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Mary Hutton

Rachel M. Kenney

Jose A. Vazquez

Susan L. Davis

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# Influence of Body Weight Category on Outcomes in Candidemia Patients Treated With Anidulafungin

**Mary Hutton, PharmD, BCIDP[1], Rachel M. Kenney, PharmD, BCPS-AQ ID[2], Jose A. Vazquez, MD, FACP, FIDSA[3], and Susan L. Davis, PharmD[4]**

## Abstract

**Background:** Case reports and pharmacokinetic data suggest off-label echinocandin dosing may be needed to reach adequate serum concentrations in obese patients. Few outcome studies exist evaluating this population. **Objectives:** Of this study were to (1) determine the association of body mass index (BMI) with clinical outcomes of candidemia patients on standard doses of anidulafungin and (2) characterize fungal infections by body weight. **Methods:** A retrospective cohort was conducted to evaluate hospitalized patients treated for candidemia with anidulafungin at Food and Drug Administration–labeled dosing for at least 72 hours from January 1, 2014, through January 31, 2018. Candidemia was diagnosed by blood culture or T2 magnetic resonance (T2MR). Patients were compared according to BMI category. **Results:** One hundred seventy-three patients were included. *Candida albicans* and *Candida glabrata* were identified in 58 (33%) and 57 (33%) patients, respectively. Mortality was comparable according to BMI category: 4 (36.4%) underweight, 8 (25.8%) normal weight, 16 (32.0%) overweight, 20 (33.9%) obese, and 7 (31.8%) morbidly obese, $P = .976$. Variables associated with mortality included: severe sepsis (adjusted odds ratio [OR] = 5.1, 95% CI: 1.7-14.8) and liver disease (adjusted OR = 3.2, 95% CI: 1.1-9.4). Variables that were protective of mortality included: line removal (adjusted OR = 0.05, 95% CI: 0.02-0.2) and receipt of anidulafungin for at least 5 days (adjusted OR = 0.35, 95% CI: 0.15-0.8). **Conclusion:** There was no difference detected in mortality among patients with candidemia across BMI category. Larger studies are needed to confirm whether standard doses of anidulafungin are sufficient for candidemia in obese patients.

## Keywords

echinocandin, candidemia, obesity, antifungal stewardship

## Introduction

Obese patients may have altered pharmacokinetic parameters when compared with normal weight patients due to their body habitus and altered drug clearance. Differences in volume of distribution and systemic clearance may indicate that these patients require a larger dose of some antimicrobials to achieve the same minimum inhibitory concentrations (MIC) as normal weight patients.[1,2] Comparative clinical outcomes data for dosing antifungal agents in obesity are scarce, and published experience with the echinocandin class is limited to case reports.[3]

Recently, Bader and colleagues questioned current dosing strategies for echinocandins, including anidulafungin. Monte Carlo simulations demonstrate that anidulafungin is unlikely to achieve target attainment with Food and Drug Administration (FDA)–labeled dosing.[4] In hospitalized patients undergoing laparoscopic gastric bypass or sleeve surgery on anidulafungin for surgical prophylaxis, anidulafungin concentrations are approximately 33% lower than expected for a normal weight adult.[5] In this patient population, anidulafungin dosing may need to be increased from FDA-labeled doses to achieve target concentrations and maintain efficacy. A 50% increase from anidulafungin FDA-labeled loading and maintenance dose has been proposed for patients who are morbidly obese.[5,6] However, current literature is lacking to determine whether obese patients treated with standard anidulafungin doses have poorer clinical and microbiologic outcomes than

[1] Department of Pharmacy Services, Utah Valley Hospital, Provo, UT, USA
[2] Department of Pharmacy Services, Henry Ford Hospital, Detroit, MI, USA
[3] Department of Medicine, Augusta University, Medical College of Georgia, Augusta, GA, USA
[4] Department of Pharmacy Practice, Wayne State University Eugene Applebaum College of Pharmacy and Health Sciences, Detroit, MI, USA

**Corresponding Authors:**
Mary Hutton, Department of Pharmacy Services, Utah Valley Hospital, 1034 N 500 W, Provo, UT 84604, USA.
Email: mary.hutton@imail.org

normal weight patients. The purpose of the present study was to characterize bloodstream infection with *Candida* species and compare patient outcomes with anidulafungin treatment, stratified by body mass index category (BMI).

## Methods

### Study Design, Setting, and Patient Population

A retrospective cohort was conducted over a 4-year time period from January 1, 2014, through January 31, 2018, at a 4-hospital health system, Henry Ford Health system, in metropolitan Detroit, Michigan. All 4 hospitals utilize a centralized clinical microbiology laboratory and have antimicrobial stewardship programs. Anidulafungin was recommended in the antimicrobial stewardship guideline as first-line therapy for candidemia among intensive care unit patients and patients with a history of azole exposure. The institutional guideline recommended a minimum of 3 to 5 days of anidulafungin prior to azole switch. Anidulafungin was restricted to infectious diseases approval throughout the entire study. Restriction was supported by an electronic medical record order entry panel which bundled Infectious Diseases consultation, the anidulafungin loading dose, and maintenance dose. This study was approved by the institutional review board on June 7, 2018 (#11755).

The study population included all hospitalized adult patients who received anidulafungin 100 mg intravenously daily for at least 72 hours and who had a diagnosis of candidemia, defined as at least one positive blood culture or T2 magnetic resonance (T2MR) for *Candida* species (T2 Biosystems). Patients were not excluded if they did not receive the 200 mg loading dose. Patients receiving any immunosuppression agents posttransplant or who had neutropenia, defined as absolute neutrophil count <500 cells/mm$^3$ or <1000 cells/mm$^3$ but expected to decrease to <500 cells/mm$^3$ within the next 24 to 48 hours at time of positive blood culture or T2MR, were excluded. Patients were also excluded if the indication for antifungal therapy was endocarditis, osteomyelitis, or meningitis, and if the initial diagnosis of candidemia was made at an outside facility.

### Outcomes and Definitions

Patients included in the study were categorized into BMI groups as defined by the World Health Organization and National Institutes of Health: underweight (BMI < 18.5), normal weight (BMI 18.5-24.9), overweight (BMI 25-29.5), obese (BMI 30-39), and extremely obese (BMI $\geq$ 40). Body mass index was calculated by the study investigators by taking the patient's weight in kilograms and dividing it by the patient's height in meters squared using the measurements in the electronic medical record that were taken nearest to the first dose of anidulafungin.

The primary outcome was 30-day all-cause mortality. Thirty-day all-cause mortality was determined by medical record review by the primary investigator. Patients were presumed to have survived if they were discharged alive prior to 30 days of follow-up and there was no documentation in the electronic medical record indicating that they were deceased. Secondary outcomes included: 14-day global clinical cure rates, suspected *Candida* eye involvement, and recurrence with need for antifungal reinitiation. Global clinical cure was defined as achieving both microbiological success and clinical cure. Microbiological success was defined as documented, 2 subsequent negative blood cultures 24 hours apart, or presumed, one repeat negative culture with no recurrence. For patients diagnosed by T2MR, microbiological success was presumed if the patient had no positive blood cultures and a successful clinical response to antifungal therapy. If a patient did not achieve documented or presumed microbiological success as defined by the above definitions, he or she was classified as microbiological failure. Clinical cure was defined as the resolution of signs and symptoms of invasive candidiasis and no need for additional systemic antifungal therapy. *Candida* eye involvement was diagnosed by ophthalmology consult notes present in the electronic medical record. Recurrent fungal infection was defined as a mycologically confirmed infection with the same baseline Candida species within 6 weeks after primary fungal culture or a suspected infection that required additional systemic antifungal therapy after the end of all antifungal therapy in patients previously considered to have a successful response. Optimal fluconazole dose was defined as fluconazole 6 mg/kg of actual body weight or 3 mg/kg if the patient's creatinine clearance was less than 30 mL/min or the patient was on hemodialysis while receiving fluconazole. In patients with fluconazole MIC 16 to 32 μg/mL, 12 mg/kg was considered optimal. Optimal voriconazole dosing was defined as voriconazole 4 mg/kg, as defined by the Infectious Diseases Society of America Candidiasis Guidelines.[7]

### Data Collection and Analysis

Patients were identified by positive blood culture and T2MR results in the study time frame using Theradoc® (Premier, Inc) and Epic version 2017 (Epic Systems Corp) and enrolled consecutively. Data were extracted from electronic medical records using a standardized case report form. Past medical history and age were collected at the time of admission. Sequential organ failure assessment score was collected at the time of candidemia identification. Candidemia risk factors,[8] microbiology data, source control, antifungal therapy, and ophthalmology data were collected from the time of first positive blood culture or T2MR through hospital discharge. Microbiology data included number and timing of positive blood cultures or T2MR, *Candida* species, antifungal susceptibilities, and time to blood culture clearance. Global clinical cure, microbiological cure, and clinical cure were evaluated at 14 days from the time of first positive blood culture or T2MR. Recurrence of candidemia and need for additional antifungal therapy were evaluated until 6 weeks after the first positive blood culture or T2MR, if data were available. Finally, *Candida* spp. MICs were determined by the microbiology

**Table 1.** Patient Characteristics.

| N (%) | BMI <18.5, N = 11 | BMI 18.5-24, N = 31 | BMI 25-29, N = 50 | BMI 30-39, N = 59 | BMI ≥40, N = 22 |
|---|---|---|---|---|---|
| Female | 3 (27.3) | 14 (45.2) | 21 (42.0) | 26 (44.1) | 16 (72.7)[a] |
| Pulmonary condition[b] | 3 (27.3) | 6 (19.4) | 11 (22.0) | 16 (27.1) | 11 (50.0)[a] |
| Congestive heart failure | 2 (18.2) | 3 (9.7) | 10 (20.0) | 12 (20.3) | 5 (22.7) |
| Diabetes mellitus | 3 (27.3) | 8 (25.8) | 16 (32.0) | 26 (44.1) | 12 (54.5) |
| Cancer | 4 (36.4) | 12 (38.7)[a] | 12 (24.0) | 13 (22.0) | 2 (9.1) |
| Liver disease | 1 (9.1) | 4 (12.9) | 10 (20.0) | 4 (6.8) | 4 (18.2) |
| Chronic kidney disease | 2 (18.2) | 6 (19.4) | 14 (28.0) | 15 (25.4) | 1 (4.5) |
| SOFA score[a] | 4 (1.5-7) | 5 (2-8) | 6 (3.25-10) | 9 (4-12) | 8.5 (5-11.75) |
| Anidulafungin for 5 days[c] | 5 (45.5) | 16 (51.6) | 29 (58.0) | 29 (49.2) | 11 (50.0) |
| Candidemia risk factors | | | | | |
| Total parenteral nutrition | 3 (27.3) | 6 (19.4) | 6 (12.0) | 4 (6.8) | 1 (4.5) |
| Surgery[d] | 1 (9.1)[a] | 15 (48.4) | 25 (50.0) | 32 (54.2) | 12 (54.5) |
| Multifocal colonization[e] | 0 (0) | 1 (3.2) | 5 (10.0) | 8 (13.6) | 2 (9.1) |
| Severe sepsis[f] | 6 (54.5) | 18 (58.1) | 33 (67.3) | 44 (74.6) | 18 (81.8) |
| Central line | 11 (100) | 26 (83.9) | 44 (88.0) | 53 (89.9) | 21 (95.5) |
| Median Candida score[8] | 3 | 3 | 3 | 3 | 3 |

Abbreviations: BMI, body mass index; SOFA, sequential organ failure assessment; T2MR, T2 magnetic resonance.
[a]$P < .05$.
[b]The patient had a chronic pulmonary disease listed in their past medical history, including cystic fibrosis, chronic obstructive pulmonary disease, asthma, pulmonary fibrosis, and interstitial lung disease.
[c]The patient received anidulafungin for at least 5 days prior to stepping down to triazole therapy.
[d]Any recent surgery in the prior 30 days to positive blood culture of T2MR.
[e]Candida isolated from 2 noncontiguous sites: oropharynx, stomach, urine, or tracheal aspirate.
[f]The patient has ≥2 systemic inflammatory response syndrome criteria plus signs of end organ damage.

laboratory using microdilution multiwell plates and was performed upon request only.

Statistical analyses were performed as follows: Dichotomous data were analyzed by Pearson $\chi 2$ or Fisher exact test, as appropriate, ordinal data by Kruskal-Wallis test, and continuous data by Student *t* test or Mann-Whitney *U* test, as appropriate. Logistic regression analysis was performed to evaluate variables independently associated with mortality while controlling for confounding factors. Variables with a *P* value of <.2 in bivariate analysis and with clinical rationale for a potential association with mortality were considered for inclusion. In the final model, an adjusted odds ratio with a CI that did not include 1.0 was considered statistically significant. All statistical analyses were performed using SPSS software version 22.0 (IBM Inc). The sample of size of 340 patients was determined assuming alpha = .05, beta = .20, and an anticipated effect size of 15% for mortality in candidemia. A baseline mortality rate of 35% was assumed for normal weight patients.[9,10]

## Results

Four hundred sixty-three patients with candidemia were screened for inclusion; 290 patients were excluded: 226 received an echinocandin for less than 72 hours, 26 patients had endocarditis, 25 patients were receiving immunosuppression for a transplanted organ, and 13 patients were neutropenic, pediatric, had osteomyelitis, or were diagnosed at an outside hospital; 173 patients met eligibility criteria and were included in the study population; 171 were managed by an Infectious Diseases consultant. Patient characteristics and candidemia risk factors are displayed in Table 1. Most patients had a central line in place at the time of positive culture/T2MR and over half of the patients had sepsis with end organ dysfunction.

*Candida albicans* (33%) and *Candida glabrata* (33%) were the most common species identified (Table 2). Sources of infection were no different between BMI groups, with the most common source of infection identified as the central line (43.3%), followed by an unknown source (30%) and intra-abdominal infection (18%). Species identified by blood culture were no different when compared with T2MR. Most patients did not have antifungal susceptibilities performed; however, 46 fluconazole, 14 voriconazole, and 34 anidulafungin MICs were available to evaluate. The $MIC_{50}$ and $MIC_{90}$ are described in Table 3. Anidulafungin MICs were low for almost all patients but were greater than or equal to 1 μg/mL in 5 *Candida parapsilosis* species. This elevation in anidulafungin MIC was not seen in any other species.

Median days to administration of anidulafungin was one day from positive T2MR or positive culture for yeast. All but one patient received a 200-mg loading dose of anidulafungin. Patients who survived that had therapy de-escalated to a triazole were less likely to receive an optimal dose, 46 (59%) of 78, compared to patients who expired, 18 (82%) of 22. All doses considered suboptimal were lower than recommended. Patients who survived received more days of anidulafungin and more days of total antifungal therapy compared to patients who expired: 5 (3-14) days versus 4 (3-6) days and 18 (15-29) days versus 8 (5-11), respectively. Similarly, survivors were more likely to achieve source control compared to patients who

**Table 2.** *Candida* spp. Characteristics by BMI.

| N (%) | BMI <18.5, N = 11 | BMI 18.5-24, N = 31 | BMI 25-29, N = 50 | BMI 30-39, N = 59 | BMI ≥40, N = 22 |
|---|---|---|---|---|---|
| *Candida albicans* | 3 (27.3) | 6 (19.4) | 10 (20.0) | 17 (28.8) | 4 (18.2) |
| *Candida glabrata* | 2 (18.2) | 7 (22.6) | 11 (22.0) | 16 (27.1) | 4 (18.2) |
| *Candida parapsilosis* | 0 | 4 (12.9) | 2 (4.0) | 6 (10.2) | 3 (13.6) |
| Other Candida spp. | 2 (18.2) | 6 (19.4) | 9 (18.0) | 10 (16.9) | 4 (18.2) |
| T2 *Candida albicans*/tropicalis | 4 (36.4) | 6 (19.4) | 7 (14.0) | 8 (13.6) | 2 (9.1) |
| T2 *Candida glabrata*/krusei | 0 | 2 (6.5) | 12 (24.0) | 8 (13.6) | 1 (4.5) |
| T2 *Candida parapsilosis* | 2 (18.2) | 2 (6.5) | 4 (8.0) | 3 (5.1) | 5 (22.7) |
| Anidulafungin MIC ≥0.12 μg/mL | 0 | 3 (9.7) | 2 (4.0) | 6 (10.2) | 0 |
| Source | | | | | |
| Intra-abdominal | 1 (9.1) | 4 (12.9) | 13 (26.0) | 8 (13.6) | 5 (22.7) |
| Central line | 7 (63.6) | 15 (48.4) | 21 (42.0) | 23 (39.0) | 9 (40.9) |
| Genitourinary | 0 | 3 (9.7) | 3 (6.0) | 3 (5.1) | 1 (4.5) |
| Skin | 0 | 0 | 1 (2.0) | 0 | 2 (9.1) |
| Other | 0 | 0 | 0 | 2 (3.4) | 0 |
| Unknown | 3 (27.3) | 9 (29.0) | 12 (24.0) | 23 (39.0) | 5 (22.7) |

Abbreviations: BMI, body mass index; MIC, minimum inhibitory concentration.

**Table 3.** Antifungal MIC Distribution.

| Antifungal | $MIC_{50}$ (μg/mL) [IQR] | $MIC_{90}$ (μg/mL) |
|---|---|---|
| Fluconazole, N = 46 | 4.0 [1.0-8.0] | 16.0 |
| Voriconazole, N = 14 | 0.25 [0.12-0.5] | 2.0 |
| Anidulafungin, N = 34 | 0.03 [0.03-0.12] | 1.0 |

Abbreviations: IQR, interquartile range; MIC, minimum inhibitory concentration.

expired, 111 (94%) of 118 and 38 (69%) of 55, respectively, and have the central line removed, 95 (94%) of 101 and 28 (52%) of 53, respectively. Time to central line removal did not differ between patients who survived and those who expired, 3 days (1.75-4.5) versus 2 days (1-4.75).

The primary end point of mortality was not significantly different between the BMI groups: underweight: 4 (36.4%), normal: 8 (25.8%), overweight: 16 (32.0%), obese: 20 (33.9%), and morbidly obese: 7 (31.8%), $P = .976$. In logistic regression, sepsis with end organ damage and liver disease were independent predictors of mortality, while receipt of an echinocandin for at least 5 days and central-line removal were protective (Table 4). Global clinical cure was achieved in 103 (87%) of patients who survived. Microbiological success was achieved in 116 (98.3%) of patients who survived: 88 (74.6%) documented and 28 (23.7%) presumed. In patients who died, 3 (5.5%) achieved global clinical cure and 51 (92.8%) achieved microbiological clearance (47.3% documented and 45.5% presumed). Among survivors, 5 patients had relapse of candidemia, and 16 patients received additional antifungal therapy. Of patients who had evaluation for *Candida* eye involvement, more patients who expired had involvement at 10 (26.3%) compared to 16 (16.8%) who survived. Distribution of *Candida* eye involvement by BMI was similar for those who underwent evaluation: underweight: 1 (12.5%) of 8, normal: 6 of 24 (25.0%), overweight: 7 of 39 (17.9%), obese: 9 of 42 (21.4%), and morbidly obese: 3 of 20 (15.0%), $P = .971$.

## Discussion

This study provides valuable patient outcome information on the relationship between BMI, echinocandin dose, and outcome. In the absence of therapeutic drug monitoring, an outcome assessment by BMI category is an important surrogate. The current echinocandin pharmacodynamic target of area under the curve to MIC ratio was derived in neutropenic murine models.[11] Although serum concentrations appear to be lower in obese patients, previous studies have reported successful outcomes with FDA-labeled echinocandin doses for candidiasis. Zomp and colleagues published a case report of a patient who weighed 230 kg with a corresponding BMI of 102 $kg/m^2$ that was treated with the FDA-labeled dose of micafungin for a *C glabrata* urinary tract infection that was suspected to have disseminated. Although micafungin serum concentrations were half of what is expected in normal weight adults, the patient had a successful clinical outcome with sterilization of cultures.[12] Furthermore, in a post hoc evaluation of 9 prospective clinical trials of caspofungin that evaluated safety and efficacy, clinical outcomes were compared in normal weight versus overweight patients. Body mass index category was not associated with clinical success or failure in this study, with clinical success ranging between 71% and 77% between the categories.[13] The "obesity paradox" may also play role in outcomes for these infections. Although obesity is associated with heightened morbidity and mortality for most adults, there are some conditions and infections that it has been described as protective for. An example of one of these conditions is severe sepsis, and no data exist that pertain to candidemia specifically.[14]

Anidulafungin MICs in this study were within expected values for the *Candida* species that were evaluated. The antifungal stewardship program and the quality of management of candidemias may have contributed to the overall success of patients in all BMI groups. Most patients had anidulafungin administered within 24 hours of candidemia onset, received the appropriate FDA-labeled anidulafungin loading dose, had

**Table 4.** Logistic Regression Analysis of Independent Predictors of Mortality.

| Variable, N (%) | Survived, N = 118 | Died, N = 55 | Unadjusted OR [CI] | Adjusted OR [CI] |
|---|---|---|---|---|
| Anidulafungin MIC ≥0.12 μg/mL | 11 (37.9) | 0 | 0.78 [0.63-0.97] | - |
| Sepsis with organ dysfunction | 73 (61.9) | 46 (83.6) | 3.15 [1.41-7.05] | 5.06 [1.73-14.8] |
| Liver disease | 10 (8.5) | 13 (23.6) | 3.34 [1.36-8.21] | 3.20 [1.09-9.35] |
| Anidulafungin ≥5 days | 68 (57.6) | 21 (38.2) | 0.45 [0.24-0.87] | 0.35 [0.15-0.82] |
| Line removal | 95 (94.1) | 28 (52.8) | 0.07 [0.03-0.19] | 0.05 [0.02-0.16] |

Abbreviations: MIC, minimum inhibitory concentration; OR, odds ratio.

source control achieved, and were transitioned to an appropriate weight-based fluconazole dose.

Interestingly, *Candida* epidemiology did not differ between the BMI groups. Some information suggests that obesity changes the mycobiome, and that differences in infecting *Candida* species would be expected.[15] Source of *Candida* infection did not differ between BMI groups.

There are some limitations to this study. Some of this study's findings could have been affected by survivor bias, including days of antifungal therapy, achievement of source control, and ophthalmologic examination completion. Study data were dependent on electronic medical record documentation, which may have led to misclassification bias in some patient information, such as determining the source of infection. Fifty-two (30%) of patients in our cohort did not have a source identified for candidemia based upon chart documentation. Source control of candidemia is a known predictor of survival, and this may have affected our outcomes. It is possible that our results could be explained from a confounding variable not evaluated in the study. Since this study was completed over a 4-year time span, improvements in the management of candidemia are possible. However, there was no evidence of maturation according to the trend in mortality by year: 2014 (36%), 2015 (20%), 2016 (45%), and 2017 (28%). Unfortunately, there were incomplete antifungal susceptibility data in this study, and the majority of isolates did not have testing performed. Interestingly, 5 of the 6 *C parapsilosis* species that had anidulafungin MIC testing completed had MICs ≥1 μg/mL. All of these patients survived, and all were transitioned to fluconazole definitive therapy. However, 23 *C parapsilosis* infections did not have anidulafungin MIC testing performed, so conclusions cannot be drawn for this subgroup. Finally, we did not meet our intended sample size. Many eligible patients did not receive an echinocandin for at least 72 hours, which excluded them from the study. It was impractical to extend our study because data older than 2014 was not available in the current electronic health record.

## Conclusion

In conclusion, we did not detect a difference in 30-day all-cause mortality when comparing candidemia patients treated with FDA-label dosing of anidulafungin by BMI category, although our study of 173 candidemia patients was underpowered. Additionally, we did not identify differences in *Candida* spp. or resistance across BMI categories. Larger studies with therapeutic drug monitoring are needed to determine whether routine, off-label dose adjustments are necessary in obesity or morbid obesity.

### Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: S.L.D. reports consulting fees from Spero Therapeutics, Allergan, and Tetraphase Pharmaceuticals.

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### ORCID iD

Mary Hutton, PharmD, BCIDP https://orcid.org/0000-0001-6397-7511

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