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Impact of First-Line Antifungal Agents on the Outcomes and Costs of Candidemia

Young Eun Ha,[a] Kyong Ran Peck,[a] Eun-Jeong Joo,[a] Shin Woo Kim,[b] Sook-In Jung,[c] Hyun Ha Chang,[b] Kyong Hwa Park,[c] and Sang Hoon Han[d]

Division of Infectious Diseases, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea[a]; Division of Infectious Diseases, Kyungpook National University Hospital, Daegu, Republic of Korea[b]; Division of Infectious Diseases, Chonnam National University Medical School, Gwangju, Republic of Korea[c]; and Division of Infectious Diseases, Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea[d]

***Candida* species are the leading causes of invasive fungal infection among hospitalized patients and are responsible for major economic burdens. The goals of this study were to estimate the costs directly associated with the treatment of candidemia and factors associated with increased costs, as well as the impact of first-line antifungal agents on the outcomes and costs. A retrospective study was conducted in a sample of 199 patients from four university-affiliated tertiary care hospitals in Korea over 1 year. Only costs attributable to the treatment of candidemia were estimated by reviewing resource utilization during treatment. Risk factors for increased costs, treatment outcome, and hospital length of stay (LOS) were analyzed. Approximately 65% of the patients were treated with fluconazole, and 28% were treated with conventional amphotericin B. The overall treatment success rate was 52.8%, and the 30-day mortality rate was 47.9%. Hematologic malignancy, need for mechanical ventilation, and treatment failure of first-line antifungal agents were independent risk factors for mortality. The mean total cost for the treatment of candidemia was $4,743 per patient. Intensive care unit stay at candidemia onset and antifungal switch to second-line agents were independent risk factors for increased costs. The LOS was also significantly longer in patients who switched antifungal agents to second-line drugs. Antifungal switch to second-line agents for any reasons was the only modifiable risk factor of increased costs and LOS. Choosing an appropriate first-line antifungal agent is crucial for better outcomes and reduced hospital costs of candidemia.**

Invasive fungal infections by *Candida* species have become increasingly important worldwide. They are the fourth most common cause of nosocomial bloodstream infections in the United States and the fifth to tenth most common causative pathogen in European studies (1–3, 13). Candidemia is responsible for substantial medical and economic burdens (5). About 33 to 55% of all episodes occur in intensive care units (ICUs) and are associated with high ICU mortality rates and resource use (9, 13, 18). Mortality rates range from 28 to 42% (16, 20), and attributable costs of candidemia range from $35,000 to $68,000 per adult case in the United States (5, 15, 20). Hospitalization charges due to increased length of stay (LOS) are the major driving force behind excess costs. Increased LOS attributable to candidemia is estimated at 10 to 20 days per episode in the United States (5). Antifungal therapy is the next largest cost item, representing up to 10% of total costs in treating candidemia (15). In addition, recent data showed that initial inappropriate antifungal therapy was a major cause of increased LOS and costs as well as poor outcomes, which suggests the importance of appropriate first-line antifungal therapy in the treatment of invasive candidiasis (21).

However, most data in previous studies were from the United States, where the health insurance system, as well as treatment strategies for invasive *Candida* infection differ from those of other countries worldwide. Although the 2009 guidelines for candidemia treatment by the Infectious Diseases Society of America recommend echinocandins as the first-line antifungal agents in the setting of neutropenia or moderate to severe illness (12), these drugs are not widely used worldwide as first-line agents due to their relatively high costs, especially in resource-limited countries (6, 10). Fluconazole is still the most widely used drug, and amphotericin B deoxycholate is also frequently used for broader coverage of candidemia. With scarce data comparing the efficacy and cost-effectiveness of these antifungal agents, additional comparative analyses would add valuable knowledge to this issue. The assessment of the economic burden attributable to the treatment of candidemia and major contributing factors that lead to increased costs are important because better treatment strategies may be justified based on such data.

The primary aims of the present study were to estimate the costs directly associated with the treatment of candidemia and to identify modifiable factors that lead to increased costs. The secondary aim was to assess the clinical impact of first-line antifungal agents on the treatment outcomes of candidemia in terms of mortality, costs, and hospital LOS.

MATERIALS AND METHODS

Study design and patient sample. We designed a retrospective, cost-of-illness study that examined the costs attributable to candidemia in 200 patients treated at four university-affiliated tertiary hospitals in South Korea: Samsung Medical Center and Yonsei University Medical Center in Seoul, Kyungpook National University Hospital in Daegu, and Chonnam National University Hospital in Gwangju. From each hospital, 50 consecutive patients who had candidemia and received antifungal treatment from July 2008 to June 2009 were included in the study. Using the elec-

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Address correspondence to Kyong Ran Peck, krpeck@skku.edu.

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tronic medical record system of each hospital, patients aged 18 years or older with positive blood cultures for *Candida* species were identified. Exclusion criteria were patients who were not treated with antifungal agents or who died too early to receive antifungal agents. One patient was excluded from final data analyses due to coinfection with invasive aspergillosis and recurrent episodes of bacterial sepsis. The study protocol was approved by the local Institutional Review Board of each institution.

Data collection. For all patients, demographic characteristics, baseline clinical characteristics of candidemia episodes, resource utilization during candidemia treatment, length of stay, treatment outcome, and survival data were collected retrospectively. Treatment outcome was assessed as either treatment success or failure. Treatment success was defined as improvement in symptoms and signs of infection or negative conversion of candidemia. Failure was defined as persistence or progression of symptoms and signs of infection, persistent candidemia, a change of antifungal agent due to poor clinical response, or death during antifungal therapy. Survival outcome was measured as 30-day all-cause mortality rate.

Resource utilization. Resource use was measured for all patients and divided into six categories: hospitalization, medication and antifungal drugs, imaging tests, laboratory tests, procedures or surgery, and other medical treatment (dialysis, use of infusion pump, electrocardiogram monitoring, oxygen supply, mechanical ventilation, and consultation). The number of units consumed by each patient was multiplied by the cost per unit of each resource to estimate the direct costs for each patient. Since the four hospitals in the present study are rated as superior general hospitals in Korea, additional 30% of costs are charged for every resource provided (total costs = the number of units consumed × the unit cost × 1.3). The unit cost of each resource was obtained from the health insurance fee schedule of Korea (Korea Health Insurance Review and Assessment Service, 2010), and the medication cost was estimated from the weighted average cost (from 2009). The cost of treating adverse reactions to antifungal therapy was estimated from resource utilization data supplied by the investigators of each institution. All costs were calculated in 2009 Korean currency (KRW) and then converted into 2009 U.S. dollars (US$). The 2009 exchange rate for $1 (hereafter, all dollar values refer to US$) was KRW 1,156.

Although caspofungin and voriconazole were approved by Korean Food and Drug Administration in 2001 and micafungin was approved in 2006 (10), the use of these drugs as first-line agents in the treatment of invasive candidiasis or candidemia was limited due to their higher cost. Fluconazole or amphotericin B deoxycholate is admitted as first-line agents against *Candida* infection in Korea, and echinocandins admitted in the setting of treatment failure or toxicities of which criteria are defined by HIRA (health insurance review and assessment).

Statistical analysis. Continuous variables such as cost, age, and length of hospital stay were expressed either as means and standard deviations (SD) for variables with normal distributions or as medians and ranges for variables with skewed distributions. Categorical variables were expressed as proportions and percentages. Student *t* tests or Mann-Whitney U tests were used to compare continuous variables, and χ^2 or Fisher exact tests were used to compare categorical variables. To define risk factors for mortality, 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. Comparisons of costs for each clinical variable were done using Student *t* tests or Mann-Whitney U tests, and then multiple linear regression analyses were used to define independent drivers for elevated costs. All reported P values were two tailed, and $P < 0.05$ was considered statistically significant. The data analyses were performed using PASW Statistics, version 18.0 (SPSS, Inc., Chicago, IL).

RESULTS

Patient characteristics. A total of 199 patients were included in the analysis: 50 patients from each hospital, except for one hospital from which 49 patients were included (Table 1). Of the 199 patients, 106 (53.3%) were male, and the median age was 68 years (range, 34 to 88 years). The majority of patients (103 patients, 51.8%) had malignancies as underlying diseases. Sixty-eight (34.2%) underwent surgery during the admission before the onset of candidemia. The most common species was *Candida albicans* (90 patients, 45.2%), followed by *C. tropicalis* (51 patients, 25.6%), *C. parapsilosis* (29 patients, 14.6%), and *C. glabrata* (19 patients, 9.5%).

TABLE 1 Baseline characteristics of study population with candidemia

Patient characteristics	Population data ($n = 199$)[a]
Gender, male	106 (53.3)
Median age in yrs (range)	68 (27–88)
Underlying disease	
Cancer	103 (51.8)
Solid tumor	80 (40.2)
Hematologic disease	23 (11.6)
Transplantation	8 (4.0)
Solid organ transplantation	5 (2.5)
Bone marrow transplantation	3 (1.5)
AIDS	1 (0.5)
Surgery	68 (34.2)
Chronic lung disease	40 (20.1)
Cerebrovascular disease	34 (17.1)
Diabetes mellitus	32 (16.1)
ICU-acquired candidemia	72 (36.2)
Need for mechanical ventilation	53 (26.6)
Identified species	
C. albicans	90 (45.2)
C. tropicalis	51 (25.6)
C. parapsilosis	29 (14.6)
C. glabrata	19 (9.5)
Others	10 (5.0)
First-line antifungal agent	
Fluconazole	129 (64.8)
Amphotericin B deoxycholate	56 (28.1)
Liposomal amphotericin B	7 (3.5)
Itraconazole	3 (1.5)
Antifungal switch to second-line agents or more	59 (29.6)
Overall treatment success rate	105 (52.8)
Toxicity during antifungal treatment[b]	
Renal	34 (17.1)
Hepatic	33 (16.6)
Median duration of antifungal therapy in days (range)	15 (1–62)
30-Day mortality[c]	81/169 (47.9)

[a] Data are expressed as the number of patients (%), unless described otherwise in column 1.
[b] Renal toxicity was defined as a ≥1.5-fold increase in the serum creatinine level above the baseline. Hepatic toxicity was defined as a ≥2.5-fold increase in the serum aminotransferase level above the baseline.
[c] A total of 30 patients lost to follow-up before day 30 were excluded.

Treatment outcomes. Fluconazole was most commonly used as a first-line antifungal agent in 130 (65.3%) of the patients, followed by amphotericin B deoxycholate in 61 patients (30.7%), liposomal amphotericin B in 7 patients (3.5%), and itraconazole

TABLE 2 Risk factors for 30-day mortality of candidemia in univariate and multivariate analysis

Patient characteristics	Population data[a]			Multivariate analysis	
	Survival ($n = 88$)	Death ($n = 81$)	P	OR (95% CI)	P
Gender, male	47 (53.4)	42 (51.9)	0.839		
Median age in yrs (range)	68.5 (34–88)	67 (38–85)	0.287		
Underlying disease					
Cancer	42 (47.7)	51 (63.0)	0.047		
Solid tumor	38 (43.2)	32 (39.5)	0.628		
Hematologic disease	4 (4.5)	19 (23.5)	<0.001	5.182 (1.055–25.457)	0.043
Transplantation	3 (3.4)	5 (6.2)	0.482		
Surgery	33 (37.5)	24 (29.6)	0.280		
Diabetes mellitus	11 (12.5)	19 (21.0)	0.138		
Central venous catheterization	41 (46.6)	51 (63.0)	0.033	0.554 (0.165–1.860)	0.339
Acquisition site of candidemia					
General ward	60 (68.2)	43 (53.1)	0.044		
Intensive care unit	28 (31.8)	38 (46.9)			
Candida species					
C. albicans	37 (42.0)	35 (43.2)	0.878		
Non-*albicans Candida*	51 (58.0)	46 (56.8)			
Disease severity					
Need for mechanical ventilation	17 (19.3)	32 (39.5)	0.004	6.761 (2.110–21.659)	0.001
Need for oxygen supply	39 (44.3)	40 (49.4)	0.510		
Need for dialysis	11 (12.5)	14 (17.3)	0.382		
First-line antifungal drug					
Fluconazole	58 (65.9)	47 (58.0)	0.291		
Amphotericin B deoxycholate	25 (28.4)	29 (35.8)	0.303		
Antifungal switch to second-line or more	27 (30.7)	26 (32.1)	0.843		
Treatment failure of first-line antifungal agents[b]	30/88 (34.1)	26/33 (78.8)	<0.001	5.133 (1.780–14.797)	0.002

[a] Data are expressed as the number of patients (%), unless described otherwise in column 1.
[b] A total of 48 patients who died on their first-line antifungal treatment within 30 days were excluded.

in 3 patients (1.5%). The median interval from candidemia onset to the start of antifungal drug treatment was 2 days (range, 0 to 21 days). The median total duration of antifungal agents was 15 days (range, 1 to 62 days). Fifty-nine (29.6%) patients switched to second-line antifungal agents due to treatment failures ($n = 20$), adverse events due to first-line agents ($n = 23$), or other reasons. Renal or hepatic adverse events occurred in 56 (28.1%) patients. Eight (14.3%) patients changed antifungal agents due to renal toxicity, and two (3.6%) patients changed due to hepatic toxicity. The overall treatment success rate was 52.8% (105 of 199 patients), whereas 92 (46.2%) failed antifungal treatment, and 2 were undetermined. The most common reason for treatment failure was death during antifungal treatment (75 of 92 patients, 81.5%).

Of the 199 patients, 30 were lost to follow-up before day 30, with their clinical outcome unknown. Of the 169 patients who were followed up until 30 days from the onset of candidemia, the overall 30-day mortality rate was 47.9% (81 of 169 patients died within 30 days of the onset of candidemia). In univariate analysis, hematologic disease, the presence of central venous catheter, the ICU stay at the onset of candidemia, the need for mechanical ventilation, and treatment failure of first-line antifungal drugs were associated with 30-day mortality (Table 2). Since the definition of first-line treatment failure also included death during antifungal treatment, we excluded patients who died within 30 days of first-line treatment and repeated the analysis. Even after excluding such patients, first-line antifungal treatment failure was a significant risk factor for mortality in univariate analysis. In multivariate analysis, hematologic diseases (OR, 5.18; 95% CI, 1.06 to 25.46; $P = 0.043$), need for mechanical ventilation (OR, 6.76; 95% CI, 2.11 to 21.66; $P = 0.001$), and first-line treatment failure (OR, 5.13; 95% CI 1.78 to 14.80; $P = 0.002$) remained statistically significant risk factors for mortality.

Cost analysis. The mean total hospital costs from the first antifungal therapy until the end of treatment were $4,743 (SD, $7,049) per patient. Hospital stay, antifungal agent, and resources for medical treatment represented the majority of total costs, with each making up a similar proportion (Table 3). Total costs were higher in the setting of ICU onset, central venous catheterization, and antifungal switch to second-line agents or more (Table 4). Age, underlying diseases, *Candida* species, and treatment success were not associated with increased costs. Multiple linear regression analysis showed that ICU onset candidemia and antifungal switch to second-line agents or more were independent risk factors for increased total costs for the treatment of candidemia ($P < 0.001$).

TABLE 3 Total cost for the treatment of candidemia per patient

Resource utilization	Cost (US$)		Proportion (%)
	Mean	SD	
Antifungal agents	1,114	2,585	23.50
Hospital stay	1,089	1,109	23.00
Laboratory tests	581	515	12.20
Imaging	302	500	6.40
Intervention or surgery	141	297	3.00
Other[a]	1,414	3,122	29.80

[a] "Other" includes dialysis, blood transfusion, mechanical ventilation, electrocardiogram monitoring, oxygen supply, consultation, etc.

When we compared the costs between patients who were treated with fluconazole and those who were treated with amphotericin B deoxycholate as first-line antifungal drugs, the mean total costs were not different, nor were the mean daily costs. Looking further into the detailed resource utilization patterns, antifungal drug costs were significantly lower in the amphotericin group, whereas the costs for other medical treatments were significantly higher in the amphotericin group, resulting in a net balance of total costs between the two groups (Table 5).

Length of hospital stay. The median LOS after the treatment of candidemia was 14 days (range, 1 to 62 days). No factors were associated with an increased LOS. Choice of first-line antifungal agent between fluconazole and amphotericin B did not influence LOS, nor did failure of first-line antifungal agents. However, total LOS and ICU LOS were significantly longer in patients who switched their first-line antifungal agents to second-line drugs or more (Table 6).

DISCUSSION

In this retrospective cost-of-illness study of candidemia, the cost of hospitalization, antifungal drugs, and other medical treatments each comprised about 25% of the total costs for the treatment of candidemia, which is in contrast to data from the United States, where costs for hospitalization account for up to 90% of the total costs. Regarding the cost-increasing factors, ICU-onset candidemia and an antifungal switch to second-line agents or more for any reason were associated with increases in the total costs. With regard to the mean daily cost, ICU onset candidemia, hematologic malignancy, the presence of a central venous line, non-*albicans* species, and the failure of first-line antifungal drugs were associated with increases in daily costs. The success of first-line antifungal therapy was found to be the only modifiable cost factor in the present study.

The reason why hospitalization costs in Korea formed a relatively small portion of the total costs being compared to those from the United States can be explained by differences in the healthcare finance systems of the two countries. Korean medical insurance system is public, patients usually pay only a small portion (5 to 20%) of the total costs and the rest is paid by the gov-

TABLE 4 Total cost for the treatment of candidemia per patient

Variable	Subvariable[a]	Cost (US$)					*P*
		Mean	SD	Median	Minimum	Maximum	
Gender	Male ($n = 106$)	4,110	3,927	3,091	112	28,177	0.199
	Female ($n = 93$)	5,463	9,399	2,570	273	61,471	
Age	<60 yrs ($n = 57$)	5,929	10,952	2,671	430	61,471	0.272
	≥60 yrs ($n = 142$)	4,266	4,618	2,753	112	32,660	
Underlying disease	Cancer ($n = 103$)	3,920	3,724	2,558	273	22,490	0.097
	No cancer ($n = 96$)	5,625	9,335	3,091	112	61,471	
Solid tumor vs. hematologic disease	Solid tumor ($n = 80$)	3,703	3,824	2,383	273	22,490	0.274
	Hematologic disease ($n = 23$)	4,672	3,322	3,642	781	11,868	
Candidemia onset	GW onset ($n = 123$)	2,753	2,218	2,172	112	13,022	<0.001
	ICU onset ($n = 76$)	7,962	10,304	5,460	718	61,471	
Candida species	*C. albicans* ($n = 90$)	4,004	4,750	2,576	273	32,660	0.18
	Non-*albicans* ($n = 109$)	5,353	8,466	3,012	112	61,471	
CVC	CVC ($n = 103$)	5,798	7,363	3,537	350	57,690	0.028
	No CVC ($n = 96$)	3,610	6,546	2,377	112	61,471	
Antifungal switch to second-line or more[b]	No switch ($n = 101$)	4,044	3,784	2,895	450	29,476	0.005
	Antifungal switch ($n = 43$)	10,203	13,376	6,429	802	64,305	
First-line antifungal agent	Fluconazole ($n = 129$)	4,292	4,965	2,617	112	32,660	0.696
	Amphotericin B deoxycholate ($n = 56$)	4,010	3,172	2,684	350	11,868	
First-line treatment outcome	Success ($n = 80$)	4,467	6,884	3,204	508	61,471	0.631
	Failure ($n = 118$)	4,960	7,203	2,541	112	57,690	

[a] GW, general ward; CVC, central venous catheterization.
[b] Patients who died within 14 days were excluded from the analysis.

TABLE 5 Comparison of cost between fluconazole ($n = 129$) and amphotericin B deoxycholate ($n = 56$) as a first-line antifungal treatment

Resource utilization	Drug[a]	Cost (US$)					*P*
		Mean	SD	Median	Minimum	Maximum	
Total cost	FLUC	4,292	4,965	2,617	112	32,660	0.696
	AMB	4,010	3,172	2,684	350	11,868	
Total daily cost	FLUC	259	185	199	40	1,166	0.081
	AMB	343	334	218	37	1,750	
Total hospitalization cost	FLUC	1,125	1,072	690	37	5,441	0.491
	AMB	882	703	730	127	3,399	
Antifungal drug cost	FLUC	1,095	1,625	710	37	10,397	<0.001
	AMB	438	459	271	16	2,229	
Lab test	FLUC	544	465	402	10	2,475	0.658
	AMB	574	328	473	41	1,375	
Imaging test cost	FLUC	336	575	176	0	4,568	0.064
	AMB	227	227	166	0	1,043	
Procedures or surgery	FLUC	147	319	19	0	2,318	0.086
	AMB	90	131	24	0	614	
Other medical treatment	FLUC	976	2,426	80	0	17,436	0.045
	AMB	1,732	2,121	501	5	8,632	

[a] FLUC, fluconazole; AMB, amphotericin B deoxycholate.

ernment. Government organizations are responsible for setting the price of medical resources as well. The cost of hospital stay per day in superior general hospitals in Korea was $28.2 for non-ICU ward and $83.7 for ICU, while the cost per day in U.S. hospitals was calculated as $1,383 for the non-ICU ward and $2,726 for the ICU in one study (14). Although hospitalization cost is not a major cost driver here, we consider that increased costs due to a switch to second-line agents might be due to an increased hospital stay (Table 6), and this finding is consistent with data from the United States in that an increase in hospital stay was associated with major costs (5, 15).

The importance of first-line therapy for candidemia has been described in previous studies. Inappropriate initial therapy for candidemia was associated with prolonged LOS and increased costs (1, 21). Significant additional costs and resources use were observed when second-line treatment was required in patients treated with fluconazole (4). The results of the present study support the finding that an antifungal switch to second-line agents or more is a significant cost-increasing factor in Korea, where hospitalization costs are relatively low. Improvements in the appropriate selection of initial antifungal agents by empirical use of echinocandins was even more cost-effective than the use of fluconazole (22) or amphotericin B deoxycholate (19) in model simulation studies, despite the higher costs of echinocandins compared to fluconazole or amphotericin B deoxycholate.

Conflicting data have been published about the relationship between first-line therapy and survival. A prospective case-control study showed that inadequate initial therapy and high APACHE score were independent variables associated with mortality (2), and a retrospective study showed that patients who switched to second-line antifungal had a higher mortality rate (34.5%) than patients without antifungal switch (25.1%) ($P < 0.001$) (4). Another study found that a longer time from culture positivity to antifungal initiation was associated with mortality in cancer patients with candidemia (17). However, two studies found that inappropriate initial therapy was not associated with mortality (1, 11), and one study demonstrated a tendency of lower mortality with appropriate initial therapy (21). In the present study, the failure of first-line antifungal therapy was an independent risk factor for mortality. Although we did not evaluate the appropriateness of initial therapy, our data emphasize the importance of choosing initial antifungal agents with lower probability of failure in order to decrease mortality.

Controversy remains as to which first-line drug is the most cost-effective. Although echinocandins appear to be more cost-

TABLE 6 Comparison of lengths of hospital stay[a]

Facility	First-line treatment regimen			First-line treatment result			Switch to second-line agents or more		
	FLUC	AMB	*P*	Success	Failure	*P*	No switch	Switch	*P*
Hospital stay	19 (4–62)	19 (3–29)	0.593	18 (4–62)	20.5 (3–61)	0.224	18 (3–62)	21 (5–61)	0.037
ICU stay[b]	20 (2–50)	18 (1–29)	0.594	16.5 (2–52)	33 (1–61)	0.002	19 (2–44)	29 (1–61)	0.009

[a] Data are median numbers of days (range). FLUC, fluconazole; AMB, amphotericin B deoxycholate. Patients who died within 30 days of treatment were excluded from the analysis.

[b] Patients who never stayed in the ICU were excluded.

effective than fluconazole or amphotericin B in the United States (19, 22), they have not been approved as first-line drugs by the Korea Food and Drug Administration due to the fact that the drug unit cost for amphotericin B deoxycholate is the lowest. Given that clinical decisions regarding drug choice are complicated by factors such as host immunity, *Candida* species, drug efficacy, and cost, data for direct cost comparisons between fluconazole and amphotericin B are scarce (7). Our data show that amphotericin B was no more cost-effective than fluconazole. Fluconazole and amphotericin B did not differ in total cost and cost per day. Even though the cost of amphotericin B was less than that of fluconazole, other medication costs and lab test costs were higher in the amphotericin B group, leading to a net zero balance between fluconazole and amphotericin B. Although 30-day mortality was not different, the treatment success rates were significantly lower when amphotericin B was used as first-line therapy (15/56 [26.8%] with amphotericin B versus 60/129 [46.5%] with fluconazole, $P = 0.011$).

With regard to the choice between fluconazole and amphotericin B deoxycholate, we could not determine the exact reason why clinicians prescribed one agent versus another as initial therapy. However, we can presume that amphotericin B deoxycholate was preferred in patients with more serious illness (Table 7). Patients who were started on amphotericin B deoxycholate had underlying cancer, CVC, or mechanical ventilation more frequently that those who were started on fluconazole, suggesting that amphotericin B is given in more critical patients. This finding is also consistent with current practice of clinicians in Korea. Although echinocandins and liposomal amphotericin B are not admitted as first-line agents against invasive candidiasis or candidemia in Korea, we usually prescribe fluconazole for the treatment of candidemia. Amphotericin B deoxycholate is chosen when it is considered necessary for broader spectrum of coverage or for immunocompromised hosts. Some may presume that the loss of cost-effectiveness of amphotericin B compared to fluconazole in this study could be partially explained by the increase in other medical treatment costs because disease severity in amphotericin B deoxycholate group might have been worse. However, significantly higher rate of treatment failure and rate of switch to second-line antifungal agents with the use amphotericin B was seen, and these have led to increased costs.

Among the limitations of the present study is its retrospective nature. First, since 30 patients were lost to follow-up prior to day 30, 30-day mortality data were available only for 169 subjects, limiting the results of the mortality analysis. Important clinical variables that would have been associated with mortality were not collected. For example, the APACHE II score, which is the only independent predictor of mortality of candidemia in one study (11), could not be calculated. Other clinical indices, such as the SOFA or SAPS II score, also were not available. Instead, we used indirect measures for disease severity, such as underlying malignancies, ICU acquisition of candidemia, central venous catheterization, and the need for mechanical ventilation (Table 2). Second, the appropriateness of antifungal therapy also was not assessable since antifungal susceptibility tests were not available at most institutions. However, we believe that most therapies might have been appropriate because the fluconazole resistance rate among *Candida* species in Korea is low (~0.8%); for example, the resistance rate of *C. glabrata* was 2.8% (8). Third, calculation of an exact estimate of costs attributable only to candidemia was complicated by other comorbidities that might have overlapped candidemia in resource utilization. Fourth, the sample size was relatively small, which might compromise the ability to generalize our results. However, we collected data at four different institutions from three provinces in Korea to overcome the small sample size and construct a representative sample. Fifth, the four university-affiliated medical centers in the present study are rated as superior general hospitals in Korea, which means that an additional 30% of fees are charged for every medical resource provided. Total costs for treatment of candidemia may be cheaper in smaller hospitals or private clinics. However, given that candidemia occurs mostly in nosocomial settings or critically ill patients, we believe our data could reflect the real practice. Finally, since patients who were not treated with antifungal agents or who died too early to receive antifungal agents were excluded from the study, the clinical outcomes of our study are not representative of all cases of candidemia.

Despite these limitations, this is the first study to estimate the attributable costs for treating candidemia in Korea, encom-

TABLE 7 Comparison of clinical characteristics of patients treated with fluconazole and amphotericin B deoxycholate prescribed as a first-line agent

Clinical patient characteristics	Treatment[a]		
	Fluconazole ($n = 129$)	Amphotericin B ($n = 56$)	*P*
Gender, male	70 (54.3)	31 (55.4)	0.891
Median age in yrs (range)	69 (27–85)	66.5 (38–87)	0.298
Underlying disease			
Cancer	56 (43.4)	41 (73.2)	<0.001
Solid tumor	50 (38.8)	29 (51.8)	0.100
Hematologic malignancy	6 (4.7)	12 (21.4)	0.001
Transplantation	2 (1.6)	4 (7.1)	0.069
Solid organ transplantation	1 (0.8)	2 (3.6)	0.218
Bone marrow transplantation	1 (0.8)	2 (3.6)	0.218
Surgery	49 (38.0)	15 (26.8)	0.141
Diabetes mellitus	25 (19.4)	6 (10.7)	0.147
ICU-acquired candidemia	53 (41.1)	16 (28.6)	0.106
Identified species, *C. albicans*	64 (49.6)	23 (41.4)	0.285
Need for mechanical ventilation	26 (20.2)	20 (35.7)	0.024
Central venous catheterization	49 (38.0)	42 (75.0)	<0.001
Infusion pump use	78 (60.5)	42 (75.0)	0.057
Consultation	105 (81.4)	53 (94.6)	0.019
Transfusion	53 (41.1)	34 (60.7)	0.014
Complications during antifungal treatment			
Hypokalemia	20 (15.5)	16 (28.6)	0.039
Nephrotoxicity	16 (12.4)	13 (23.2)	0.063
Hepatotoxicity	22 (17.1)	9 (16.1)	0.869
Switch to second-line treatment	22 (17.1)	28 (50.0)	<0.001
Treatment failure of first-line agent	68 (52.7)	41 (73.2)	0.011
Median duration of first-line treatment	13 (1-62)	9 (2-27)	0.020
Death during first-line treatment	12 (9.3)	5 (8.9)	0.936
30-Day mortality	46 (44.7)	29 (53.7)	0.281

[a] Data are expressed as the number of patients (%), unless described otherwise in column 1.

passing epidemiology, treatment strategies, and outcome altogether. Comparing direct costs between treatment with fluconazole and amphotericin B deoxycholate and demonstrating the importance of first-line antifungal agents in association with cost and mortality may contribute to establishing cost-effective treatment strategies for candidemia in resource-poor countries. Further studies are warranted to prospectively compare the direct costs of amphotericin B deoxycholate to those of fluconazole and to compare the costs of these older drugs to those of new echinocandins in the treatment of candidemia.

Conclusion. In summary, an antifungal switch to second-line agents for any reason was the only modifiable factor that increased attributable costs for treating candidemia and hospital LOS in the present study. In addition, treatment failure of first-line antifungal agents was an independent risk factor for mortality. Treatment with fluconazole and amphotericin B did not differ in terms of mortality and total costs. Our data show that the selection of appropriate first-line antifungal agents is important for the reduction of medical costs and to improve outcomes.

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