CLINICAL OUTCOMES BY TREATMENT TYPE AND FACTORS ASSOCIATED WITH MORTALITY AMONG PATIENTS WITH CANDIDEMIA AT A THAI UNIVERSITY HOSPITAL

Wichai Santimaleeworagun[1,2], Weerayuth Saelim[1,2], Petch Wacharasint[3], Jantima Traipattanakul[4], Juthathip Suphanklang[1,5], Atdhasit Aubonban[6], Sudaluck Thunyaharn[7], Rinrada Donchimplee[1], Arada Chawanonpitak[1], Assama Tiangnoi[1], and Thanjira Panyaphu[1]

[1]Department of Pharmacy, Faculty of Pharmacy, [2]Antibiotic Optimization and Patient Care Project by Pharmaceutical Initiative for Resistant Bacteria and Infectious Diseases Working Group (PIRBIG), Silpakorn University, Nakhon Pathom Province;[3]Division of Pulmonary and Critical Care, [4] Division of Infectious Disease, Department of Medicine, Phramongkutklao Hospital, Bangkok, [5]Silpakorn University Research Program (SURP), Silpakorn University, Nakhon Pathom Province; [6]Army Institute of Pathology, Bangkok; [7]Faculty of Medical Technology, Nakhonratchasima College, Nakhon Ratchasima Province, Thailand

Abstract: Candidemia is a major cause of morbidity and mortality among hospitalized patients in Thailand. In this study we aimed to retrospectively investigate the clinical outcomes by treatment regimen and the factors associated with mortality among patients with candidemia at a hospital in Thailand in order to inform future treatment strategies. Inclusion criteria for study subjects were patients admitted to Phramongkutklao Hospital during January 2016-December 2019 who had laboratory confirmed candidemia. Exclusion criteria for subjects were: patients with candidemia who had a positive fungal blood culture prior to 48-hours hospitalization, who had incomplete medical records or who were referred to another hospital. The medical records of each subject were reviewed and the following recorded: demographic data, antifungal regimen, length of hospitalization, *Candida* species identified and treatment outcome. A total of 159 subjects were included in the study; 57.9% male. The median (interquartile range) age of subjects was 70 (58-81) years. Of the 159 subjects, 81.8% received antifungal therapy: amphotericin B in 67.9%, echinocandins in 5.7%, and fluconazole in 8.2%. The overall mortality rate among the 159 subjects was 72.3%, the mortality rate among the subjects with no antifungals was 100%, and the mortality rate among those treated with antifungals was 54.1%. The mortality rates among those treated with amphotericin B, echinocandins, and fluconazole were 64.8%, 44.4%, and 92.3%, respectively. The factors significantly positively associated on multivariate analysis with an increase in mortality at 30 days hospitalization were: shock (odds ratio (OR): 6.29; p-value $\leq$0.001), endotracheal intubation and mechanical ventilation (OR: 4.11; p-value = 0.017) and disseminated intravascular coagulation (OR: 6.05; p-value = 0.038). The factors significantly negatively associated with increased mortality at 30 days hospitalization were: the use of amphotericin B (OR: 0.34; p-value = 0.035) and the use of echinocandins (OR: 0.03;

p-value = 0.002). In our study, there was a high mortality rate even when treated, especially among those with shock, those who were intubated and those who had disseminated intravascular coagulation. Our results show that early treatment with either amphotericin B or echinocandins, but not fluconazole, were associated with improved mortality. Further studies are needed to determine if application of these factors in the treatment of these patients can improve mortality at the study institution.

Keywords: candidemia, mortality, amphotericin B, echinocandins

INTRODUCTION

Candidemia is a major cause of morbidity and mortality. Candidemia is the fourth most common cause of nosocomial bloodstream infections in the United States (Chai and Tambyah, 2018; Wisplinghoff *et al*, 2004). The most common cause of candidemia is *Candida albicans*, but there has been an increase in the number of non-*albicans Candida* species, such as *C. glabrata*, *C. tropicalis*, and *C. parapsilosis* (Banerjee *et al*, 2015; Cortés *et al*, 2014; Ha *et al*, 2012).

The most cases of candidemia world-wide are reported from Asia, followed by the Americas, Europe, and Africa (Kaur and Chakrabarti, 2017). Developed countries, such as Switzerland, Canada and the United States, have candidemia mortality rates less than 50% but developing countries, such as China, Brazil and South Africa, have mortality rates greater than 50% (Kaur and Chakrabarti, 2017). These high mortality rates in developing countries occur due to the misuse and overuse of antibiotics and steroids, poor healthcare systems, inadequate knowledge about fungal infections and their treatment and the lack of advanced tests due to their high cost (Kaur and Chakrabarti, 2017).

The mortality rate among patients with candidemia has a range of 27-61% (Colombo *et al*, 2007; Falcone *et al*, 2019; Kmeid *et al*, 2019; Lortholary *et al*, 2014; Ohki *et al*, 2020), in spite of the use of newer antifungal agents, resulting in prolonged hospital stays and higher health care costs. The factors associated with mortality in candidemia cases vary by country. There are few studies from Thailand about mortality in candidemia cases (Jutiamornlerd *et al*, 2011; Boonyasiri *et al*, 2013). Most studies have focused on antifungal susceptibilities, the epidemiology of candidemia, the fungal pathogens causing invasive fungal infections, the distribution of these fungal pathogens, virulence factors and host factors associated with candidemia (Chaiwarith *et al*, 2011; Faksri *et al*, 2014).

In this study we aimed to retrospectively investigate the clinical outcomes by treatment regimen and the factors associated with mortality among patients with candidemia at a hospital in Thailand in order to inform future treatment strategies.

MATERIALS AND METHODS

Study design and setting

We retrospectively reviewed the

Correspondence: Weerayuth Saelim, Faculty of Pharmacy, Silpakorn University Sanam Chandra Palace Campus, No. 6 Rajamankha Nai Road, Amphoe Muang Nakorn Pathom, Nakorn Pathom 73000, Thailand
Tel: +66 (034) 255 800; Fax: +66 (034) 255 801; E-mail: saelim_w6@su.ac.th

charts of subjects diagnosed and treated at Phramongkutklao Hospital, Bangkok, Thailand during January 2016-December 2019.

Study subjects

Inclusion criteria for study subjects were those aged ≥18 years with a positive fungal blood culture for *Candida* confirmed by a physician treated at the study institution during the study period. The exclusion criteria for study subjects were patients with candidemia who had a positive fungal blood culture prior to 48-hours hospitalization, who had incomplete medical records or were referred to another hospital.

Data collection

The medical records of each subject were reviewed and the following data were recorded for each subject: age, gender, admitting ward, associated conditions, causative fungal pathogen, history of previous invasive procedures, such as having mechanical ventilation, having a central venous catheter, having a urinary catheter, having a parenteral nutrition catheter, having previous antibiotic use, antifungal drug use, clinical laboratory data after three days treatment with an antifungal drug and duration from antifungal treatment onset until death among those who died.

Definitions and evaluation of clinical outcomes

We defined candidemia as isolation of a *Candida* species from the blood along with signs and symptoms of a systemic infection. The antifungal drug regimen was defined as the first antifungal drug used (amphotericin B, echinocandins or fluconazole). Clinical data were assessed to determine if the patient had clinical improvement after three days treatment with the antifungal drug. Clinical improvement was defined as no signs or symptoms of infection, a body temperature of 36-38°C, or absolute neutrophil count (ANC) of 500-7500 cells/mm^3 (Chandrasekar *et al*, 2018).

The mortality rate was assessed 30 days after candidemia diagnosis. Potential factors associated with mortality that we assessed were: age ≥60 years, shock (inotropic or vasopressor agents required to maintain a mean arterial pressure >65 mm Hg), endotracheal intubation, receiving parenteral nutrition, receiving an empiric antifungal drug (amphotericin B, echinocandins (micafungin, and anidulafungin) and fluconazole), receiving prolonged treatment with corticosteroids (a dose >0.5 mg/kg/day of prednisone or equivalent or a cumulative prednisolone dose >700 mg), having pneumonia, having a solid tumor, having cardiovascular disease, having abdominal surgery, having chronic kidney disease (glomerular filtration rate (GFR) <60 ml/min/1.73 m^2 for three months or kidney disease treated with dialysis or a renal transplant) or having disseminated intravascular coagulation (DIC) (Cortés *et al*, 2014).

Statistical analysis

The statistical analysis was conducted by Statistical Package for the Social Sciences (SPSS) statistics version 27.0. (IBM Corp, Armonk, NY). The data were summarized as medians with interquartile ranges (IQR). Descriptive analysis was used to determine the causative pathogens in sterile and non-sterile specimens, antifungal regimens, and clinical outcomes among study subjects. Univariate analysis was performed using the Chi-square test and Fisher's exact test. All significant variables on univariate analysis ($p < 0.1$) were included in multivariate logistic regression analysis,

which was then used to evaluate potential associations between studied factors and mortality. A p-value <0.05 on multivariate analysis was considered statistically significant.

As this study was conducted using a retrospective review of clinical outcomes, the study, no written informed consent was obtained from the study subjects. This study was approved by the ethics committees of the institutional review board of the Royal Thai Army Medical Department and Phramongkutklao Hospital, Bangkok, Thailand (approval No. Q026h/62 issued on January 21, 2020). Permission to perform the study was also obtained from the Director of Phramongkutklao Hospital.

RESULTS

A total of 159 subjects were included in the study (Fig 1). Ninety-two subjects (57.9%) were male. The median (IQR) patient age was 70 (58-81) years. The three most common comorbidities identified in our study among subjects were: type 2 diabetes mellitus (29.6%), cardiovascular disease (28.9%), and chronic kidney disease (26.4%). Antibacterial therapy (91.8%) and mechanical ventilation (78.6%) were the most common therapies used to treat our study subjects. The three most commonly found *Candida* species were *C. albicans* (54.1%), *C. glabrata* (33.3%), and *C. tropicalis* (3.1%) while unidentified *Candida* sp accounted for 7.6% (Table 1).

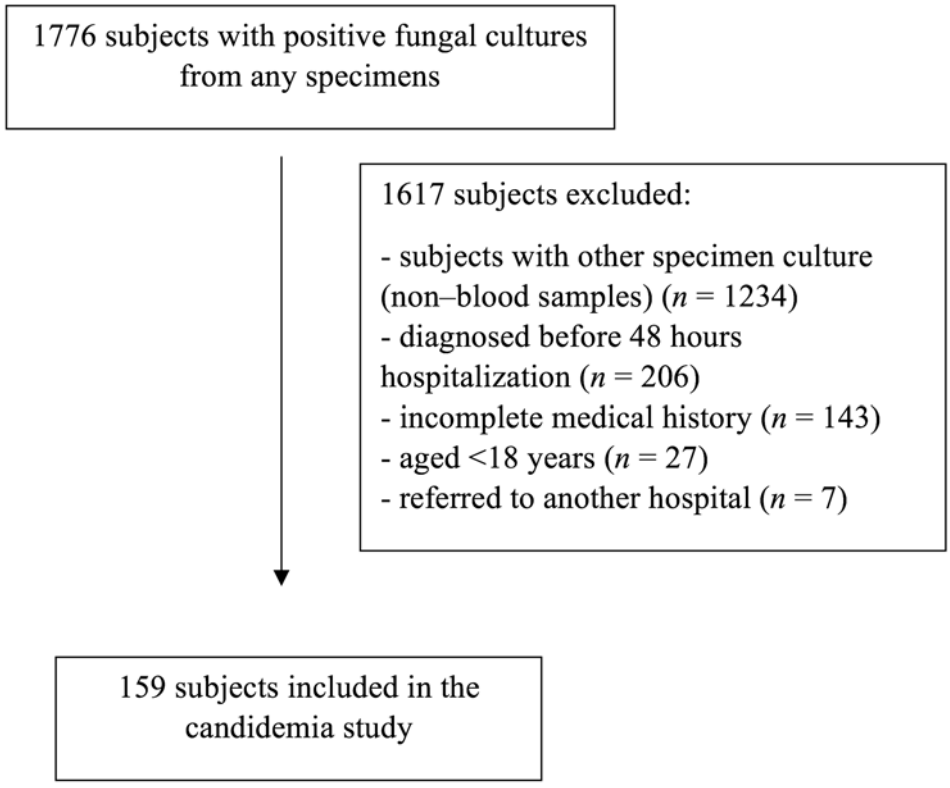

Fig 1-Subject selection.

Table 1
Study subject characteristics (n = 159).

Characteristics	Values
Median (IQR) age in years	70 (58-81)
Male gender, *n* (%)	92 (57.9)
Median (IQR) SOFA score	7 (4-13)
Shock, *n* (%)	121 (76.1)
Admitting ward, *n* (%)	
Medical ICU	94 (59.1)
Medical ward	41 (25.8)
Surgical ICU	15 (9.4)
Surgical ward	9 (5.7)
Comorbidities, *n* (%)	
Type 2 diabetes mellitus	47 (29.6)
Cardiovascular disease	46 (28.9)
Chronic kidney disease	42 (26.4)
Neurological disease	41 (25.8)
Solid tumor	35 (22.0)
Liver disease	32 (20.1)
Hematologic malignancy	18 (11.3)
Peripheral vascular disease	3 (1.9)
Primary immunodeficiency	1 (0.6)
Causative fungal pathogen, *n* (%)	
Candida albicans	86 (54.1)
Candida glabrata	53 (33.3)
Candida tropicalis	5 (3.1)
Candida parapsilosis	2 (1.3)
Candida guilliermondii	1 (0.6)
Un-identified *Candida* sp	12 (7.6)
Interventions, *n* (%)	
Previously received antibacterial agent	146 (91.8)
Mechanical ventilation	125 (78.6)
Endotracheal intubation	120 (75.5)
Had a central venous catheter	120 (75.5)
Had a urinary catheter	97 (61.0)
Received parenteral nutrition	72 (45.3)

IQR: interquartile range; SOFA: sequential organ failure assessment; ICU: intensive care unit.

Clinical outcomes and risk factors associated with 30-day mortality

During the study period, 159 subjects were included. Among them, patients were treated with amphotericin B (67.9%), echinocandins (5.7%), fluconazole (8.2%), and no treatment (18.2%). (Table 2)

One hundred and sixteen patients treated with antifungals were evaluated after 3 day of the treatments. Clinical improvement was observed in 24.2% of amphotericin B-treated group, 33.3%

in echinocandins-treated group and 0.0% in fluconazole-treated group, respectively. The overall mortality rate among 159 subjects was 72.3% while the mortality rate among the subjects with no antifungals was 100%, and the mortality rate among those treated with antifungals was 54.1%. The mortality rates among study subjects treated with amphotericin B, echinocandins and fluconazole were 64.8%, 44.4% and 92.3%, respectively. (Table 2)

On univariate analysis, factors significantly positively associated with mortality at 30 days were: age ≥ 60 years, shock, having a solid tumor, having DIC and being intubated and on mechanical ventilation. On univariate analysis, the significant factors negatively associated with mortality at 30 days were: receiving amphotericin B (odds ratio (OR): 0.54; $p = 0.09$) and receiving echinocandins (OR: 0.18; $p = 0.05$). On multivariate analysis factors significantly positively associated with mortality were shock (OR: 6.29; $p<0.001$), having DIC (OR: 6.05; $p = 0.038$) and being intubated and on mechanical ventilation (OR: 4.11; $p = 0.017$). Factors significantly negatively associated with mortality at 30 days on multivariate analysis were: receiving treatment with amphotericin B (OR: 0.34; $p = 0.035$) and

Table 2
Treatment and outcomes among study subjects.

Variables	Results
Total number of subjects	159
Treatment type, *n* (%)	
Amphotericin B	108 (67.9)
Echinocandins	9 (5.7)
Fluconazole	13 (8.2)
No treatment	29 (18.2)
Number of subjects who improved clinically within 3 days of antifungal treatment (*n* = 116) classified by treatment type, *n* (%)	
Amphotericin B	23/95 (24.2)
Echinocandins*	3/9 (33.3)
Fluconazole	0/12 (0)
Overall mortality rate, number of death/total number of subject (%)	115/159 (72.3)
Mortality rates by type of antifungal treatment, number of death/ number of subjects treated by specified antifungal (%)	
Amphotericin B	70/108 (64.8)
Echinocandins*	4/9 (44.4)
Fluconazole	12/13 (92.3)
Median (IQR) duration from first antifungal dose until death in days by treatment	
Amphotericin B	12.5 (4-20)
Echinocandins*	8.5 (4.25, 26.25)
Fluconazole	18 (9-24)

*Echinocandins (micafungin, anidulafungin).

echinocandins (OR: 0.03; $p = 0.002$). (Table 3)

DISCUSSION

Candidemia is a major cause of morbidity and mortality and the rate of candidemia also have been rising (Xiao *et al*, 2019). In our study, *C. albicans* was the most common *Candida* species among our study subjects, similar to another study from Asia-Pacific (Wang *et al*, 2016). In our study, the most common non-albicans *Candida* species found among study subjects was *C. glabrata*, similar to a previous study conducted among subjects in northern Europe, the United States and Canada (Kullberg and Arendrup, 2015).

In our study, the overall mortality rate was 72.3%, higher than 27-61% reported in several other studies (Colombo *et al*, 2007; Lortholary *et al*, 2014; Kmeid *et al*, 2019; Ohki *et al*, 2020). The higher mortality rate might be from the high percentage of patients with shock and more severe conditions.

In our study, shock was significantly associated with increased mortality, similar to a previous study from Columbia (Cortés *et al*, 2014). In our study, DIC was significantly associated with increased mortality, similar to the results of previous study from China (Zhang *et al*, 2019). In our study, intubation and mechanical ventilation were significantly associated with increased mortality that was similar to the study in Thailand (Jutiamornlerd *et al*, 2011).

Table 3
Evaluation of factors potentially associated with the 30-day mortality rate among study subjects.

Factors	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	*p*-value	Odds ratio (95% CI)	*p*-value
Age ≥ 60 years	2.15 (1.03-4.49)	0.039	1.33 (0.47-3.71)	0.592
Shock	9.16 (4.13-20.29)	<0.001	6.29 (2.30-17.21)	<0.001
Amphotericin B used	0.54 (0.27-1.10)	0.090	0.34 (0.12-0.93)	0.035
Echinocandins used	0.18 (0.03-1.00)	0.050	0.03 (0.004-0.29)	0.002
Had solid tumor	0.41 (0.19-0.90)	0.023	0.65 (0.22-1.92)	0.431
DIC	9.19 (2.11-40.08)	0.001	6.05 (1.10-33.15)	0.038
ET intubation	8.00 (3.58-17.88)	<0.001	4.11 (1.29-13.11)	0.017
Had pneumonia	2.03 (0.98-4.23)	0.055	0.65 (0.23-1.83)	0.412
Received parenteral nutrition	1.90 (0.92-3.91)	0.079	1.70 (0.64-4.51)	0.290
Underlying cardiovascular disease	1.55 (0.69-3.48)	0.286		
Had abdominal surgery	0.53 (0.24-1.19)	0.121		
Had chronic kidney disease	1.57 (0.68-3.61)	0.292		
Received steroids	1.81 (0.76-4.31)	0.175		

CI: confidence interval; DIC: disseminated intravascular coagulation; ET: endotracheal tube.

In our study, the use of amphotericin B had a higher clinical improve than fluconazole group which is different from the previous meta-analysis showing no difference in mortality by observed with fluconazole versus amphotericin B (Gafter-Gvili *et al*, 2008). However, the increased rate of clinical failure in fluconazole group might be from the high number of patients with *C. glabrata* which is naturally resisting to fluconazole (Wang *et al*, 2016). In our study, echinocandins use was negatively associated with mortality, similar to a study from South Korea (Jung *et al*, 2020). A previous meta-analysis from the highest treatment success rate at 3 days was with echinocandin use (Demir *et al*, 2019), on the current Infectious Diseases Society of America (IDSA) recommendation for patients admitted to the intensive care unit or who are immunocompromised and have symptoms of candidemia should be treated empirically with echinocandins (Pappas *et al*, 2016).

Factors associated with mortality among candidemia patients from other studies include: intensive care unit admission, inappropriate antifungal therapy within 72 hours and renal failure (Boonyasiri *et al*, 2013). We did not find these associations in our study, possibly due to the small sample size at a single institution. A multicenter study with a larger sample size might detect other factors not found in our current study.

Weaknesses of our study were the failure in reporting the antifungal susceptibility test for *Candida* isolates and the missing of factors leading to a delay of antifungal therapy initiation which was significantly resulting in mortality among patients with candidemia (Garey *et al*, 2006). However, the strength of our study found that this study was the first in revealing risk factors related to the clinical outcomes among candidemic patients in Thailand.

In summary, in our study, the mortality rate among those with candidemia was high but lower among those treated with amphotericine B and echinocandins, but not fluconazole. The factors significantly negatively associated with mortality among study subjects were receiving amphotericin B or echinocandins and the factors significantly positively associated with mortality among study subjects were shock, having DIC, and being intubated and on mechanical ventilation. These factors need to be considered when considering empiric treatment of suspected candidemia patients at the study institution. Further studies are needed to determine if application of these data to prevention plans can reduce mortality among candidemia subjects at the study institution.

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