International Journal of Infectious Diseases 83 (2019) 49–55

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Changes in the utilization patterns of antifungal agents, medical cost and clinical outcomes of candidemia from the health-care benefit expansion to include newer antifungal agents

Heun Choi[a], Jung Ho Kim[a], Hye Seong[a], Woonji Lee[a], Wooyong Jeong[a], Jin Young Ahn[a], Su Jin Jeong[a], Nam Su Ku[a], Joon Sup Yeom[a], Young Keun Kim[b], Hyo Youl Kim[b], Young Goo Song[a], June Myung Kim[a], Jun Yong Choi[a,*]

[a] Department of Internal Medicine and AIDS Research Institute, Yonsei University College of Medicine, Seoul, Republic of Korea
[b] Department of Internal Medicine, Yonsei University Wonju College of Medicine, Wonju, Republic of Korea

A R T I C L E I N F O

Article history:
Received 21 November 2018
Received in revised form 11 February 2019
Accepted 31 March 2019
Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Candidemia
Health care costs
Hospital mortality
Antifungal agents
Echinocandins

A B S T R A C T

Objectives: In 2014, South Korea expanded its national health insurance coverage to include newer antifungal agents, such as echinocandins. This study aimed to investigate the effects of policy change on the prescription patterns of antifungals, medical costs and clinical outcomes of candidemia.
Methods: This retrospective cohort enrolled hospitalized patients with candidemia at three tertiary care hospitals in South Korea from January 2012 to December 2015. The utilization of antifungal agents, medical costs, length of hospital stay (LOS), and mortality before and after the health-care benefit expansion were compared, and the factors associated with all-cause 28-day mortality during the study period were analyzed.
Results: A total of 769 candidemia cases were identified. The incidence of candidemia did not significantly vary during the study period ($P = 0.253$). The proportion of echinocandins, as the initial antifungal agent, and medical costs associated with candidemia significantly increased since the change in insurance coverage ($P < 0.001$). There was no significant difference in LOS and mortality associated with candidemia before and after the health-care benefit expansion ($P =$ 0.696 and 0.931, respectively). Multivariate logistic regression analysis showed that initial treatment with caspofungin was associated with decreased mortality (adjusted odds ratio: 0.784; 95% confidence interval: 0.681–0.902; reference: fluconazole).
Conclusions: Although the utilization of newer antifungal agents and medical cost for candidemia has significantly increased since the health-care benefit expansion, there has been no change in the outcome of candidemia. However, the further increased use of newer antifungals may improve the outcome of candidemia in this country.

Introduction

Candidemia is a major cause of morbidity and mortality in hospitalized patients worldwide. A multicenter point-prevalence survey identified *Candida* species as the most commonly isolated health-care-associated bloodstream pathogen in the United States (Magill et al., 2014). Particularly, non-albicans *Candida* species constitute larger proportions of candidemia isolates than in the past years (Diekema et al., 2012). Some of these species are relatively less susceptible or resistant to fluconazole (Hope et al., 2002; Playford and Sorrell, 2007). In general, echinocandins are fungicidal against most *Candida* species and resistance is rare (Colombo et al., 2010; Sucher et al., 2009). Echinocandins are now the preferred first-line agents for the treatment of candidemia (Cornely et al., 2012; Pappas et al., 2016). A combined analysis of seven randomized clinical trials showed that initial therapy with an echinocandin was a significant predictor of survival (Andes et al., 2012). A clinical trial comparing the anidulafungin to fluconazole for the treatment of invasive candidiasis showed a

* Corresponding author. Present address: Division of Infectious Diseases, Department of Internal Medicine, Yonsei University College of Medicine, Yonsei University Health System, 50-1, Yonsei-ro, Seodaemun-gu, Seoul 03722, Republic of Korea.
E-mail address: SERAN@yuhs.ac (J.Y. Choi).

https://doi.org/10.1016/j.ijid.2019.03.039
1201-9712/

trend toward more favorable outcomes with anidulafungin compared with fluconazole (Reboli et al., 2007). Accordingly, the use of echinocandins has significantly increased in many hospitals (Forrest et al., 2008).

In South Korea, the national health insurance did not cover newer antifungal agents, such as echinocandins, voriconazole, or liposomal amphotericin B, as the first-line treatment for invasive fungal disease until December 2013 because of the higher prices of these agents. Therefore, fluconazole or amphotericin B deoxycholate was used as initial antifungal agent for *Candida* infection (Cornely et al., 2012). However, the national health insurance coverage has been changed, and echinocandins for the treatment of critically ill patients with invasive candidiasis have been covered since January 2014.

This study aimed to investigate (1) the effects of the change of national health insurance coverage on the prescription patterns of antifungals and medical costs and clinical outcomes of candidemia and (2) the risk factors for the 28-day mortality in patients with candidemia in Korean hospitals.

Materials and methods

Study design and subjects

This retrospective cohort study enrolled patients with candidemia at 3 tertiary teaching hospitals (Severance Hospital, Seoul, 2400 beds; Gangnam Severance Hospital, Seoul, 810 beds; Wonju Severance Christian Hospital, Wonju, 850 beds) in South Korea from January 2012 to December 2015. All patients aged $\geq$18 years with candidemia were screened via the microbiological database of each hospital, and electronic medical records of the cases were reviewed. The primary objective of this study was to investigate the change in utilization of antifungal agents and medical costs and clinical outcomes of candidemia since the change in national health insurance coverage for antifungal agents in 2014. Clinical outcomes were evaluated according to length of hospital stay since candidemia and 28-day all-cause mortality. In addition, we evaluated the risk factors for 28-day mortality of candidemia with a multivariable logistic regression model. This study was performed with the approval by the Institutional Review Board of Severance Hospital (4-2015-1095). Written informed consent was waived owing to the retrospective nature of the study.

Data collection and definitions

For calculating the incidence of candidemia, total inpatient days per year were obtained from administrative database of each hospital. The clinical data collected for each patient included sex, date of culture, *Candida* species, admission wards at the time of culture, presence of CVC, total parenteral nutrition, Charlson Comorbidity Index at the time of admission, SOFA score at the onset of candidemia, antifungal agents, length of hospital stay since candidemia, and survival data. The presence of the following comorbid conditions was documented: cardiovascular disorder, central nervous system disorder, solid cancer, hematologic malignancy, trauma; renal disease, liver disease, lung disease, organ transplant, connective tissue disease, metabolic disease, HIV infection, and hematologic disorder.

Candidemia was defined as the presence of at least one positive blood culture for *Candida* species in a patient with clinical signs and symptoms of sepsis. In case of several episodes of *Candida* infection for a given patient, only data on the first occurrence of candidemia were obtained. Patients who were not treated with antifungal agents were excluded.

Calculation of medical costs for candidemia

Candidemia-related costs were captured to calculate direct medical costs, which were inflated to 2015 prices. Including both the costs covered by the national insurance and those not covered, each resource cost was calculated according to the medical fee schedules of the Korea Health Insurance Review and Assessment Service, 2015. To capture the medical costs only from candidemia, the following approach has been used: (1) for hospitalization costs, (1.1) only costs from the day of initiation of antifungal treatment were included; (1.2) costs for complication of candidemia and antifungal treatment were included; and (1.3) direct costs for other comorbidities, such as solid cancer and hematologic malignancy, were excluded; (2) for outpatients, costs of medications and procedures confirmed for candidemia were included. All costs were calculated in 2015 Korean currency (KRW) value and then converted into 2015 US dollars (USD) value. The 2015 exchange rate for 1 USD was 1,172.5 KRW.

Statistical analysis

Incidence rates were calculated as the number of candidemia episodes per 1000 inpatient days. Continuous variables were expressed as median and interquartile range (IQR) and were compared using the Student's t-tests or Kruskal-Wallis test, as appropriate. Categorical variables were expressed as proportions and percentages and were compared using Chi-square or Fisher's exact tests. Risk factors for mortality were determined via multivariate logistic regression analysis and adjusted odds ratio (OR) with 95% confidence interval (CI) were calculated. Variables that were associated with mortality in univariate analyses with a P value of < 0.10 were entered into multivariate analysis. All statistical analyses were conducted using SAS version 9.4 (SAS Inc., Cary, NC, USA) as well as R version 3.4.0 (The R Foundation for Statistical Computing, Vienna, Austria), and P value < 0.05 was considered to indicate statistical significance.

Results

Baseline characteristics of patients with candidemia

From 2012 to 2015, 769 candidemia cases were recorded (Table 1). No cases were caused by more than two or more *Candida* species. The incidence of candidemia was 0.155 episodes per 1,000 inpatient days. Of the 769 patients with candidemia, 469 (60.99%) were men, and the median age was 71.56 years (IQR, 61.87–79.93 years). *C. albicans* (43.82%) was the most common isolate, followed by *C. tropicalis* (17.43%), *C. parapsilosis* (15.99%), and *C. glabrata* (16.25%). No significant difference in the incidence ($P = 0.253$) and species distribution ($P = 0.954$) of candidemia was noted during the study period. The median Charlson Comorbidity Index was 3 (IQR, 2–5), and the most common comorbidities were cardiovascular disease (52.93%) and solid tumor (48.89%). Regarding hospitalization ward at the time of diagnosis, 523 (68.01%) patients were admitted to the general wards and 246 (31.99%) in intensive care units. The majority of patients had central venous catheters (CVCs) (66.71%) and were on total parenteral nutrition (70.61%). The severity of illness as assessed according to the Sequential Organ Failure Assessment (SOFA) score was quite similar among the study population of each year ($P = 0.583$).

Initial antifungal regimens and outcomes

Overall, fluconazole (60.60%) and amphotericin B deoxycholate (28.61%) were commonly prescribed as the first-line antifungal agent (Table 2). A small number of echinocandins (10.14%) were

Table 1
Baseline characteristics of patients with candidemia.

	Total (N = 769)	2012 (N = 196)	2013 (N = 199)	2014 (N = 201)	2015 (N = 173)	*P*-value
Age (years), median (IQR)	71.56 (61.87-79.93)	72.04 (61.94-80.91)	73.13 (61.63-79.77)	70.60 (61.96-79.44)	69.99 (61.54-78.21)	0.340
Sex (male), N (%)	469 (60.99%)	129 (65.82%)	121 (60.8%)	116 (57.71%)	103 (59.54%)	0.394
Candida species, N (%)						0.954
C. albicans	337 (43.82%)	88 (44.9%)	94 (47.24%)	80 (39.8%)	75 (43.35%)	
C. tropicalis	134 (17.43%)	36 (18.37%)	29 (14.57%)	41 (20.4%)	28 (16.18%)	
C. parapsilosis	123 (15.99%)	29 (14.8%)	32 (16.08%)	33 (16.42%)	29 (16.76%)	
C. glabrata	125 (16.25%)	28 (14.29%)	31 (15.58%)	33 (16.42%)	33 (19.08%)	
C. krusei	12 (1.56%)	3 (1.53%)	4 (2.01%)	3 (1.49%)	2 (1.16%)	
Others	38 (4.94%)	12 (6.12%)	9 (4.52%)	11 (5.47%)	6 (3.47%)	
Underlying condition, N (%)						
Cardiovascular disorder	407 (52.93%)	97 (49.49%)	122 (61.31%)	98 (48.76%)	90 (52.02%)	**0.046**
CNS disorder	174 (22.63%)	45 (22.96%)	42 (21.11%)	50 (24.88%)	37 (21.39%)	0.799
Solid tumor	376 (48.89%)	102 (52.04%)	82 (41.21%)	112 (55.72%)	80 (46.24%)	0.021
Hematologic malignancy	45 (5.85%)	9 (4.59%)	9 (4.52%)	11 (5.47%)	16 (9.25%)	0.181
Trauma	73 (9.49%)	20 (10.2%)	24 (12.06%)	15 (7.46%)	14 (8.09%)	0.391
Renal disease	211 (27.44%)	51 (26.02%)	60 (30.15%)	56 (27.86%)	44 (25.43%)	0.729
Liver disease	159 (20.68%)	44 (22.45%)	37 (18.59%)	44 (21.89%)	34 (19.65%)	0.755
Lung disease	298 (38.75%)	81 (41.33%)	79 (39.7%)	70 (34.83%)	68 (39.31%)	0.583
Organ transplant	27 (3.51%)	4 (2.04%)	7 (3.52%)	7 (3.48%)	9 (5.2%)	0.438
Connective tissue disease	48 (6.24%)	15 (7.65%)	8 (4.02%)	11 (5.47%)	14 (8.09%)	0.313
Metabolic disease	113 (14.69%)	30 (15.31%)	34 (17.09%)	25 (12.44%)	24 (13.87%)	0.599
HIV infection	3 (0.39%)	0 (0%)	3 (1.51%)	0 (0%)	0 (0%)	**0.045**
Hematologic disorder	146 (18.99%)	33 (16.84%)	29 (14.57%)	43 (21.39%)	41 (23.7%)	0.095
Charlson comorbidity index, median (IQR)	3.00 (2.00–5.00)	3.00 (2.00–5.00)	3.00 (2.00–5.00)	3.00 (2.00–6.00)	3.00 (2.00–5.00)	0.342
SOFA score, median (IQR)	3.00 (1.00–6.00)	3.00 (1.00–6.00)	4.00 (1.00–6.00)	4.00 (1.00–6.00)	4.00 (1.00–6.00)	0.583
CVC, N (%)	513 (66.71%)	123 (62.76%)	126 (63.32%)	139 (69.15%)	125 (72.25%)	0.148
TPN, N (%)	543 (70.61%)	144 (73.47%)	133 (66.83%)	148 (73.63%)	118 (68.21%)	0.320
ICU, N (%)	246 (31.99%)	58 (29.59%)	63 (31.66%)	57 (28.36%)	68 (39.31%)	0.112
Incidence of candidemia per 1,000 inpatient days	0.155	0.160	0.163	0.163	0.136	0.253

Abbreviations: CNS, central nervous system; CVC, central venous catheter; HIV, human immunodeficiency virus; ICU, intensive care unit; IQR, interquartile range; SD, standard deviation; SOFA, Sequential Organ Failure Assessment; TPN, total parenteral nutrition.

prescribed for initial treatment, the majority of which included caspofungin (9.10%). Among 70 patients treated with caspofungin, 47 (67.14%) cases were identified as non-albicans *Candida* infection, and 18 (25.71%) cases were *C. glabrata* and *C. krusei* infections. Three patients were initially treated with itraconazole, which was not started for candidemia. One patient was receiving itraconazole for oral candidiasis before the diagnosis of candidemia, and the other two patients were already on itraconazole for treatment of aspergillosis. The median length of stay (LOS) since the onset of candidemia was 17 days (IQR, 7–34 days), and the overall 28-day mortality was 38.88%. During the study period, the rate of echinocandin use as the initial antifungal regimen significantly increased from 1.53% in 2012 to 18.5% in 2015 ($P < 0.001$). LOS significantly increased from 15 days in 2012 to 20 days in 2015 ($P = 0.044$), and 28-day mortality slightly decreased with marginal significance from 38.27% in 2012 to 31.79% in 2015 ($P = 0.067$). Overall, the direct medical cost per one candidemia case was 7,295 USD (IQR, 3,887–14,190 USD), of which 500 USD (IQR, 141–2,252 USD) accounted for the cost of antifungal agent. The cost significantly increased every year ($P < 0.001$).

Changes before and after the health-care benefit expansion

We compared the changes in initial antifungal regimens, clinical outcomes, and medical costs of candidemia before (2012, 2013) and after (2014, 2015) the health-care benefit expansion to include echinocandins (Table 3). The initial prescription of echinocandins significantly increased from 2.28% to 18.45%

Table 2
Initial antifungal regimens, clinical outcomes, and medical costs of candidemia cases.

	total (N = 769)	2012 (N = 196)	2013 (N = 199)	2014 (N = 201)	2015 (N = 173)	*P*-value
Initial antifungal regimens, N (%)						**<0.001**
Amphotericin B deoxycholate	220 (28.61%)	69 (35.20%)	80 (40.20%)	51 (25.37%)	20 (11.56%)	
Fluconazole	466 (60.60%)	123 (62.76%)	112 (56.28%)	113 (56.22%)	118 (68.21%)	
Caspofungin	70 (9.10%)	3 (1.53%)	6 (3.02%)	33 (16.42%)	26 (16.56%)	
Anidulafungin	5 (0.65%)	0 (0%)	0 (0%)	2 (1.00%)	2 (1.27%)	
Micafungin	3 (0.39%)	0 (0%)	0 (0%)	2 (1.00%)	1 (0.64%)	
Voriconazole	2 (0.26%)	0 (0%)	0 (0%)	0 (0%)	2 (1.27%)	
Itraconazole	3 (0.39%)	1 (0.51%)	1 (0.50%)	0 (0%)	1 (0.64%)	
Initial antifungal regimens category						**<0.001**
Echinocandin	78 (10.14%)	3 (1.53%)	6 (3.02%)	37 (18.41%)	32 (18.50%)	
Non-echinocandin	691 (89.86%)	193 (98.47%)	193 (96.98%)	164 (81.59%)	141 (81.50%)	
Length of hospital stay since candidemia, days (IQR)	17.00 (7.00-34.00)	15.00 (7.00– 29.25)	18.00 (8.00–36.00)	15.00 (7.00– 29.50)	20.00 (8.00– 42.00)	**0.044**
28-day mortality, N (%)	299 (38.88%)	75 (38.27%)	78 (39.2%)	91 (45.27%)	55 (31.79%)	0.067
Medical costs per case, USD (IQR)	7,295 (3,887–14,190)	5,591 (3,038–10,821)	6,522 (3,958–12,842)	7,331 (3,694–13,683)	10,413 (5,671–19,089)	**<0.001**
Cost for antifungals per case, USD (IQR)	500 (141–2,252)	282 (112–746)	312 (127–840)	619 (158–3,522)	1,432 (383–4,602)	**<0.001**

1 US Dollar = 1,172.5 Korean Won.
USD, US dollar; IQR, interquartile range.
Significant variables are reflected in bold.

($P < 0.001$) and the resulting costs for antifungals rose from 288 USD to 909 USD ($P < 0.001$). Direct medical costs per case, including costs for antifungals, also rose significantly from 5,905 USD to 8,424 USD ($P = 0.001$), but LOS and 28-day mortality did not show any significant difference. The median LOS (17.0 days vs. 17.0 days, $P = 0.696$) and 28-day mortality (38.73% vs. 39.04%, $P = 0.931$) were not significantly different.

Risk factors of mortality in patients with candidemia

Univariate analysis showed that history of trauma, renal disease, liver disease, lung disease, and hematologic disorder; an increased Charlson Comorbidity Index; higher SOFA score; presence of CVC; and ICU stay at the onset of candidemia were significantly associated with 28-day mortality (Table 4). *C. parapsilosis* infection and initial treatment with fluconazole and caspofungin were associated with better outcomes. Meanwhile, multivariate logistic regression analysis showed that increased Charlson comorbidity index (AOR: 1.184; 95% CI: 1.093–1.282) and higher SOFA score (AOR: 1.228; 95% CI: 1.167–1.292) were independent risk factors associated with 28-day mortality (Table 5). *C. parapsilosis* species (AOR: 0.522; 95% CI: 0.304–0.897; reference: *C. albicans*) and initial treatment with caspofungin (AOR: 0.784; 95% CI: 0.681–0.902; reference: fluconazole) were associated with decreased 28-day mortality.

Discussion

In this study, the incidence of candidemia appeared to be constant, ranging from 0.136 to 0.163 per 1,000 inpatient days since 2012. It is similar to the incidence in recent studies, and nearly 10 times higher than a previous study in 2004 (Huh et al., 2017; Lee et al., 2007; Shin et al., 2004; Won et al., 2015). Regarding the species distribution, *C. albicans* remained the most prevalent species, whereas non-*albicans* species accounted for more than 50% of candidemia cases. We found that as members of the non-*albicans Candida* species, the frequency of *C. glabrata* and *C. krusei*, known to be resistant to azoles, has increased from 11.3 to 16.3% and 0.5 to 1.7%, respectively, compared to previous studies (Jung et al., 2010; Lee et al., 2007). Although caspofungin was approved by the Korean Food and Drug Administration in 2001, there were cost-related barriers to its prescription because the total drug costs could not be covered by the national health insurance before the policy change (Kim and Kang, 2010). After the change in national health insurance coverage for newer antifungal agents, the patient's out-of-pocket share was reduced to 20% of the overall cost. Since 2014, the prescription of echinocandins, particularly caspofungin, has significantly increased, and the annual cost for antifungals per case has more than doubled from 619 USD to 1,432 USD.

Direct medical costs increased annually, with the highest in 2015. This might be attributed to the longer LOS and higher proportion of ICU patients. The cost of hospital stay per day for ICU admission is approximately five times higher than that for general ward admission in Korea (Cornely et al., 2012). Because we did not analyze each resource cost except for the antifungals, it is hard to identify resources associated with the cost increase. However, because costs of resources covered by the national insurance were fixed, out-of-pocket expenditure, increasing annually, seemed to be one of the major reasons of the costs increase (Organisation for Economic Co-operation and Development, 2017).

Although the costs have increased significantly, clinical outcomes such as LOS and mortality did not differ from before the policy change. Several studies have reported that inappropriate antifungal therapy (i.e., inadequate antifungal dosage, delayed antifungal therapy, or administration of antifungals to resistant isolates) increases LOS and costs (Arnold et al., 2010; Cornely et al., 2012; Zilberberg et al., 2010). However, only the effects on the outcomes of changes in prescription pattern of antifungals were assessed in this study. In addition, the frequency of echinocandin prescription has increased, but the number was not large.

We found several factors associated with 28-day mortality; of these, Charlson Comorbidity Index and SOFA score as mortality predictors were similar in previous studies (Chen et al., 2013; Kim et al., 2013; Luzzati et al., 2016). By contrast, factors associated with low mortality were *C. parapsilosis* candidemia and initial treatment with caspofungin. The association of *C. parapsilosis* with lower risk of mortality in bloodstream infection has been reported (Chen et al., 2013). Previous studies have reported decreased in vitro activity of echinocandin to *C. parapsilosis* and persistent candidemia due to *C. parapsilosis* in patients treated with echinocandin (Bassetti et al., 2013; Forrest et al., 2008; Mora-Duarte et al., 2002). However, a recent observational study of patients with *C. parapsilosis* candidemia showed no difference in outcome between patients treated with echinocandins and those treated with other antifungals (Fernandez-Ruiz et al., 2014). Therefore, the current treatment guidelines do not recommend fluconazole over echinocandins for *C. parapsilosis* (Pappas et al., 2016).

Fluconazole remains an effective antifungal agent, especially for *C. albicans* infection. However, among the *C. albicans* isolates in our study, 205 cases were testing antifungal susceptibility interpreted by the Clinical and Laboratory Standards Institute (CLSI) M27-A3 guidelines, while eight (3.90%) cases of fluconazole resistance and four (1.95%) cases of dose-dependent susceptibility were reported. Considering how fluconazole resistance was not reported in a multicenter study in 2011, this was an alarming result (Won et al., 2015). Among 231 non-albicans *Candida* isolates, fluconazole resistance and dose-dependent susceptibility were reported in 15 (6.49%) and 41 (17.7%), respectively ($P < 0.001$). The increase in non-albicans *Candida* infection, which is considered to be due to the increased use of fluconazole, has been reported in several studies (Diekema et al., 2012; Teo et al., 2017). Empirical or pre-emptive echinocandin therapy is preferred especially in critically ill patients who are at risk of exposure to azole or colonization of azole-resistant species (Cornely et al., 2012; Pappas et al., 2016). Although it is not clear whether empirical or pre-emptive antifungal therapy reduces mortality in invasive candidiasis in critically ill patients, recent studies have reported that this policy is

Table 3
Changes in initial antifungal regimens, clinical outcomes, and medical costs of candidemia cases before and after the health-care benefit expansion.

	Total (N = 769)	Before (2012, 2013) (N = 395)	After (2014, 2015) (N = 374)	*P*-value
Initial antifungal regimens category, N (%)				<**0.001**
Echinocandin	78 (10.14%)	9 (2.28%)	69 (18.45%)	
Non-echinocandin	691 (89.86%)	386 (97.72%)	305 (81.55%)	
Length of hospital stay since candidemia, days (IQR)	17.00 (7.00–34.00)	17.00 (7.25–32.75)	17.00 (7.00–36.00)	0.696
28-day mortality, N (%)	299 (38.88%)	153 (38.73%)	146 (39.04%)	0.931
Medical costs per case, USD (IQR)	7,295 (3,887–14,190)	5,905 (3,541–12,449)	8,424 (4,408–15,448)	**0.001**
Cost for antifungals per case, USD (IQR)	500 (141–2,252)	288 (119–824)	909 (232–4,072)	<**0.001**

USD, US dollar; IQR, interquartile range.

Table 4
Univariate analysis of factors associated with 28-day mortality.

	Total (N = 769)	Survival (N = 470)	Non-survival (N = 299)	OR (95% CI)	*P*-value
Age (years), median (IQR)	71.56 (61.87, 79.93)	71.17 (61.44, 79.90)	72.09 (61.98, 79.97)	1.008 (0.998–1.018)	0.122
Sex, N (%)					
Female	300 (39.01%)	195 (41.49%)	105 (35.12%)	Reference	
Male	469 (60.99%)	275 (58.51%)	194 (64.88%)	1.310 (0.970–1.769)	0.078
Species, N (%)					
C. albicans	337 (43.82%)	201 (42.77%)	136 (45.48%)	Reference	
C. tropicalis	134 (17.43%)	74 (15.74%)	60 (20.07%)	1.198 (0.800–1.795)	0.380
C. parapsilosis	123 (15.99%)	92 (19.57%)	31 (10.37%)	0.498 (0.314–0.790)	**0.003**
C. glabrata	125 (16.25%)	72 (15.32%)	53 (17.73%)	1.088 (0.718–1.649)	0.691
C. krusei	12 (1.56%)	7 (1.49%)	5 (1.67%)	1.056 (0.328–3.395)	0.928
Others	38 (4.94%)	24 (5.11%)	14 (4.68%)	0.862 (0.431–1.726)	0.675
Cardiovascular disorder, N (%)					
No	362 (47.07%)	217 (46.17%)	145 (48.49%)	Reference	
Yes	407 (52.93%)	253 (53.83%)	154 (51.51%)	0.911 (0.681–1.218)	0.529
CNS disorder, N (%)					
No	595 (77.37%)	358 (76.17%)	237 (79.26%)	Reference	
Yes	174 (22.63%)	112 (23.83%)	62 (20.74%)	0.836 (0.589–1.188)	0.318
Solid tumor, N (%)					
No	393 (51.11%)	243 (51.7%)	150 (50.17%)	Reference	
Yes	376 (48.89%)	227 (48.3%)	149 (49.83%)	1.063 (0.796–1.421)	0.678
Hematologic malignancy, N (%)					
No	724 (94.15%)	445 (94.68%)	279 (93.31%)	Reference	
Yes	45 (5.85%)	25 (5.32%)	20 (6.69%)	1.276 (0.696–2.341)	0.430
Trauma, N (%)					
No	696 (90.51%)	417 (88.72%)	279 (93.31%)	Reference	
Yes	73 (9.49%)	53 (11.28%)	20 (6.69%)	0.564 (0.330–0.964)	**0.036**
Renal disease, N (%)					
No	558 (72.56%)	367 (78.09%)	191 (63.88%)	Reference	
Yes	211 (27.44%)	103 (21.91%)	108 (36.12%)	2.015 (1.461–2.779)	<**0.001**
Liver disease, N (%)					
No	610 (79.32%)	387 (82.34%)	223 (74.58%)	Reference	
Yes	159 (20.68%)	83 (17.66%)	76 (25.42%)	1.589 (1.117–2.260)	**0.010**
Lung disease, N (%)					
No	471 (61.25%)	309 (65.74%)	162 (54.18%)	Reference	
Yes	298 (38.75%)	161 (34.26%)	137 (45.82%)	1.623 (1.206–2.184)	**0.001**
Organ transplant, N (%)					
No	742 (96.49%)	452 (96.17%)	290 (96.99%)	Reference	
Yes	27 (3.51%)	18 (3.83%)	9 (3.01%)	0.779 (0.345–1.758)	0.548
Connective tissue disease, N (%)					
No	721 (93.76%)	438 (93.19%)	283 (94.65%)	Reference	
Yes	48 (6.24%)	32 (6.81%)	16 (5.35%)	0.774 (0.417–1.436)	0.417
Metabolic disease, N (%)					
No	656 (85.31%)	401 (85.32%)	255 (85.28%)	Reference	
Yes	113 (14.69%)	69 (14.68%)	44 (14.72%)	1.003 (0.666–1.510)	0.989
HIV infection, N (%)					
No	766 (99.61%)	468 (99.57%)	298 (99.67%)	Reference	
Yes	3 (0.39%)	2 (0.43%)	1 (0.33%)	0.785 (0.071–8.698)	0.844
Hematologic disorder, N (%)					
No	623 (81.01%)	394 (83.83%)	229 (76.59%)	Reference	
Yes	146 (18.99%)	76 (16.17%)	70 (23.41%)	1.585 (1.102–2.279)	**0.013**
Charlson Comorbidity Index, median (IQR)	3.00 (2.00, 5.00)	3.00 (2.00, 5.00)	4.00 (2.00, 6.00)	1.178 (1.097–1.264)	<**0.001**
SOFA score, median (IQR)	3.00 (1.00, 6.00)	2.00 (1.00, 5.00)	5.00 (3.00, 8.00)	1.254 (1.197–1.314)	<**0.001**
CVC, N (%)					
No	256 (33.29%)	176 (37.45%)	80 (26.76%)	Reference	
Yes	513 (66.71%)	294 (62.55%)	219 (73.24%)	1.639 (1.194–2.250)	**0.002**
CVC removal, N (%)					
No	562 (73.08%)	342 (72.77%)	220 (73.58%)	Reference	
Yes	207 (26.92%)	128 (27.23%)	79 (26.42%)	0.959 (0.691–1.331)	0.804
TPN, N (%)					
No	226 (29.39%)	148 (31.49%)	78 (26.09%)	Reference	
Yes	543 (70.61%)	322 (68.51%)	221 (73.91%)	1.302 (0.943–1.799)	0.109
ICU, N (%)					
GW	523 (68.01%)	345 (73.4%)	178 (59.53%)	Reference	
ICU	246 (31.99%)	125 (26.6%)	121 (40.47%)	1.876 (1.378–2.554)	<**0.001**
Initial antifungal regimens, N (%)					
Fluconazole	466 (60.60%)	297 (63.19%)	169 (56.52%)	Reference	
Amphotericin B deoxycholate	220 (28.61%)	117 (24.89%)	103 (34.45%)	1.555 (1.107–2.185)	**0.011**
Caspofungin	70 (9.10%)	47 (10.00%)	23 (7.69%)	0.788 (0.445–1.393)	0.412
Anidulafungin	5 (0.65%)	3 (0.64%)	2 (0.67%)	1.103 (0.106–11.516)	0.935
Micafungin	3 (0.39%)	3 (0.64%)	0 (0.00%)	0.263 (0.009–8.087)	0.445

Table 4 (*Continued*)

	Total (N = 769)	Survival (N = 470)	Non-survival (N = 299)	OR (95% CI)	*P*-value
Voriconazole	2 (0.26%)	2 (0.43%)	0 (0.00%)	0.368 (0.009–15.233)	0.599
Itraconazole	3 (0.39%)	1 (0.21%)	2 (0.67%)	3.064 (0.293–31.990)	0.350
Initial antifungal regimen category, N (%)					
Echinocandins	78 (10.14%)	53 (11.28%)	25 (8.36%)	Reference	
Non-echinocandins	691 (89.86%)	417 (88.72%)	274 (91.64%)	1.573 (0.914-2.706)	0.102

ICU, intensive care unit; OR, odds ratio; CI, confidence interval; SOFA, Sequential Organ Failure Assessment; CVC, central venous catheter; TPN, total parenteral nutrition; GW, general ward.

Table 5
Multivariate logistic regression analysis of factors associated with 28-day mortality.

Variable	Adjusted OR (95% CI)	*P*-value
Species		
C. albicans	Reference	
C. tropicalis	1.223 (0.758–1.973)	0.409
C. parapsilosis	0.522 (0.304–0.897)	**0.019**
C. glabrata	1.127 (0.696–1.827)	0.627
C. krusei	0.988 (0.282–3.466)	0.985
Others	0.814 (0.385–1.721)	0.590
Charlson comorbidity index	1.184 (1.093–1.282)	<**0.001**
SOFA score	1.228 (1.167–1.292)	<**0.001**
Initial antifungal regimens		
Fluconazole	Reference	
Amphotericin B deoxycholate	1.036 (0.993–1.080)	0.099
Caspofungin	0.784 (0.681–0.902)	**0.001**
Anidulafungin	1.071 (0.062–18.417)	0.962
Micafungin	0.734 (0.031–17.547)	0.848
Voriconazole	0.219 (0.000–180.732)	0.658
Itraconazole	2.132 (0.142–31.894)	0.583

OR, odds ratio; CI, confidence interval; SOFA, Sequential Organ Failure Assessment.

effective in prevention of proven candidiasis (Ostrosky-Zeichner et al., 2014; Timsit et al., 2016). In a prospective multicenter study, early empirical antifungal therapy was associated with better prognosis in combination with catheter removal (Puig-Asensio et al., 2014). In this study, only caspofungin was associated with low mortality, but if the use of other echinocandins is increased, similar results will be obtained. Accordingly, the importance of echinocandins is expected to increase, but attention is required because of higher cost and resistance emergence (Cho et al., 2015). A step-down antifungal therapy after the patient has clinically stabilized should be considered (Cornely et al., 2012; Pappas et al., 2016).

This study had several limitations due its retrospective nature. First, because the costs of each resource were not included in the analysis, the effect of each resource cost on the overall cost increase could not be determined. Second, factors that might affect clinical outcomes were not included such as adequacy of antifungal dose, complication incidence of each antifungal, switch to second-line agents, and time to CVC removal. Third, because the 2015 mortality rate was the lowest in the study period, meaningful results may have been obtained if the study was conducted over a wider period.

Conclusion

In conclusion, although the utilization of echinocandins and medical cost for candidemia have significantly increased since the health-care benefit expansion, there has been no change in the outcome of candidemia during the study period. However, we may expect the further increased use of newer antifungals will improve the outcome of candidemia in this country. Further studies on the cost-effectiveness of antifungal agents should be performed in various settings of each country.

Funding source

This work was supported by a grant from the Ministry of Health & Welfare, Republic of Korea (grant number: HI14C1324), and a faculty research grant of Yonsei University College of Medicine (6-2015-0153).

Conflict of interest statement

The authors declare that they have no competing interests.

Ethical approval

This study was performed with the approval by the Institutional Review Board of Severance Hospital (4-2015-1095). Written informed consent was waived owing to the retrospective nature of the study.

Contributions

HC acquired, analyzed and interpreted the data, drafted and revised the manuscript, and approved the final manuscript as submitted. JYC conceptualized and designed the study, and is responsible for the content of the manuscript, including the data and analysis. JHK, HS, WL, WJ, YKK, HYK and YGS collected data, interpreted data, revised and approved the manuscript. JYA, SJJ, NSK, JSY and JMK interpreted data, revised and approved the final manuscript.

References

Andes DR, Safdar N, Baddley JW, Playford G, Reboli AC, Rex JH, et al. Impact of treatment strategy on outcomes in patients with candidemia and other forms of invasive candidiasis: a patient-level quantitative review of randomized trials. Clin Infect Dis 2012;54(8):1110–22.

Arnold HM, Micek ST, Shorr AF, Zilberberg MD, Labelle AJ, Kothari S, et al. Hospital resource utilization and costs of inappropriate treatment of candidemia. Pharmacotherapy 2010;30(4):361–8.

Bassetti M, Merelli M, Righi E, Diaz-Martin A, Rosello EM, Luzzati R, et al. Epidemiology, species distribution, antifungal susceptibility, and outcome of candidemia across five sites in Italy and Spain. J Clin Microbiol 2013;51 (12):4167–72.

Chen LY, Kuo SC, Wu HS, Yang SP, Chan YJ, Chen LK, et al. Associated clinical characteristics of patients with candidemia among different Candida species. J Microbiol Immunol Infect 2013;46(6):463–8.

Cho EJ, Shin JH, Kim SH, Kim HK, Park JS, Sung H, et al. Emergence of multiple resistance profiles involving azoles, echinocandins and amphotericin B in *Candida glabrata* isolates from a neutropenia patient with prolonged fungaemia. J Antimicrob Chemother 2015;70(4):1268–70.

Colombo AL, Ngai AL, Bourque M, Bradshaw SK, Strohmaier KM, Taylor AF, et al. Caspofungin use in patients with invasive candidiasis caused by common non-albicans Candida species: review of the caspofungin database. Antimicrob Agents Chemother 2010;54(5):1864–71.

Cornely OA, Bassetti M, Calandra T, Garbino J, Kullberg BJ, Lortholary O, et al. ESCMID guideline for the diagnosis and management of Candida diseases 2012: non-neutropenic adult patients. Clin Microbiol Infect 2012;18 Suppl 7:19–37.

Diekema D, Arbefeville S, Boyken L, Kroeger J, Pfaller M. The changing epidemiology of healthcare-associated candidemia over three decades. Diagn Microbiol Infect Dis 2012;73(1):45–8.

Fernandez-Ruiz M, Aguado JM, Almirante B, Lora-Pablos D, Padilla B, Puig-Asensio M, et al. Initial use of echinocandins does not negatively influence outcome in *Candida parapsilosis* bloodstream infection: a propensity score analysis. Clin Infect Dis 2014;58(10):1413–21.

Forrest GN, Weekes E, Johnson JK. Increasing incidence of *Candida parapsilosis* candidemia with caspofungin usage. J Infect 2008;56(2):126–9.
Hope W, Morton A, Eisen DP. Increase in prevalence of nosocomial non-*Candida albicans* candidaemia and the association of *Candida krusei* with fluconazole use. J Hosp Infect 2002;50(1):56–65.
Huh K, Ha YE, Denning DW, Peck KR. Serious fungal infections in Korea. Eur J Clin Microbiol Infect Dis 2017;36(6):957–63.
Jung S-I, Shin JH, Song J-H, Peck KR, Lee K, Kim M-N, et al. Multicenter surveillance of species distribution and antifungal susceptibilities of Candida bloodstream isolates in South Korea. Med Mycol 2010;48(4):669–74.
Kim SH, Yoon YK, Kim MJ, Sohn JW. Clinical impact of time to positivity for Candida species on mortality in patients with candidaemia. J Antimicrob Chemother 2013;68(12):2890–7.
Kim SI, Kang MW. Current usage and prospect of new antifungal agents in Korea. Infect Chemother 2010;42(4):209–15.
Lee JS, Shin JH, Lee K, Kim MN, Shin BM, Uh Y, et al. Species distribution and susceptibility to azole antifungals of Candida bloodstream isolates from eight university hospitals in Korea. Yonsei Med J 2007;48(5):779–86.
Luzzati R, Merelli M, Ansaldi F, Rosin C, Azzini A, Cavinato S, et al. Nosocomial candidemia in patients admitted to medicine wards compared to other wards: a multicentre study. Infection 2016;44(6):747–55.
Magill SS, Edwards JR, Bamberg W, Beldavs ZG, Dumyati G, Kainer MA, et al. Multistate point-prevalence survey of health care-associated infections. N Engl J Med 2014;370(13):1198–208.
Mora-Duarte J, Betts R, Rotstein C, Colombo AL, Thompson-Moya L, Smietana J, et al. Comparison of caspofungin and amphotericin B for invasive candidiasis. N Engl J Med 2002;347(25):2020–9.
Organisation for Economic Co-operation and Development. Health spending. OECD; 2017 Available at: https://data.oecd.org/healthres/health-spending.htm. [Accessed 21 August 2018].
Ostrosky-Zeichner L, Shoham S, Vazquez J, Reboli A, Betts R, Barron MA, et al. MSG-01: a randomized, double-blind, placebo-controlled trial of caspofungin prophylaxis followed by preemptive therapy for invasive candidiasis in high-risk adults in the critical care setting. Clin Infect Dis 2014;58(9):1219–26.
Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis 2016;62(4):e1–50.
Playford EG, Sorrell TC. Optimizing therapy for Candida infections. Semin Respir Crit Care Med 2007;28(6):678–88.
Puig-Asensio M, Peman J, Zaragoza R, Garnacho-Montero J, Martin-Mazuelos E, Cuenca-Estrella M, et al. Impact of therapeutic strategies on the prognosis of candidemia in the ICU. Crit Care Med 2014;42(6):1423–32.
Reboli AC, Rotstein C, Pappas PG, Chapman SW, Kett DH, Kumar D, et al. Anidulafungin versus fluconazole for invasive candidiasis. N Engl J Med 2007;356(24):2472–82.
Shin JH, Kim MN, Shin DH, Jung SI, Kim KJ, Cho D, et al. Genetic relatedness among Candida tropicalis isolates from sporadic cases of fungemia in two university hospitals in Korea. Infect Control Hosp Epidemiol 2004;25(8):634–40.
Sucher AJ, Chahine EB, Balcer HE. Echinocandins: the newest class of antifungals. Ann Pharmacother 2009;43(10):1647–57.
Teo JQ, Candra SR, Lee SJ, Chia SY, Leck H, Tan AL, et al. Candidemia in a major regional tertiary referral hospital—epidemiology, practice patterns and outcomes. Antimicrob Resist Infect Control 2017;6:27.
Timsit JF, Azoulay E, Schwebel C, Charles PE, Cornet M, Souweine B, et al. Empirical micafungin treatment and survival without invasive fungal infection in adults with ICU—acquired sepsis, Candida colonization, and multiple organ failure: the EMPIRICUS randomized clinical trial. JAMA 2016;316(15):1555–64.
Won EJ, Shin JH, Choi MJ, Lee WG, Park YJ, Uh Y, et al. Antifungal susceptibilities of bloodstream isolates of Candida species from nine hospitals in Korea: application of new antifungal breakpoints and relationship to antifungal usage. PLoS One 2015;10(2)e0118770.
Zilberberg MD, Kollef MH, Arnold H, Labelle A, Micek ST, Kothari S, et al. Inappropriate empiric antifungal therapy for candidemia in the ICU and hospital resource utilization: a retrospective cohort study. BMC Infect Dis 2010;10:150.