKS* mutations seen among echinocandin-naïve patients, suggesting nosocomial transmission [42]. Using WGS and epidemiological analyses, a recent Korean study identified two potential clusters of *C. glabrata* BSIs within the same hospital. Clonal *C. glabrata* strains with differences in fluconazole susceptibility and distinct Pdr1p AAS profiles were isolated from patients receiving antifungal therapy [43].

3) *Candida auris*

C. auris poses a significant threat to global health [2,44]. *C. auris* was first described in Japan and South Korea in 2009 [45,46]. The first Japanese *C. auris* was isolated from an inpatient's external ear canal [45]. In the same year, *Candida haemulonii* and other closely related species from five Korean university hospitals were reported [46]. Of these, 15 ear isolates of the new *Candida* species were identified as *C. auris;* all from patients with chronic otitis media. Persistently positive cultures were obtained from seven patients, three of whom received antifungal therapy. However, no histopathological evidence of a fungal infection was

observed in any patient. Thus, the clinical significance of *C. auris* isolation from the ears remains unclear. Two years later, the first three cases of *C. auris* fungemia were identified at three Korean university hospitals [47]. The first case was incidentally discovered through molecular analysis of an unidentified yeast isolated in 1996; the earliest strain of *C. auris* was thus from Korea. Two of these three cases were identified in the 2009 Korean multicenter candidemia surveillance study. These three cases show, for the first time, that *C. auris* is a human pathogen. Since then, *C. auris* has been found in more than 45 countries across six continents [48] and has been associated with many outbreaks of invasive diseases. The mortality rate ranged from 29% to 62%, and the median hospital stay was typically 46–68 days but reached up to 140 days [49].

C. auris differs from other *Candida* species in three respects [50]. First, *C. auris* is primarily associated with the skin and not the gut or mucosal surfaces. Second, because *C. auris* can persist on the skin, it can spread widely in healthcare environments, affecting both patients and the environment, and hospital outbreaks are frequent. Third, *C. auris* is the first nosocomial fungal pathogen to exhibit marked (sometimes complete) resistance to all known antifungals, including azoles, AMB, and echinocandins. The global fluconazole resistance rate was 87%–100%. The MIC_{90} of isavuconazole, itraconazole, and posaconazole are 0.06–1.0 mg/L. The voriconazole resistance rate was 28%–98%. The AMB resistance rate is 8%–35% and that of echinocandin resistance is 0%–8% [49].

In the initial WGS analysis, *C. auris* isolates were grouped into four major clades: South Asia clade I, East Asia clade II, African clade III, and South American clade IV [51]. Only clade II isolates were detected in Korean hospitals between 1996 and 2018 [52]. Pulsed-field gel electrophoresis showed that the patterns of the Korean blood and ear isolates were similar or identical and distinct from those of other countries. Almost all Korean isolates were obtained from ears. No nosocomial outbreaks caused by clade II *C. auris* have yet been reported. Two Korean studies found that 66% of 157 isolates of clade II *C. auris* were fluconazole-resistant, but all were susceptible to AMB and the three echinocandins, and MDR was not found [20,52]. Thus, clade II Korean isolates of *C. auris* are less resistant to antifungals and differ in terms of clinical characteristics compared to other geographic clades [52]. In 2022, Kor-GLASS identified nine *C. auris* clade I BSIs in a single hospital [20]. This is the first nosocomial outbreak in Korea, highlighting the importance of multicenter surveillance for identifying and managing *C. auris* outbreaks. Clade II Korean isolates were less tolerant to 42°C than clade I isolates. Furthermore, in a model using *Galleria mellonella* larvae, the clade II isolates were less virulent than the clade I isolates [20]. The growth rate of clade II isolates was fivefold lower than that of *C. albicans* SC5314, but the clade I growth rate was 4.3-fold higher than that of *C. albicans*. The low virulence of clade II may explain its lack of nosocomial transmission [20]. A detailed summary of microbiological studies on the clinical isolates of *C. auris* in Korea is provided in Table 2. Infections caused by *C. auris* have been documented in at least 40 countries across six continents. Although clade II *C. auris* lacks MDR and does not appear to cause nosocomial candidemia, the increasing incidence of clade I *C. auris* infections in Korea is alarming. The timely identification and implementation of effective control measures are critical.

Table 2. Summary of the microbiological studies of the clinical isolates of *Candida auris* in Korea

Year of publication	No. of patient (No. of isolate)	Specimen (No. of isolate)	Molecular epidemiologic test (No. of isolate)[a]	Resistance rate of antifungal agent (%)[b]					Possible genetic marker of FLU resistant isolate	Reference
				FLU	AMB	CSF	MCF	ANF		
2009	15 (15)	Ear (15)	NT	53.3	0	0	0	NT	NT	[46]
2011	3 (6)	Blood (6)	NT	33.3	0	0	0	NT	NT	[44]
2018	61 (61)	Blood (4), Ear (57)	Clade Ⅱ (61)	62.3	0	0	0	NT	Erg11p (L43H, K143R, Q357K)	[52]
2023	104 (104)	Blood (5), Ear (91)	Clade Ⅰ (8)	25.0	75.0	0	0	0	Erg11p (K143R), Tac1Bp (A640V)	[20]
			Clade Ⅱ (96)	68.8	0	0	0	0	Erg11p (L43H, Y132F, K143R, Q357K), Tac1Bp (F214S, P595L)	

[a]Clade of isolates were determined by multilocus sequence typing.

[b]Applying tentative breakpoints of the Centers for Disease Control and Prevention.

Abbreviations: FLU, fluconazole; AMB, amphotericin B; CSF, Caspofungin; MCF, micafungin; ANF, anidulafungin; NT, not tested.

Conclusion

Candidemia, the epidemiology of which differs geographically, remains an important issue. The global landscape has evolved over time and is likely influenced by selective drug pressure, innate characteristics of *Candida* species, and host- and drug-related parameters. Increasing antifungal resistance, particularly in azole-resistant *C. parapsilosis*, MDR *C. glabrata* and *C. auris*, complicates treatment strategies and is associated with an increasing incidence of candidemia in healthcare settings. The interrelationships between virulence, epidemiology, and antifungal susceptibility/resistance must be understood if management is effective. Because person-to-person transmission among hospitalized patients may be more frequent than previously recognized, adherence to established infection prevention protocols is imperative. WGS will yield insights into drug resistance mechanisms, virulence factors, genotypic characteristics, and sources of infection. Given the link between antifungal resistance in *Candida* isolates and their evolutionary adaptations, it is vital to sustain the ongoing multicenter surveillance of antifungal resistance rates, the underlying mechanisms of resistance, and also the clonal relationships of *Candida* isolates sourced from healthcare settings.

Ethics statement

This was not a human population study; therefore, approval by the institutional review board and informed consent were not required.

Conflicts of interest

No potential conflicts of interest relevant to this article were reported.

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Data availability

None.

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