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Epidemiology of Candidemia in Children and Neonates in Korea, 2009–2018: A Multi-Center Study

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ABSTRACT

Background: Invasive candidal infection is a serious health threat to high-risk pediatric populations. Data on pediatric epidemiology of candidemia in Korea are limited.
Methods: A retrospective chart review was performed for patients aged 0–18 years who were diagnosed with candidemia from 2009 to 2018 in tertiary hospitals. Patients were divided into two groups; a neonatal group of babies with postnatal age 28 days or younger or any patients hospitalized in neonatal intensive care unit and a pediatric group of the rest of patients. Only the first candidemia episode for each patient was included. *Candida* species, antifungal sensitivity, underlying condition, and outcomes were investigated.
Results: A total of 228 patients with candidemia were identified from five hospitals. Of them, 87 and 141 were assigned into the neonatal group and the pediatric group, respectively. The most common underlying condition was prematurity (88.5%) in the neonatal group and hematology-oncology diseases (49.6%) in the pediatric group. Non-*albicans Candida* spp. (65.4%) was more common than *C. albicans*. *C. parapsilosis* was the most commonly identified species (35.1%), followed by *C. albicans* (34.6%), *C. tropicalis* (9.6%), *C. glabrata* (9.6%), and *C. krusei* (2.2%) in all patients. *C. parapsilosis* was the most common pathogen in the neonatal group, while *C. albicans* was the most common pathogen in the pediatric group. Results of antifungal sensitivity to fluconazole were available for 160 patients. About 11.2% of isolates were either intermediate or resistant to fluconazole (10.0% for non-*albicans*, 1.2% for *C. albicans*) ($P = 0.036$). Overall mortality within 30 days after candidemia was 25.4%.
Conclusion: Candidemia caused by non-*albicans Candida* was more common in pediatric patients during the study period. Resistance to antifungal agents was noted. Monitoring for epidemiologic change is warranted.

Keywords: Epidemiology; Candidemia; Children; Neonates; Korea

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Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Choi JS, Kim YJ. Data curation: Ahn JG, Cho HK, Choi JS, Choi SH, Kang JM, Kim YK, Yoon Y. Formal analysis: Choi JS, Heo SJ. Funding acquisition: Choi JS. Investigation: Choi JS. Methodology: Choi JS, Kim YJ. Validation: Choi JS, Choi SR. Visualization: Choi JS. Writing - original draft: Choi JS. Writing - review & editing: Choi SR, Kim YJ.

INTRODUCTION

Candidemia is the most frequent invasive fungal infection in pediatric patients. It is the third or fourth most common isolate from pediatric cases of healthcare-associated bloodstream infections in the United States and worldwide.[1-4] Although *Candida albicans* is the most common pathogen,[5] recent studies have reported trends of its decreasing proportion, particularly in the non-neonatal population.[6] Annual incidence rates of candidemia in children have been estimated to be 0.8–10.5/1,000 admissions.[2-4,6-13] Mortality rate in children with candidemia varies from 19% to over 40%, possibly reflecting geographical and socioeconomic differences.[7,8,10,13-15]

In 2022, the World Health Organization (WHO) listed fungal priority pathogens requiring global attention as causes of invasive fungal diseases associated with high mortality and morbidities.[16] Among *Candida* species, *C. auris* and *C. albicans* were listed as a critical priority group and *C. parapsilosis* and *C. tropicalis* were listed as a high priority group. The WHO also provides a protocol to organize and incorporate national fungal antimicrobial resistance surveillance for invasive *Candida* infections as a part of the Global Antimicrobial Resistance and Use Surveillance System.[17]

Considering the severity and global burden of candidemia, studies on candidemia in neonatal and pediatric populations in Korea have been sparse.[18-22] All published studies on candidemia were retrospective studies with relatively small participants, mostly from single centers. Furthermore, the necessity to update epidemiologic characteristics of candidemia arises because no other studies have been reported since the last study in 2007.[21]

This study aimed to investigate the epidemiology of candidemia in pediatric patients including neonates and antifungal resistance of invasive candida isolates.

METHODS

Study setting and population

The study period was from January 2009 to December 2018. The study population included patients aged 18 years old or younger who were diagnosed with candidemia from five university hospitals: Gil Medical Center, Korea University Ansan Hospital, Pusan National University Hospital, Samsung Medical Center, and Severance Children's Hospital. The population was divided into two groups according to their age: a neonatal group and a pediatric group. The neonatal group was defined as neonates whose postnatal age was younger than 28 days or hospitalized in the neonatal intensive care unit (NICU) if older than 28 days. The pediatric group covered the rest of the study population.

Clinical data were collected via a retrospective electronic medical chart review. Demographic information, primary underlying diseases, and 30-day overall mortality were investigated. The most representative one was chosen if a patient had more than one underlying condition or disease. Data on the distribution of *Candida* species and antifungal susceptibility were collected. Only the first episode for each patient was included in this study.

Statistical analysis

For continuous and categorical variables, medians and percentages were used for descriptive analyses, respectively. Difference in 30-day mortality between neonate and pediatric groups was tested using Pearsons's chi-square test. For investigating epidemiologic trends, a linear regression model was used. Fisher exact test was applied to compare proportion of non-susceptibility to fluconazole between *C. albicans* and non-*albicans Candida*. To analyze risk factors for non-*albicans* candidemia, logistic regression model was used. A *P* value less than 0.05 was considered statistically significant.

Ethics statement

This study was reviewed and approved by the Samsung Medical Center Institutional Review Board (approval No. 2019-09-087). Informed consent was waived owing to its retrospective design. All other participating centers individually obtained approval from their ethical committees.

RESULTS

Patient characteristics and outcomes

A total of 228 patients with candidemia were identified from five hospitals. Eighty-seven and 141 patients were in the neonatal group and the pediatric group, respectively (**Table 1**). The median age of the total study population was 1.4 years. Males (59.2%) were dominant. The most common underlying condition in the neonatal group was prematurity (88.5%), followed by cardiologic disease (3.4%). In the pediatric group, hematology-oncology diseases (49.6%) were the most common underlying diseases, followed by neurologic disease (17.7%) and gastrointestinal disease (8.5%). Among the 228 patients, overall mortality within 30 days after candidemia onset was 25.4% (58/228) with a median time interval of 7 days ranging 0 to 28 days. Mortality was not significantly different between neonatal and pediatric group (28.7% vs. 23.4%, $P = 0.458$). There were no statistically significant differences in demographic, clinical, or microbiological characteristics between the 30-day mortality cases and survivors, nor were any risk factors for 30-day mortality identified (**Supplementary Tables 1** and **2**).

Table 1. Characteristics of patients

Characteristics	Neonatal	Pediatric	Total
Patient number	87	141	228
Age	28 (0–321) days	5.9 (0.2–18.8) years	1.4 (0.0–18.8) years
Sex, male	51 (58.6)	84 (59.6)	135 (59.2)
Underlying disease			
Prematurity	77 (88.5)		77 (34.2)
Hematology/oncology		70 (49.6)	70 (30.7)
Neurology		25 (17.7)	25 (11.0)
Cardiology	3 (3.4)	8 (5.7)	11 (4.8)
Gastroenterology	1 (1.1)	12 (8.5)	13 (5.7)
Primary immune deficiency disease		1 (0.7)	1 (0.4)
Others[a]	5 (5.7)	15 (10.6)	20 (8.8)
30 days mortality	25 (28.7)	33 (23.4)	58 (25.4)

Values are presented as median (range) or number (%).
[a]Genetic or chromosomal disorders (n = 5), nephrology (n = 5), esophageal atresia (n = 2), multiple congenital anomaly (n = 2), urology (n = 2), anorexia nervosa (n = 1), connective tissue disease (n = 1), lipoid pneumonia (n = 1), metabolic disease (n = 1).

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Distribution of *Candida* species and antifungal susceptibility

Non-*albicans Candida* spp. (65.4%) predominated over *C. albicans* (34.6%) (**Fig. 1**). *C. parapsilosis* was the most commonly identified species (35.1%), followed by *C. albicans* (34.6%), *C. tropicalis* (9.6%), *C. glabrata* (9.6%), and *C. krusei* (2.2%) in all patients. *C. parapsilosis* (44.8%) was the most common pathogen in the neonatal group, while *C. albicans* (34.8%) was the most common pathogen in the pediatric group. There were no changes in trends over time in the distribution of each *Candida* species or the comparison of *C. albicans* and non-*albicans* analyzed by a linear regression model (coefficient, −1.408 to 0.675; *P* value, 0.282 to 0.957) (**Fig. 2** and **Supplementary Table 3**). Distribution of *Candida* species by each centers is designated in **Supplementary Table 4**. Comparing the distribution differences between *C. albicans* and non-*albicans* strains by dividing the entire study period into three segments, a significant difference emerged (*P* value, 0.007) (**Table 2**).

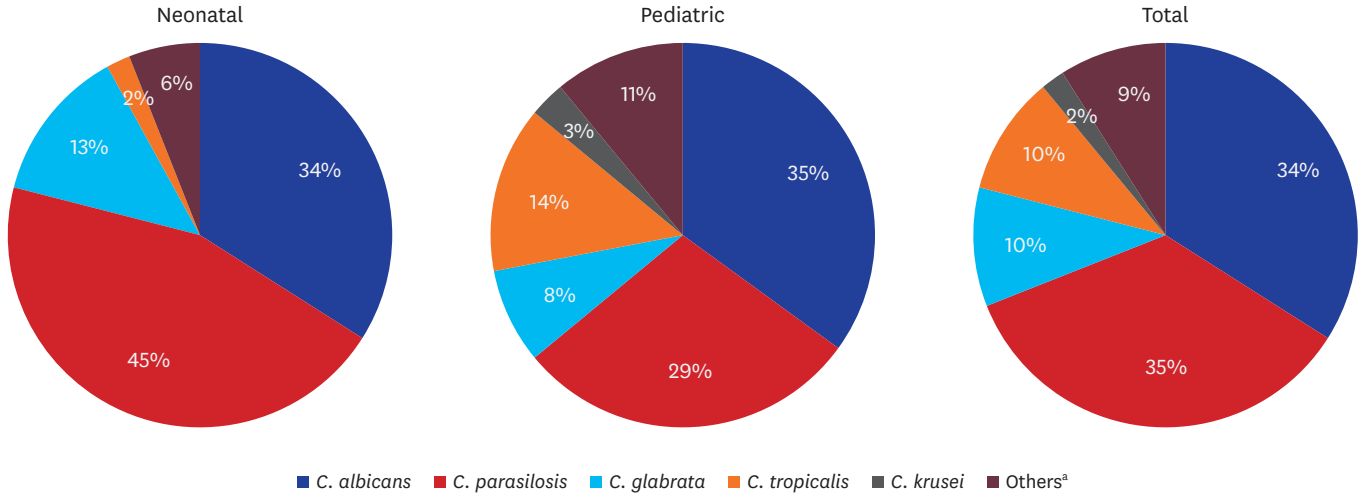


Fig. 1. Distribution of *Candida* species.
[a]*C. lusitaniae* (n = 8), *C. guillermondii* (n = 3), *C. kefyr* (n = 1), *C. orthopsilosis* (n = 1), *C. fanianii* (n = 1), species not identified which is not *albicans* (n = 6).

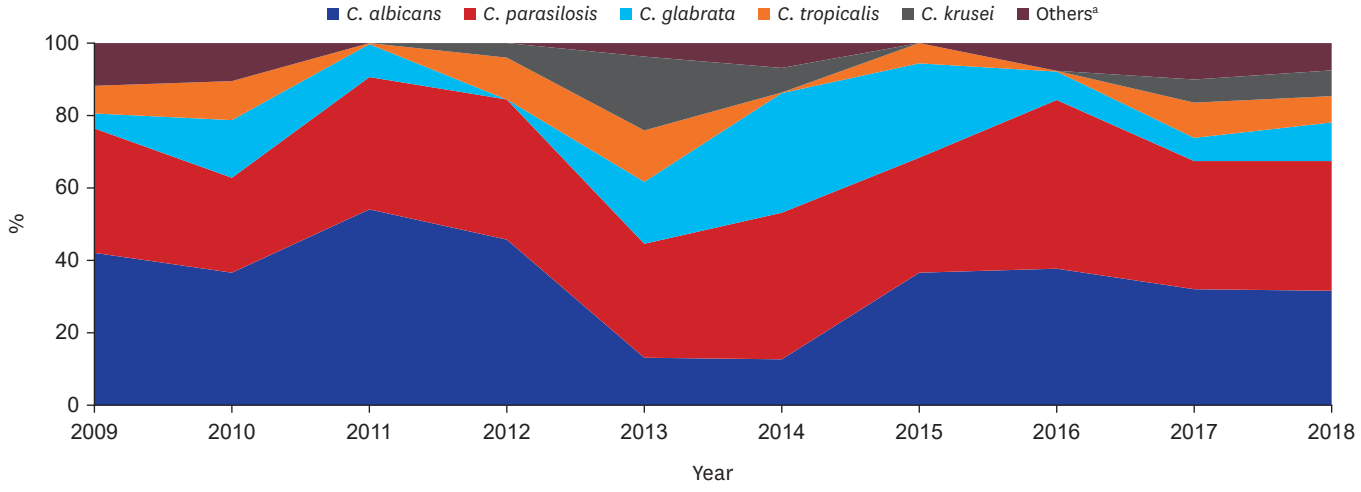


Fig. 2. Trends in proportional distribution of *Candida* species.
[a]*C. lusitaniae*, *C. guillermondii*, *C. kefyr*, *C. orthopsilosis*, *C. fanianii*, species not identified which is not *albicans*.

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Table 2. The χ^2 analysis for three consecutive phases of the study period

Species	2009–2012	2013–2015	2016–2018	*P* value
C. albicans	42 (45.2)	13 (20.6)	24 (33.3)	0.007[a]
Non-*albicans*	51 (54.8)	50 (79.4)	48 (66.7)	
C. parapsilosis	32 (34.4)	21 (33.3)	27 (37.5)	
C. glabrata	6 (6.5)	10 (15.9)	6 (8.3)	
C. tropicalis	7 (7.5)	10 (15.9)	5 (6.9)	
C. krusei	1 (1.1)	2 (3.2)	2 (2.8)	
Others[b]	5 (5.4)	7 (11.1)	8 (11.1)	

Values are presented as number (%).
[a]*P* value indicates the differences in the distribution of *C. albicans* and all non-*albicans* species across phases.
[b]*C. lusitaniae* (n = 8), *C. guillermondii* (n = 3), *C. kefyr* (n = 1), *C. orthopsilosis* (n = 1), *C. fanianii* (n = 1), species not identified which is not *albicans* (n = 6).

Risk factors for non-*albicans* candidemia was also analyzed. Age, gender, underlying conditions were not identified as significant risk factors (**Supplementary Table 5**). Likewise, a comparative subgroup analysis for infants, from 29 days to under one year of age, included in both the neonatal and pediatric cohorts, yielded similar results (**Supplementary Tables 6** and **7**).

Antifungal sensitivity results were available for 160 (70.2%) participants (**Table 3**). About 11.2% of isolates were either intermediate or resistant to fluconazole. Non-susceptibility to fluconazole was significantly higher in non-*albicans* species ($P = 0.036$). Overall, most isolates were sensitive to antifungal agents tested, including caspofungin to which the sensitivity was 100%. In terms of *Candida* species, 3.8% of *C. albicans* were not susceptible to fluconazole or voriconazole. Notably, 13.6% of isolated *C. parapsilosis* were not susceptible to fluconazole. While 16.7% of *C. glabrata* demonstrated non-susceptibility to fluconazole, all isolates of *C. tropicalis* were susceptible to fluconazole. One isolate of *C. parapsilosis*, two isolates of *C. guillermondii*, and one isolate of unidentified species showed non-susceptibility to amphotericin.

Table 3. Antifungal susceptibility by species

Species	Susceptibility[a]	Fluconazole	Voriconazole	Caspofungin	Amphotericin B	Flucytosine
C. albicans (n = 79)	S	51 (96.2)	51 (96.2)	30 (100.0)	51 (100.0)	37 (100.0)
	I	2 (3.8)	-	-	-	-
	R	-	2 (3.8)	-	-	-
C. parapsilosis (n = 80)	S	51 (86.4)	58 (98.3)	34 (100.0)	55 (98.2)	43 (100.0)
	I	4 (6.8)	1 (1.7)	-	1 (1.8)	-
	R	4 (6.8)	-	-	-	-
C. glabrata (n = 22)	S	15 (83.3)	18 (100.0)	14 (100.0)	18 (100.0)	16 (100.0)
	I	2 (11.1)	-	-	-	-
	R	1 (5.6)	-	-	-	-
C. tropicalis (n = 22)	S	16 (100.0)	16 (100.0)	12 (100.0)	16 (100.0)	13 (100.0)
	I	-	-	-	-	-
	R	-	-	-	-	-
C. krusei (n = 5)	S	-	4 (100.0)	4 (100.0)	4 (100.0)	1 (33.3)
	I	-	-	-	-	1 (33.3)
	R	4 (100.0)	-	-	-	1 (33.3)
Others[b] (n = 20)	S	9 (90.0)	10 (100.0)	7 (100.0)	7 (70.0)	7 (100.0)
	I	1 (10.0)	-	-	2 (20.0)	-
	R	-	-	-	1 (10.0)	-
Total (N = 228)	S	142 (88.8)	157 (98.1)	101 (100.0)	151 (97.4)	117 (98.3)
	I	9 (5.6)	1 (0.6)	-	3 (1.9)	1 (0.8)
	R	9 (5.6)	2 (1.3)	-	1 (0.6)	1 (0.8)

Values are presented as number (%).
[a]S: susceptible, I: intermediate, R: resistant.
[b]*C. lusitaniae* (n = 8), *C. guillermondii* (n = 3), *C. kefyr* (n = 1), *C. orthopsilosis* (n = 1), *C. fanianii* (n = 1), species not identified which is not *albicans* (n = 6).

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DISCUSSION

Our study is the first multicenter study on the epidemiology of candidemia in Korean pediatric and neonatal population. A total of 228 patients were included in our study. This was the largest number among existing regional studies on this issue. Prematurity (88.5%) and hematology-oncology diseases (49.6%) were the most common underlying conditions in neonates and children, respectively. Overall, non-*albicans* species were more frequently isolated throughout the study period. About 11.2% of isolates were either intermediate or resistant to fluconazole (non-*albicans*, 10.0%; *C. albicans*, 1.2%). Overall mortality within 30 days after candidemia was 25.4%.

Invasive fungal diseases in pediatric and neonatal patients are receiving attention with progress in various pediatric fields dealing with immunocompromised populations, such as chemotherapy in malignancies, hematopoietic stem cell or solid organ transplantations, graft-versus-host diseases, inborn errors of immunity, and extremely low birth weight infants. Risk factors vary by studies. *Candida* stands as the most common pathogenic fungi causing invasive infections in humans. Invasive candidiasis causes significant healthcare and economic burden and increases the risk of morbidity and mortality in high-risk patients.[23-26] However, little is known about the situations in children and neonates in Korea. One single-center study included 16 infants with systemic candidiasis. However, it was focused on differences in clinical features of candidiasis by *C. albicans* and *C. parapsilosis*.[18] Another retrospective study included 19 very low birth weight infants with systemic candidiasis and reported that *C. parapsilosis* was the most common isolate. It found a significant difference in gestational age between survivors and died, with a mortality of 21.2%.[20] One retrospective study included 20 neonates and found that *C. albicans* was the predominant pathogen, causing a mortality of 30%.[19] For pediatric populations other than neonates, Yoo et al.[22] have reviewed medical records of 28 patients with candidemia under 14 years of age. Non-*albicans* accounted for 81.5% of all isolates, causing an overall mortality of 25%.[22] Another study by Lee et al.[21] included 39 neonates and infants under 28 months of age and reported that *C. albicans* (56%) was the most common isolate. It showed a tendency of a proportional increase of candidemia due to non-*albicans* species from 13% in 2001 to 91% in 2006.[21] Of previous reports, most were single-center studies and mainly focused on neonates. Our study is the first study on both neonatal and pediatric population in multi-centers with a larger number of patients included.

Comorbidities and risk factors associated with candidemia in neonates and children have been identified in previous studies. In neonates, prematurity has been identified as a major risk factor for candidemia and invasive candidiasis. Other related factors include intensive care unit (ICU) admissions, use of parenteral nutrition, respiratory disease, and mechanical ventilation.[10,27] Hematologic malignancy and neutropenia are frequent predisposing conditions or comorbidities in children. Neurological disease, gastrointestinal disease, solid cancer, congenital heart disease, and use of corticosteroids have also been suggested as additional factors in this population. The presence of central venous catheter and previous antimicrobial therapy tend to be similar in both age groups.[7,10,11,13,27,28] Additionally, Zaoutis et al.[29] have reported risk factors and predictors for candidemia in pediatric ICU (PICU), namely presence of a central venous catheter, malignancy, use of vancomycin or agents against anaerobic organisms. A multi-center study of Greek PICU has found that presence of central venous and urinary catheters, mechanical ventilation, and administration of antibiotics with anti-anaerobic activity are common in patients with candidemia.[12] A

multi-center, laboratory-based surveillance from South Africa noted that available serostatus of maternal human immunodeficiency virus (HIV) was 34% and overall prevalence of HIV infection in study population was 17%, reflecting the regional epidemiologic state of HIV.[15] Our study is comparable to previous studies aforementioned in that prematurity was common in the neonatal group and hematologic/oncologic disease and neurologic diseases were the 1st and 2nd most common diseases in the pediatric group, although specific risk factor analysis was not available.

Overall 30-day mortality in this study was 25.4%. Although it was higher in the neonatal group than in the pediatric group, the difference between the two was not statistically significant. Reported crude mortality of pediatric and neonatal candidemia or invasive candidiasis varies from 8 to 43%.[6,10-15,27,28] Neonates tend to show higher mortality than other age groups in most studies. Hsu et al.[13] have reported that neonates have a significantly longer duration of candidemia, higher rates of septic shock, sepsis-attributable mortality, and in-hospital mortality. However, a prospective study conducted by the International Pediatric Fungal Network on 196 children and 25 neonates with invasive candidiasis from 42 sites in the US and elsewhere has found that the mortality of pediatric patients is higher than that of neonates (19% vs. 8%).[28] It also stated that 84% of deaths among pediatric patients seemed to result from complications due to underlying diseases or infection other than candidiasis. Santolaya et al.[10] have demonstrated that renal disease and receipt of corticosteroids are independent predictors of 30-day mortality in children based on a multivariate analysis. Shuping et al.[15] have reported a high mortality rate (43%) in both neonates and adolescents and lower mortality rates of candidemia due to *C. parapsilosis* than those due to other species.

Our study demonstrated the predominance of non-*albicans* species in the overall and neonatal population, while *C. albicans* was the most common species in the non-neonatal population. In terms of time, *C. albicans* was not predominant in the overall study period except in 2011. Any trend in the distribution of *Candida* species was not noted. Although some studies have pointed out a shift from *C. albicans* to non-*albicans* species,[2,7,15] distributions of species have been reported variously. A multi-center laboratory-based surveillance from South Africa reported a decline in distribution of *C. albicans*, from 41% in 2012–2013 to 33% in 2016–2017.[15] A nationwide cohort study by Lausch et al.[7] also reported a decline in the proportion of *C. albicans*. In addition, the prospective multi-center study from Australia which included 110 children and 33 neonates reported that non-*albicans* were predominant in both populations. *C. albicans* (43.9%) and *C. parapsilosis* (42.4%) were the most common single pathogens in pediatric and neonatal groups, respectively.[27] On the other hand, Piqueras et al.[14] have analyzed patients from NICU, PICU, and pediatric ward and demonstrated the predominance of *C. albicans* in NICU (53%) and *C. parapsilosis* in both PICU (59%) and wards (50%). Other studies also showed that *C. albicans* was the most common isolate, with or without a predominance.[10,11,13,28,30] These differences in species distribution might reflect each center's different epidemiologic and clinical situations related to their microbiologic characteristics, although data on specific relations to each species are not available in epidemiologic studies. Clearly, these various results underlie the importance of continuous monitoring local epidemiology of candidemia and invasive candidiasis.

Species distribution is important because it could affect the resistance pattern to antifungal agents, especially if proportions of species resistant to azole, such as *C. glabrata* and *C. tropicalis*, increased. Compared with those from adults, isolates from children tended to be

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more susceptible to fluconazole due to a prominence of *C. parapsilosis* rather than *C. glabrata*, *C. tropicalis*, or *C. krusei*.[6,10,13,14,27,30,31] In our study, amongst available isolates, 18 (11.2%) were either resistant or dose-dependent susceptible to fluconazole. Non-susceptibility in species other than *C. albicans* was statistically significant. Most of the non-susceptible isolates were *C. parapsilosis* (n = 8, 13.6%). The emergence of fluconazole-resistant *C. parapsilosis* isolates with Y132F mutation in *ERG11* gene has been reported previously in Korean children and neonates.[32] Unlike ours, in a study by Shuping et al.,[15] 55% of *C. parapsilosis* isolates were resistant to fluconazole. Of them, 60% were isolated from neonates. Relatively high resistance of *C. parapsilosis* to fluconazole was similar to our study, although overall resistance to fluconazole was unusually high (35%). This may reflect regional epidemiologic characteristics and spread of resistant clones in or between facilities.[33-35]

This study has some limitations. Firstly, we were not able to establish incidence, partially due to the nature of our study. Besides, due to the lack of comprehensive data on underlying conditions, it was not possible to conduct a risk factor analysis. In patients with more than one comorbidities, we selected only one comorbidity that was likely to be the most representative of each patient or considered more relative to the occurrence of candidemia such as prematurity chosen over congenital heart disease. This might have overestimated or underestimated the contribution of specific underlying conditions to candidemia. Also, as previously suggested by other researchers,[26] since sensitivity of blood culture for candidemia is known to be low traditionally, our study may not represent true cases of candidemia. Secondly, since we did not include matched-controlled group, without candidemia, risk factor analysis for developing candidemia was not performed. The limited number of participating centers may raise concerns about generalizability. However, the authors believe that the data can still reflect national trends in pediatric candidemia to some extent. All the included hospitals were tertiary centers, located in Seoul (one in the southern region and one in the northern), Incheon, southern Gyeonggi Province, and Busan. Lastly, since the chance of discrepancies by laboratory facilities of each institution participated is high, interpretation of antifungal susceptibility may not be standardized. We were unable to collect antifungal susceptibility data for all invasive *Candida* isolates. Only 160 isolates were available from 228 participants. In addition, not all hospitals had antifungal susceptibility data during the study period since the year of introduction for antifungal tests varied among hospitals.

In conclusion, candidemia still remains a high-mortality condition in neonates and children. *Candida* species (i.e., *C. albicans* and *C. parapsilosis*) known to be susceptible to azole conventionally were found to be resistant to azole. Finally, our study highlights the importance of consistent monitoring of candidemia in neonatal and pediatric populations and the pattern of antifungal resistance.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1
Comparison of clinical and microbiological characteristics between 30-day mortality cases and survivals

Supplementary Table 2
Risk factor analysis of 30-day mortality using Cox proportional hazard model

Supplementary Table 3
Yearly proportional trends of each *Candida* species (%) by linear regression

Supplementary Table 4
Distribution of *Candida* species by each center

Supplementary Table 5
Logistic regression model for risk factors of non-*albicans* candidemia

Supplementary Table 6
Subgroup analysis: comparison of infants in each study group by distribution of *Candida* species

Supplementary Table 7
Subgroup analysis: comparison of infants in each study group by underlying conditions

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