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ORIGINAL ARTICLE

# Risk factors of mortality and comparative *in-vitro* efficacy of anidulafungin, caspofungin, and micafungin for candidemia

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**KEYWORDS**
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Fluconazole;
Micafungin

*Background:* Although echinocandins have high *in vitro* antifungal efficacy according to prior reports, comparative studies on the clinical cure rates of anidulafungin, caspofungin, and micafungin in systemic candida infections have not yet been reported.
*Methods:* Interpretation of clinical and microbiological responses to anidulafungin, caspofungin, and micafungin in 109 cases of candidemia was done according to the published criteria. The clinical cure rates between patients treated with echinocandins and patients treated with fluconazole were also compared. The minimal inhibitory concentrations (MICs) of anidulafungin, caspofungin, micafungin, and fluconazole for these 109 blood isolates of candida were determined with the Clinical and Laboratory Standards Institute M27-A reference microdilution method. Logistic regression with forward selection was used to determine the important factors of prognosis with variables such as age, underlying diseases, acute physiology and chronic health evaluation (APACHE) III score, persistent candidemia, and antimicrobial therapy.
*Results:* Among the 109 cases of candidemia, 70 were treated with echinocandins, azoles, or amphotericin B for $\geq$7 days. The clinical cure rate of cases treated with antifungal agents adequately ($\geq$7 days) and inadequately ($<$7 days) were 44/70 (62.9%) and 4/39 (10.2%),

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respectively, with significant difference ($p < 0.0001$). Clinical cure rates of anidulafungin, caspofungin, micafungin, and fluconazole were 18/30 (60.0%), 8/9 (88.9%), 5/7 (71.4%), and 9/18 (50%), respectively. The difference in APACHE III score between treatment success and failure cases was significant. The $MIC_{50}/MIC_{90}$ of anidulafungin, caspofungin, and micafungin for all *Candida* spp. were 0.03/1 μg/mL, 0.06/0.5 μg/mL, and 0.008/1 μg/mL, respectively.
*Conclusion:* Adequate antifungal therapy and APACHE III score are both independent factors affecting the clinical outcome. The clinical cure rate of the echinocandins group was higher than that of the fluconazole group without significant difference. Although caspofungin had the best clinical cure rate in this study, there was no significant difference between the clinical cure rates among these three echinocandins. All *Candida* spp. were susceptible *in vitro* to these three echinocandins.


## Introduction

Significant factors affecting the clinical outcome of candidemia and the associated mortality among critical patients in medical intensive care units have been reported.[1,2] Prior studies indicate that echinocandins such as anidulafungin, caspofungin, and micafungin manifest *in vitro* fungicidal activity against candida.[3—10] Furthermore, the clinical cure rate of caspofungin has been compared with that of micafungin and liposomal amphotericin B in invasive candida infections.[11,12] Anidulafungin has also been compared with fluconazole in the treatment of candidemia.[9] Nonetheless, to our knowledge, comparative studies on the clinical cure rates of anidulafungin, caspofungin, and micafungin in systemic candida infections has not yet been reported.[10—17] Therefore, this study sought to compare the clinical efficacy of these three echinocandins, as well as their *in vitro* efficacy in patients of candidemia. The clinical cure rates between patients treated with echincandins and patients treated with fluconazole were compared. Associated risk factors for treatment failure and mortality in candidemia were also investigated.

## Methods

### Patient enrollment

Keelung Chang Gung Memorial Hospital is a 1088-bed, tertiary-care, teaching hospital in Taiwan. This research was started in March 1, 2010 after being approved in February 2010. All candidemia patients in Keelung Chang Gung Memorial Hospital were enrolled between March 1, 2010 and December 31, 2011 for retrospective clinical analysis. Inclusion criteria were: (1) at least one blood culture positive for *Candida* spp.; (2) pre-existing risk factors for invasive *Candida* infection mentioned in literature[2]; and (3) clinical manifestation of sepsis. The patients' *Candida* isolates were stored for *in vitro* susceptibility study.

### Treatment regimens

All candidemia patients were treated with fluconazole or echinocandins with approval from an infectious disease specialist according to the Clinical Practice Guidelines for the Management of Candidiasis by the Infectious Diseases Society of America in 2009.[18] In patients with serum creatinine levels below 3 mg/dL, 200 mg of fluconazole was administered intravenously twice daily after a loading dose of 300 mg for 1—4 weeks (at least 1 week after blood culture-negative), depending on the patients' clinical response.[19] In patients with serum creatinine levels above 3 mg/dL, a 200 mg dose of fluconazole was administered intravenously once daily.[19] The loading dose of anidulafungin was 200 mg followed by a maintenance dose of 100 mg intravenously once daily for 1—4 weeks. The loading dose of caspofungin was 70 mg followed by a maintenance dose of 50 mg intravenously once daily for 1—4 weeks.[9,10,20] In the case of micafungin, there was no loading dose and a maintenance dose of 100 mg intravenously was given once daily for 1—4 weeks.[21] Coexisting bacterial infections were treated with appropriate antibiotics according to the antimicrobial susceptibility.[19] Surgery was performed if necessary to eradicate the infections upon obtaining informed patient consent.[19] Dosage of echinocandins including anidulafungin, caspofungin, and micafungin remained unchanged for patients with abnormal renal function.

### Evaluation criteria

Follow-up evaluations were performed daily by the attending physician in charge after the start of treatment. Standard clinical laboratory evaluations (blood chemistry, urinalysis, complete blood count, blood bacterial and fungal culture, and chest roentgenogram) were performed prior to, during, and after treatment as medically indicated. Interpretation of the clinical and microbiological responses was done according to the following criteria.[19] Clinical cure was indicated by the resolution of clinical signs and symptoms of infection due to the original *Candida* species, without signs of infection relapse caused by the original *Candida* species within 3 months after the discontinuation of the antifungal agent and the absence of the original *Candida* species in repeated post-therapy cultures.[19] Any coexisting bacterial infection was treated with appropriate antibiotics as recommended by infectious diseases specialists. Clinical treatment failure was indicated by an absence of clinical response to antifungal therapy after a minimum of 1 week of therapy, with persistence of