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ORIGINAL RESEARCH

Optimizing Micafungin Dosing in Patients with Critically Ill Candidemia and Trends of *Candida* Species Causing Bloodstream Infections in a Tertiary Hospital in Thailand: A Monte Carlo Simulation Approach

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Purpose: This study aimed to determine the optimal micafungin dosage for treating candidemia in critically ill adult patients using Monte Carlo simulation.

Patients and Methods: Clinical *Candida* isolates were obtained from blood cultures collected between September 2023 and December 2024 at Phramongkutklao Hospital, Thammasat University Hospital, and Udonthani Hospital. Susceptibility testing was performed using the Sensititre® YeastOne® system, applying a broth microdilution method in 96-well plates to determine minimum inhibitory concentrations (MICs). Monte Carlo simulations were conducted to identify optimal micafungin dosing regimens, using cumulative fraction of response (CFR) and probability of target attainment (PTA) as key parameters.

Results: In total, 128 clinical *Candida* isolates were identified. *Candida tropicalis* was the most frequently isolated species (32%), followed by *C. albicans* (22.7%), *C. parapsilosis* (16.4%), *C. glabrata* (*Nakaseomyces glabrata*) (12.5%), and *C. auris* (*Candidozyma auris*) (9.4%). The micafungin MIC ranges were as follows: *C. tropicalis*, 0.015–0.25 µg/mL; *C. albicans*, 0.008–0.015 µg/mL; *C. parapsilosis*, 0.5–2 µg/mL; *C. glabrata*, 0.015–>8 µg/mL; and *C. auris*, 0.12–0.25 µg/mL. Pan-echinocandin-resistant *C. glabrata* was also detected. A standard micafungin dose (100 mg/day) may be effective for *C. tropicalis* infections when MIC is ≤0.015 µg/mL. In patients with Sequential Organ Failure Assessment scores >10 and alanine aminotransferase >120 U/L, the standard micafungin dose adequate CFR for empirical therapy and PTA for documented treatment at MICs up to 0.03 µg/mL, with the target threshold set at ≥90%. However, in the absence of MIC data and with increasing MIC trends, a higher empirical dose (up to 400 mg/day) may be warranted.

Conclusion: Non-*albicans Candida* bloodstream infections are increasing, along with higher MIC trends, signaling emerging resistance. Standard dosing may be insufficient in critically ill patients. Empirical high-dose micafungin could improve treatment efficacy.

Keywords: MIC distribution, ICU patient, empirical dosing, invasive candidiasis

Introduction

Candida species are common components of the normal human microbiota but can act as opportunistic pathogens, especially in immunocompromised individuals. The five most common species causing invasive infections are

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C. albicans (38%), *C. glabrata* (*Nakaseomyces glabrata*) (29%), *C. parapsilosis* (17%), *C. tropicalis* (10%), and *C. krusei* (*Pichia kudriavzevii*) (1%).[1] A major concern with invasive *Candida* infections is candidemia, which carries significant morbidity and mortality, particularly in critically ill patients. In the United States, a 2020 report indicated that *Candida* accounted for up to 28% of central line–associated bloodstream infections in this population.[1,2] In Thailand, candidemia-related mortality is notably high, ranging from 50.8% to 71.2%, exceeding rates reported in China, South Korea, and Europe.[3–6]

Despite its clinical significance, conventional diagnostic methods such as fungal cultures are often slow and insensitive, making timely diagnosis challenging.[7] Therefore, empirical antifungal therapy is commonly used, guided by local epidemiological data, which can vary widely by region.[8] The current guidelines for the treatment of *Candida* bloodstream infections from the Infectious Diseases Society of America (IDSA) 2016 and the global guideline for the diagnosis and management of candidiasis: an initiative of the European Confederation for Medical Mycology in cooperation with the International Society of Human and Animal Mycology and the American Society for Microbiology 2025[9,10] recommend echinocandins as the first-line therapy, due to the increasing resistance to fluconazole and its reduced efficacy against certain *Candida* species. Micafungin, an echinocandin, is commonly used, but current dosing recommendations are not adjusted for critically ill patients, potentially impacting treatment success.

Micafungin resistance in *C. glabrata* is an increasing concern in clinical practice. A national surveillance report from the United States, conducted between 2008 and 2014, documented a resistance rate of 4.8%.[11] In Thailand, *C. glabrata* generally remains susceptible to micafungin; however, recent data from university hospitals indicate a gradual decline in susceptibility.[3,12,13] Furthermore, *C. auris* has emerged as a significant fungal pathogen known for causing severe infections and exhibiting resistance to multiple antifungal agents. The Centers for Disease Control and Prevention (CDC) has highlighted the urgent threat posed by this organism. Despite global concern, reports of *C. auris* in Thailand are still relatively limited.[10,13,14]

Considering these developments, this study aimed to evaluate the in vitro activity of micafungin against various *Candida* species and to use these susceptibility data in Monte Carlo simulations. The goal was to determine the optimal micafungin dosing strategy based on pharmacokinetic/pharmacodynamic (PK/PD) targets in critically ill patients with candidemia.

Materials and Methods

Sample Collection

Candida isolates were obtained from the blood of hospitalized patients aged ≥20 years at Phramongkutklao Hospital, Thammasat University Hospital, and Udonthani Hospital, Thailand, between September 2023 and December 2024. Duplicate isolates from the same patient were excluded from the analysis.

Fungal Strains and Antifungal Susceptibility Testing

Species identification was conducted using matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS). Antifungal susceptibility of *Candida* isolates was assessed using the Sensititre YeastOne system, a broth microdilution–based method, following the manufacturer's instructions (Thermo Fisher Scientific, Cleveland, OH, USA). Isolates were first grown on blood agar at 35°C in a non-CO_2 incubator for 24–25 h, after which the inoculum was standardized to a 0.5 McFarland turbidity. A 20-µL aliquot of the suspension was added to the broth, mixed, and further diluted with Sensititre YeastOne broth. The plates were prepared with serial twofold dilutions of antifungal agents, including micafungin, ranging from 0.008 to 8 µg/mL. Minimum inhibitory concentrations (MICs) were determined after 24 h of incubation, based on a color change from blue (no growth) to pink or purple (growth). Quality control was ensured using *C. parapsilosis* ATCC 22019 and *C. krusei* ATCC 6258, following the Clinical and Laboratory Standards Institute (CLSI) M27 guidelines.[15] MICs were interpreted according to the breakpoints specified in CLSI M27M44S (3rd edition). For antifungals lacking defined breakpoints, epidemiological cutoff values (ECVs) from CLSI M57S (4th edition) were used.[16,17]

Monte Carlo Simulation

The present analysis utilized micafungin PK parameters obtained from a study by Zhong et al[18] involving critically ill patients are summarized in Supplementary Table 1. A two-compartment model was applied to describe the PK behavior of micafungin in relation to time and concentration, with the PK/PD target being the 24-h area under the concentration–time curve to the MIC (AUC_{0-24}/MIC). Although no specific PK/PD target has been universally established to define the safety of micafungin, its safety profile is well characterized and has been used at doses exceeding the standard recommended regimen. The model of the plasma concentration of micafungin, equations incorporating alanine aminotransferase (ALT) and the Sequential Organ Failure Assessment (SOFA) score as covariate factors were used.[18] The target AUC_{0-24}/MIC values indicating the efficacy of micafungin were >3000 for all *Candida* species, >5000 for *Candida* species excluding *C. parapsilosis*, and >285 for *C. parapsilosis*.[19]

Micafungin regimens were administered intravenously at a loading dose ranging from 100 to 400 mg, followed by 100–400 mg every 24 h. The highest dose used in this study was determined according to doses administered in earlier clinical trials involving patients. The PK/PD of the micafungin regimens was evaluated using a 10,000-subject Monte Carlo simulation (Oracle Crystal Ball Classroom Faculty Edition-Oracle 1-Click Crystal Ball 201, Thailand). The predicted likelihood that each dosage regimen would reach the established PK/PD index and target at each MIC was defined as the probability of target attainment (PTA). Furthermore, the cumulative fraction of response (CFR) for each regimen calculated by multiplying the proportion of *Candida* isolates at each MIC by the corresponding PTA. Dosage regimens were considered appropriate if the CFR and PTA were at least 90% in empirical and documented therapy, respectively.

Results

Candida Isolates the Distribution

Over the course of the investigation, 128 clinical isolates of *Candida* were identified. In our study, the five most frequently isolated *Candida* species included *C. tropicalis* (32%), *C. albicans* (22.7%), *C. parapsilosis* (16.4%), *C. glabrata* (12.5%), and *C. auris* (9.4%). Other *Candida* species accounted for 8.1% of the isolates, including *C. orthopsilosis* (3.1%), *C. guilliermondii* (*Meyerozyma guilliermondii*) (1.6%), *C. lusitaniae* (0.8%), *C. dubliniensis* (0.8%), and *C. krusei* (0.8%).

In vitro Susceptibility of Micafungin

All *C. albicans* isolates exhibited 100% susceptibility to micafungin, with MIC50 and MIC90 values of 0.008 and 0.015 μg/mL, respectively. Among the non-*albicans Candida* species, susceptibility to micafungin remained generally high; however, an increasing trend in MIC values was observed. *C. tropicalis* exhibited MIC50 and MIC90 values of 0.03 and 0.06 μg/mL, respectively. For *C. parapsilosis*, the MIC50 and MIC90 values were 1 and 2 μg/mL, respectively; the MIC90 corresponds to the upper limit of the susceptibility breakpoint. *C. glabrata* exhibited MIC50 and MIC90 values of 0.015 and 0.03 μg/mL, respectively; however, an isolate with an MIC exceeding 8 μg/mL was also detected. Furthermore, *C. auris* exhibited relatively high MIC values, with MIC50 and MIC90 values at 0.12 and 0.25 μg/mL, respectively. Table 1 presents the MIC distribution, as well as the MIC50 and MIC90 values of micafungin for each *Candida* species. Additional susceptibility data for caspofungin and anidulafungin are presented in Supplementary Table 2.

Table 1 MIC Distribution of Micafungin Against *Candida* Species Isolates

Candida Species	Frequency, n (%)	Micafungin MIC (μg/mL)														Susceptible Breakpoint or ECV (μg/mL)
		0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	>8	MIC50	MIC90	
C. tropicalis	41 (32)		4	24	12		1							0.03	0.06	≤0.25[a]
C. albicans	29 (22.7)	6	23											0.008	0.015	≤0.25[a]
C. parapsilosis	21 (16.4)							3	13	5				1	2	≤2[a]

(*Continued*)

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Table 1 (Continued).

Candida Species	Frequency, n (%)	Micafungin MIC (μg/mL)													Susceptible Breakpoint or ECV (μg/mL)
		0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	>8	MIC50	MIC90	
C. glabrata	16 (12.5)		10	5									1	0.015	0.03	≤0.06[a]
C. auris	12 (9.4)					9	3							0.12	0.25	≤0.5[b]
C. orthopsilosis	4 (3.1)						1	3						0.5	0.5	≤1[b]
C. guilliermondii	2 (1.6)									2				2	2	≤2[a]
C. dubliniensis	1 (0.8)		1											N/A	N/A	≤0.12[b]
C. krusei	1 (0.8)					1								N/A	N/A	≤0.25[a]
C. lusitaniae	1 (0.8)					1								N/A	N/A	≤0.5[b]

Notes: For the MIC breakpoint for susceptibility interpretation, [a]clinical breakpoints were based on the Clinical and Laboratory Standards Institute (CLSI); [b]epidemiological cutoff values were based on CLSI; color codes: gray boxes indicate the susceptible breakpoint or ECV.
Abbreviations: *C., Candida*; ECV, epidemiological cutoff values; MIC, minimum inhibitory concentration; MIC50, minimum inhibitory concentration required to inhibit the growth of 50% of organisms; MIC90, minimum inhibitory concentration required to inhibit the growth of 90% of organisms; N/A, not applicable.

Monte Carlo Dose Simulation

In critically ill patients with normal ALT levels (<40 U/L), micafungin therapy at a standard dose of 100 mg/day was sufficient to cover *Candida* isolates with MICs up to 0.015 μg/mL. For critically ill patients with ALT levels ≥40 U/L, the same regimen provided adequate coverage for isolates with MICs up to 0.03 μg/mL. Isolates with MICs as high as 0.25 μg/mL required increased micafungin doses to achieve PK/PD targets, defined as a PTA of ≥90%. PTA values for different micafungin dosing regimens against *Candida* species are summarized in Supplementary Table 3.

If the *Candida* species has been identified, critically ill patients receiving the standard micafungin dose with ALT levels <40 U/L, regardless of SOFA score, achieved the CFR target only for *C. albicans*. In contrast, patients with ALT ≥40 U/L, regardless of SOFA score, attained the CFR target for *C. albicans* and *C. glabrata*, but not for *C. tropicalis* or *C. auris*. Notably, in patients with SOFA scores ≥10 and ALT levels >120 U/L, the standard micafungin dose achieved the CFR target for *C. albicans, C. glabrata*, and *C. tropicalis*. However, achieving the CFR target for *C. auris* requires a higher dose (up to 400 mg/day). The results demonstrated that the CFR target was attained only when high-dose micafungin and elevated ALT levels were present. Simulated PK/PD target attainment differed across *Candida* species and depended on the micafungin dosing regimen, as presented in Table 2.

Table 2 PTA and CFR of Various Micafungin Dosage Regimens Was Evaluated in Critically Ill Patients at Steady State, Stratified by Sequential Organ Failure Assessment (SOFA) Score and Alanine Aminotransferase (ALT), Using a PK/PD Target of AUC_{0-24}/MIC > 5000 Against *Candida* Species Not Included *C. parapsilosis*

Dosage Regimens of Micafungin			PTA (%)						CFR (%)			
			Micafungin MIC (μg/mL)						*Candida* Species			
LD	MD	Infusion time	0.008	0.015	0.03	0.06	0.12	0.25	*C. albicans*	*C. glabrata*	*C. tropicalis*	*C. auris*
SOFA score 1–9, ALT 1–39 U/L												
100 mg	100 mg q 24 h	1 h	100	100	31	0	0	0	100	72	28	0
150 mg	150 mg q 24 h	1 h	100	100	100	0	0	0	100	94	68	0
200 mg	200 mg q 24 h	1 h	100	100	100	31	0	0	100	94	78	0
250 mg	250 mg q 24 h	1 h	100	100	100	100	0	0	100	94	98	0

(*Continued*)

Table 2 (Continued).

Dosage Regimens of Micafungin			PTA (%)						CFR (%)			
			Micafungin MIC (μg/mL)						*Candida* Species			
LD	**MD**	**Infusion time**	**0.008**	**0.015**	**0.03**	**0.06**	**0.12**	**0.25**	***C. albicans***	***C. glabrata***	***C. tropicalis***	***C. auris***
300 mg	300 mg q 24 h	1 h	100	100	100	100	0	0	100	94	98	0
350 mg	350 mg q 24 h	1 h	100	100	100	100	4	0	100	94	98	3
400 mg	400 mg q 24 h	1 h	100	100	100	100	31	0	100	94	98	23
SOFA score 1–9, ALT 40–79 U/L												
100 mg	100 mg q 24 h	1 h	100	100	100	0	0	0	100	94	68	0
150 mg	150 mg q 24 h	1 h	100	100	100	15	0	0	100	94	73	0
200 mg	200 mg q 24 h	1 h	100	100	100	100	0	0	100	94	98	0
250 mg	250 mg q 24 h	1 h	100	100	100	100	0	0	100	94	98	0
300 mg	300 mg q 24 h	1 h	100	100	100	100	16	0	100	94	98	12
350 mg	350 mg q 24 h	1 h	100	100	100	100	88	0	100	94	98	66
400 mg	400 mg q 24 h	1 h	100	100	100	100	100	0	100	94	98	75
SOFA score 1–9, ALT 80–120 U/L												
100 mg	100 mg q 24 h	1 h	100	100	100	0	0	0	100	94	68	0
150 mg	150 mg q 24 h	1 h	100	100	100	100	0	0	100	94	97	0
200 mg	200 mg q 24 h	1 h	100	100	100	100	0	0	100	94	98	0
250 mg	250 mg q 24 h	1 h	100	100	100	100	33	0	100	94	98	25
300 mg	300 mg q 24 h	1 h	100	100	100	100	100	0	100	94	98	73
350 mg	350 mg q 24 h	1 h	100	100	100	100	100	0	100	94	98	75
400 mg	400 mg q 24 h	1 h	100	100	100	100	100	0	100	94	98	75
SOFA score 1–9, ALT 121–200 U/L												
100 mg	100 mg q 24 h	1 h	100	100	100	65	0	0	100	94	87	0
150 mg	150 mg q 24 h	1 h	100	100	100	100	3	0	100	94	98	2
200 mg	200 mg q 24 h	1 h	100	100	100	100	65	0	100	94	98	49
250 mg	250 mg q 24 h	1 h	100	100	100	100	100	0	100	94	98	74
300 mg	300 mg q 24 h	1 h	100	100	100	100	100	1	100	94	98	75
350 mg	350 mg q 24 h	1 h	100	100	100	100	100	15	100	94	98	79
400 mg	400 mg q 24 h	1 h	100	100	100	100	100	52	100	94	99	88
SOFA score 10–24, ALT 1–39 U/L												
100 mg	100 mg q 24 h	1 h	100	100	34	0	0	0	100	73	30	0
150 mg	150 mg q 24 h	1 h	100	100	100	0	0	0	100	94	68	0
200 mg	200 mg q 24 h	1 h	100	100	100	35	0	0	100	94	78	0
250 mg	250 mg q 24 h	1 h	100	100	100	100	0	0	100	94	98	0
300 mg	300 mg q 24 h	1 h	100	100	100	100	0	0	100	94	98	0

(*Continued*)

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Table 2 (Continued).

Dosage Regimens of Micafungin			PTA (%)						CFR (%)			
			Micafungin MIC (μg/mL)						*Candida* Species			
LD	**MD**	**Infusion time**	**0.008**	**0.015**	**0.03**	**0.06**	**0.12**	**0.25**	***C. albicans***	***C. glabrata***	***C. tropicalis***	***C. auris***
350 mg	350 mg q 24 h	1 h	100	100	100	100	5	0	100	94	98	3
400 mg	400 mg q 24 h	1 h	100	100	100	100	35	0	100	94	98	26
SOFA score 10–24, ALT 40–79 U/L												
100 mg	100 mg q 24 h	1 h	100	100	100	0	0	0	100	94	68	0
150 mg	150 mg q 24 h	1 h	100	100	100	21	0	0	100	94	75	0
200 mg	200 mg q 24 h	1 h	100	100	100	100	0	0	100	94	98	0
250 mg	250 mg q 24 h	1 h	100	100	100	100	0	0	100	94	98	0
300 mg	300 mg q 24 h	1 h	100	100	100	100	21	0	100	94	98	16
350 mg	350 mg q 24 h	1 h	100	100	100	100	94	0	100	94	98	70
400 mg	400 mg q 24 h	1 h	100	100	100	100	100	0	100	94	98	75
SOFA score 10–24, ALT 80–120 U/L												
100 mg	100 mg q 24 h	1 h	100	100	100	1	0	0	100	94	69	0
150 mg	150 mg q 24 h	1 h	100	100	100	100	0	0	100	94	97	0
200 mg	200 mg q 24 h	1 h	100	100	100	100	1	0	100	94	98	0
250 mg	250 mg q 24 h	1 h	100	100	100	100	53	0	100	94	98	40
300 mg	300 mg q 24 h	1 h	100	100	100	100	100	0	100	94	98	75
350 mg	350 mg q 24 h	1 h	100	100	100	100	100	0	100	94	98	75
400 mg	400 mg q 24 h	1 h	100	100	100	100	100	0	100	94	98	75
SOFA score 10–24, ALT 121–200 U/L												
100 mg	100 mg q 24 h	1 h	100	100	100	84	0	0	100	94	93	0
150 mg	150 mg q 24 h	1 h	100	100	100	100	14	0	100	94	98	10
200 mg	200 mg q 24 h	1 h	100	100	100	100	84	0	100	94	98	63
250 mg	250 mg q 24 h	1 h	100	100	100	100	100	1	100	94	98	75
300 mg	300 mg q 24 h	1 h	100	100	100	100	100	9	100	94	98	77
350 mg	350 mg q 24 h	1 h	100	100	100	100	100	38	100	94	99	85
400 mg	400 mg q 24 h	1 h	100	100	100	100	100	75	100	94	99	94

Notes: Color codes: green boxes Strongly recommended dose based on ≥90% PTA, blue boxes Strongly recommended dose based on ≥90% CFR.
Abbreviations: ALT, alanine aminotransferase; q, every; h, hour; LD, loading dose; MD, maintenance dose; mg, milligram; MIC, minimum inhibitory concentration; SOFA, sequential organ failure assessment.

In cases involving *C. parapsilosis* with unknown MIC values, high-dose micafungin therapy was associated with a CFR exceeding 90% among critically ill patients presenting with elevated SOFA scores and ALT levels. In contrast, the standard-dose regimen failed to achieve the CFR target in patients with normal ALT levels. A daily dose of 400 mg was necessary to reach CFR values of 92.14% and 93.27% in patients with SOFA scores <10 and ≥10, respectively. When the MIC was known, a standard dose of micafungin was sufficient to achieve PTA when the MIC was ≤0.25 μg/mL, regardless of the SOFA score or ALT level. In patients with ALT levels ≥40 U/L, micafungin doses of at least 200 mg/day

were effective in achieving PTA against *C. parapsilosis* isolates with MICs up to 1 μg/mL. Notably, the MICs of *C. parapsilosis* isolates in this study ranged from 0.5 to 2 μg/mL. Moreover, a 400-mg/day regimen achieved CFR targets even for isolates with MICs as high as 4 μg/mL. Comprehensive results for each dosing regimen against *C. parapsilosis* are presented in Supplementary Table 4.

Discussion

In this study, *C. tropicalis* was the most isolated species (32%), followed by *C. albicans* (22.7%), *C. parapsilosis* (16.4%), and *C. glabrata* (12.5%). Notably, *C. auris* was also detected, accounting for 9.4% of the isolates. Other *Candida* species accounted for 8.1% of the isolates, including *C. orthopsilosis* (3.1%), *C. guilliermondii* (1.6%), *C. lusitaniae* (0.8%), *C. dubliniensis* (0.8%), and *C. krusei* (0.8%). Between 2009 and 2017, the distribution of *Candida* species in the United States was dominated by *C. albicans* (48%), followed by *C. glabrata* (24%), *C. parapsilosis* (11%), and *C. tropicalis* (6%). The analysis of *Candida* isolates revealed that 57% were obtained from patients diagnosed with candidemia.[20] In the Asia-Pacific region, a 2022 study conducted in China reported the distribution of *Candida* species across all clinical specimens. Only 6.1% of these isolates were derived from blood. The predominant species were *C. albicans* (49.4%), *C. tropicalis* (21.9%), *C. parapsilosis* (13.9%), and *C. glabrata* (11.4%). In contrast, *C. auris* accounted for a mere 0.2% of all clinical isolates and was absent from bloodstream infection isolates.[21] In Japan, the distribution of *Candida* species isolated from blood between 2010 and 2019 was as follows: *C. albicans*, 43.6%; *C. glabrata*, 19.5%; *C. parapsilosis*, 18.8%; and *C. tropicalis*, 6.7%. Notably, no *C. auris* isolates were identified.[22] Based on blood culture data from separate single-center studies conducted at different hospitals across Thailand, *C. albicans* (53%) was the most common *Candida* species from 2012 to 2013, followed by *C. tropicalis* (27.3%) and *C. glabrata* (15.2%).[12] Between 2013 and 2016, *C. tropicalis* became predominant (36.9%), followed by *C. albicans* (29.2%), *C. glabrata* (17.7%), and *C. parapsilosis* (6.9%).[13] During the 2016–2017 period, the predominant *Candida* species were *C. tropicalis* (49.4%), followed by *C. albicans* (28.8%), *C. glabrata* (16.7%), and *C. parapsilosis* (5.1%).[13] In the subsequent study period (2018–2019), *C. tropicalis* remained the most frequently isolated species (33%), followed closely by *C. albicans* (29.6%).[23] The distribution of *Candida* species in Thailand has shifted over time, with a marked increase in non-*albicans Candida* species. This trend is clearly reflected in our study, where non-*albicans Candida* species accounted for as much as 77.3% of all isolates, whereas *C. albicans* was identified in only 22.7%. Although our results differ from those of previous research in this area, our study collected clinical *Candida* isolates from blood from multiple tertiary hospital centers. This study provides a comprehensive overview of *Candida* species distribution in Thailand and highlights the current epidemiological landscape.

C. auris is an emerging fungal pathogen of major clinical concern due to its capacity to cause severe infections that are often resistant to multiple classes of antifungal drugs. This study presents the first report of the highest prevalence of *C. auris* in Thailand. Historically, *C. auris* was rarely detected in global surveillance, with only six cases of bloodstream infection reported across 135 medical centers in 39 countries from 2009 to 2016.[24] Recent data reveal a notable epidemiological shift: by 2023, the United States reported 4514 new *C. auris* cases, prompting the CDC to classify it as an urgent public health threat due to multidrug resistance. In this study, micafungin MICs for *C. auris* isolates ranged from 0.12 to 0.25 μg/mL, with 0.5 μg/mL representing the established ECV.[17] The proximity of MIC values to the ECV indicates a potential trend toward reduced susceptibility, which is significant compared to United States data showing that fewer than 2% of *C. auris* isolates exhibit resistance to echinocandin-class antifungals.[14] These findings highlight the importance of ongoing surveillance and the need for adaptable antifungal treatment strategies, especially in areas where multidrug-resistant strains are emerging.

Therefore, this study also evaluated the susceptibility of *Candida* isolates to micafungin to support clinical decision-making and monitor emerging resistance trends. Notably, susceptibility testing in this study used a standardized MIC method, recognized for its accuracy and reliability in clinical practice. Micafungin was chosen as the primary antifungal due to its wider availability in resource-limited settings like Thailand, where it is listed on the National List of Essential Medicines. Conversely, caspofungin is unavailable in Thailand, and anidulafungin is rarely used because of its high cost and exclusion from the essential medicines list. Although these agents were not included in the main analysis, their MIC data are provided in Supplementary Table 2 to support reference and future investigations. Previous research conducted between

2012 and 2013 reported that micafungin had a 90% susceptibility rate against *C. glabrata*, with MIC values of 0.015–0.25 μg/mL.[12] Further research from 2013 to 2016 demonstrated that *C. albicans* (MIC range: 0.008–0.015 μg/mL), *C. tropicalis* (MIC range: 0.015–0.06 μg/mL), and *C. glabrata* (MIC range: 0.008–0.015 μg/mL) all exhibited 100% susceptibility to micafungin.[25] The findings revealed that *C. glabrata* isolates from bloodstream infections were resistant to echinocandins, which are currently recommended as the first-line therapy for candidemia, particularly in critically ill patients. In particular, one sixteenth of *C. glabrata* isolates exhibited resistance to micafungin (MIC range from 0.015 to >8 μg/mL). Because MIC values were progressively higher, pan-resistant strains were also detected, raising serious concerns regarding the efficacy of current antifungal treatments. Compared with other reports, the resistance rate of *C. glabrata* to micafungin was previously reported as 0.4%, 0.6%, 0%, and 2.8% in the Asia-Pacific region, Europe, Latin America, and North America, respectively, between 2006 and 2016.[24]

In this study, *C. parapsilosis* remained susceptible to echinocandins, though MIC values showed an upward trend compared to earlier reports. Specifically, micafungin MICs for *C. parapsilosis* ranged from 0.5 to 2 μg/mL, with MIC50 and MIC90 values of 1 and 2 μg/mL, respectively both higher than previously documented.[12,23] Notably, some micafungin dosing regimens did not achieve the established PK/PD target. In contrast, *C. albicans* remained uniformly susceptible to echinocandins, with micafungin MICs ranging from 0.008 to 0.015 μg/mL, an MIC50 of 0.008 μg/mL, and an MIC90 of 0.015 μg/mL (susceptibility breakpoint: ≤0.25 μg/mL).[16] All regimens of micafungin successfully met the CFR target for *C. albicans*.

Based on Monte Carlo simulations using population PK parameters from Zhong et al,[18] high-dose micafungin regimens tailored to specific *Candida* species were essential to achieve PTA and CFR targets. The relatively high simulated doses in this study likely reflect reliance on PK/PD targets from prior literature, which do not fully account for all relevant pathogens, notably *C. auris*. Future research establishing species-specific PK/PD targets would enable more precise and clinically relevant dose optimization. Safety concerns are limited, as multiple real-world studies have demonstrated that high-dose micafungin is well tolerated. Repeated dosing up to 8 mg/kg/day (maximum 896 mg/day) for 1–4 weeks showed no dose-limiting toxicities in adults.[26] Similarly, doses exceeding 200 mg/day (median 300 mg; IQR 275–400) for at least three consecutive days were well tolerated, with no severe hepatic or hematologic adverse events observed.[27] Clinical evidence also suggests that higher-than-standard doses can shorten treatment duration and improve success rates compared with standard regimens.[28] Despite this, careful monitoring for adverse reactions remains essential. The high simulated doses also highlight the potential benefit of exploring combination therapy with other antifungals for synergistic effects and underscore the importance of defining species-specific targets, which could guide more effective and personalized treatment strategies in future studies.

Our study suggests that a standard daily dose of micafungin (100 mg/day) is appropriate for *Candida* species, excluding *C. parapsilosis*, when the MIC is ≤0.015 μg/mL, regardless of SOFA score or ALT level. A minimum micafungin dose of 200 mg/day is required to achieve the PTA target at an MIC of 0.06 μg/mL in patients with SOFA scores ≥10 and ALT levels ≥40 U/L. For *C. parapsilosis*, the standard micafungin dose is sufficient to achieve the PTA target when the MIC is up to 0.25 μg/mL, regardless of the SOFA score or ALT level. However, in patients with ALT ≥40 U/L, target attainment can be achieved for isolates with MICs up to 0.5 μg/mL. Micafungin clearance in adult ICU patients was 30–51% higher than that in non-ICU adult patients. The $AUC_{0\text{-}24}$ at steady state was 96.8 mg·h/L (72.0–132.3 mg·h/L) in ICU patients with SOFA scores ≥10 and 89.7 mg·h/L (70.7–131.7 mg·h/L) in those with SOFA scores <10. In contrast, non-ICU adult patients had a higher $AUC_{0\text{-}24}$ of 125.6 mg·h/L (95.3–149.4 mg·h/L). A dose adjustment may be necessary when treating infections caused by resistant *Candida* strains. Although previous studies have recommended 250-mg/day micafungin for treating *C. glabrata*-associated infections,[29] our findings demonstrated that a dose of 150 mg/day may be sufficient to achieve the CFR target in certain scenarios. However, even with simulated doses as high as 400 mg/day, effective coverage was only achievable for isolates with MICs ≤0.12 μg/mL. Notably, our study also identified isolates with MICs exceeding 8 μg/mL for which alternative antifungal agents outside the echinocandin class should be considered.

This study has several limitations that should be acknowledged. First, the dosing regimens used in our simulations were optimized to achieve established PK/PD targets; however, they have not yet been validated in real-world clinical settings. Second, this study did not collect isolates for investigating gene mutations. Finally, one limitation of this simulation study was the lack of measured PK data from the study participants. However, the population PK model of micafungin adequately describes the variability in PK parameters among critically ill patients.

Conclusion

Micafungin is one of the first-line treatment in critically ill patients with *Candida* bloodstream infections. Optimizing treatment outcomes requires appropriate dosing that takes local MIC values into account. *C. auris* should be acknowledged as an emerging and clinically significant pathogen in Thailand. Although administering doses higher than standard recommendations may enhance the likelihood of achieving PK/PD targets, particularly in cases of *C. auris* septicemia accompanied by high SOFA scores and elevated ALT levels, the safety of such regimens must be thoroughly assessed. Future studies evaluating clinical outcomes are necessary to determine the most effective micafungin dosing strategies for candidemia management.

Ethics Approval

Informed consent was obtained from all participants before their enrollment in the study. The study protocol was approved by the institutional ethics committee, including the Institutional Review Board of the Royal Thai Army Medical Department at Phramongkutklao College of Medicine and Phramongkutklao Hospital (approval number Q013h/66_Exp), the Research and Ethics Committee of Thammasat University Hospital (approval number 021/2566), and the Ethics Committee of Udonthani Hospital (approval number IRBRTA 1343/2566). The study was conducted in accordance with the Declaration of Helsinki, the Belmont Report, the CIOMS guidelines, and the International Conference on Harmonisation Good Clinical Practice (ICH-GCP) standards.

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