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Received: 3 March 2020 | Revised: 16 December 2020 | Accepted: 28 December 2020

DOI: 10.1111/aas.13783

ORGINAL ARTICLE

acta Anaesthesiologica Scandinavica

Use and outcome of empiric echinocandins in critically ill patients

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Funding Information
None.

Abstract

Background: Echinocandins are recommended as a first-line empiric treatment for fungal infections of patients in an intensive care unit (ICU) with critical illness. The primary aim of the study was to compare outcomes among ICU patients treated with empiric anidulafungin (ANI), caspofungin (CASPO), or micafungin (MICA).

Methods: A retrospective cohort study in a mixed adult ICU. Patient demographics, reason for ICU admission, ICU risk scores and organ support therapies were analyzed. Outcome parameters included ICU and hospital stay, 30-day mortality and 1-year mortality.

Results: Empiric echinocandin therapy was given to 367 patients (ANI; 73 patients, CASPO; 84 patients, and MICA; 210 patients) with a median duration of 3 days in an ICU. Patient median age was 60.7 years. As a first-line therapy, 52% of patients received fluconazole. Positive *Candida* cultures were found in the following samples: blood, 16 (4.4%); central line, 27 (7.4%); deep site, 92 (25.1%). Median ICU stay (ANI 6.4 days, CASPO 5.3 days, MICA 8.1 days), hospital stay (ANI 33 days, CASPO 30 days, MICA 30 days), 30-day mortality (ANI 27%, CASPO 32%, MICA 32%), and 1-year mortality (ANI 33%, CASPO 44%, MICA 45%) did not differ between the groups . The cost of antifungal therapy during the ICU period was similar in the three echinocandin groups (ANI; €1 872, CASPO; €1 799, and MICA; €1783).

Conclusion: Our results show that ICU, hospital stay, and mortality (hospital, 30-day and 1-year) did not differ among patients with empiric anidulafungin, caspofungin, or micafungin treatment in a mixed adult ICU.

Editorial Comment

This retrospective single-center study identified patients in a mixed ICU during a 6-year period who were treated empirically with caspofungin, micafungin, or anidulafungin. None of the following, ICU stay, hospital stay, mortality, or costs differed between these treatment groups.

Abbreviations: ANI, anidulafungin; APACHE II, acute physiology and chronic health evaluation II score; CASPO, caspofungin; CRI, catheter-related infection; LOS, length of stay; MICA, micafungin; MV, mechanical ventilation; NA, noradrenaline; RRT, renal replacement therapy; SAPS II, simplified acute physiology score; SMR, standardized mortality ratio; SOFA, sequential organ failure assessment scores; TISS, therapeutic interventions scoring system; WBC, white blood cell.

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1 | INTRODUCTION

Fungal infections are an increasing problem in intensive care, and contribute significantly to morbidity and mortality as well as costs.[1-4] Prophylaxis with fluconazole in high-risk, critically ill patients has reduced the incidence of invasive fungal infections and mortality.[5]

Blood culture is the "gold standard" for the diagnosis of invasive candidiasis (IC). However, the overall sensitivity of blood culture is only 50% and there may be an identification time lag of up to 5 days.[6,7] The assay time of many blood culture independent methods requiring DNA extraction is only about 2 hours.[8] However, many of these assays have thus far not been validated for diagnosing IC in multi-center studies. So, the empiric antifungal therapy belongs to everyday practice in the ICU because timely and appropriate empiric antifungal therapy improves survival among patients with septic shock due to candidemia.[9]

According to recent guidelines, echinocandins (caspofungin, micafungin, and anidulafungin) are recommended for first-line empiric treatment for critically ill patients in the ICU.[10] They have less severe side effects than amphotericin B, the gold standard of antifungal agents.[11-13] The echinocandins are semisynthetic lipopeptides which inhibit the synthesis of the 1,3-beta-D-glucan component of the fungal cell wall.[14] They have rather similar pharmacological and efficacy profiles, as well as few drug-drug interactions.[15]

Only a limited number of studies compare the clinical efficacy of echinocandins in patients with critical illness. Anidulafungin has been shown to be non-inferior to fluconazole in the treatment of invasive candidiasis.[16] Recent studies have not shown the superiority of caspofungin or micafungin over fluconazole prophylaxis for high-risk patients in the ICU.[17-20]

Because empirical antifungal therapy with echinocandins is commonly used in the ICU, real-life observations of possible differences between three available echinocandins are warranted. The primary aim of this retrospective study was to compare outcomes among ICU patients treated with empiric anidulafungin (ANI), caspofungin (CASPO), or micafungin (MICA) in an adult mixed ICU.

2 | METHODS

2.1 | Ethics

This non-interventional study using routine clinical data was approved by the Department of Operative Care of the Oulu University Hospital and the Data Protection Ombudsman. The requirement for written informed consent was waived due to the retrospective nature and lack of intervention. Our database guaranteed patient confidentiality.

2.2 | Study setting

This was a retrospective single-center observational cohort study performed at the Oulu University Hospital, Finland, which is an academic tertiary-level unit with a 26-bed mixed adult closed intensivist-led ICU. In our multidisciplinary team, intensivists do daily rounds together with an infectious disease specialist, gastroenterology surgeon, pharmacist, cardiologist, and radiologist. All the patients receiving systemic echinocandins ANI, CASPO, or MICA during their intensive care unit stay between 2009 and 2014 were included in the study. Patients were allocated to echinocandin groups (ANI, CASPO, and MICA) according to the first echinocandin used.

2.3 | Data extraction

Data were extracted from our ICU electronic patient data management system (Clinisoft), the electronic hospital information system, and hospital pharmacy databases. The following data were obtained: age, gender, body mass index (BMI), pre-existing comorbidities, Acute Physiology and Chronic Health Evaluation II (APACHE II) scores, Simplified Acute Physiology Score (SAPS II), Sequential Organ Failure Assessment scores (SOFA), use of fluconazole, type of admission, focus of infection, C-reactive protein (CRP), procalcitonin (PCT), and platelet and leukocyte count on admission. The intensity of treatment was recorded according to the Therapeutic Interventions Scoring System (TISS).[21,22] Time to echinocandin administration from ICU admission, fluconazole administration, as well as length of both antifungal treatments in the ICU were obtained.

Treatments for organ dysfunctions were recorded as needed for mechanical ventilation, renal replacement therapy, and vasopressor requirements. Microbiological results of yeast cultures from blood, central line, and any deep-site foci were recorded as well. According to our standard guidelines, cultures are to be taken from any suspected infection focus if a new infection is suspected during the ICU stay. Hospital and 30-day and 365-day mortalities were recorded. The data on survival up to 365 days were obtained from the Finnish Population Register Centre. The ratio between observed and predicted deaths (standardized mortality ratio, SMR) was calculated for 30-day mortality according to the APACHE II score and SAPS II score on admission and retrieved from the electronic data management system. Empiric therapy was recommended as a medication in patients with symptoms of sepsis and suspected fungal infection. Empiric treatment with antifungal agents was supervised by an infectious disease physician (PY or HS). The decision to initiate or withdraw echinocandin therapy was based on guidelines and updated literature, patient risk assessment, and response to prior antifungal therapy.

Empiric echinocandin therapy was given to patients with surgical intra-abdominal infections with a poor response to fluconazole treatment and patients with uncontrolled sepsis and long-term, broad-spectrum antibiotic therapy with fluconazole. Echinocandins have been the first choice in cases when a deep *Candida* infection cannot be ruled out in a hemodynamically unstable patient, or if there have been allergies or serious interactions between the azole group of antifungals and a patient's other medications. Adjustment of dosage for renal and/or hepatic insufficiency was taken into account.

The total expense of antifungal treatment was calculated by multiplying the actual daily cost of each echinocandin and fluconazole by the days it was used for each patient during their ICU stay. The cost of a daily dose covered the acquisition price, dose of the echinocandin, and was calculated with the aid of the hospital pharmacy. During the study period, the cheapest echinocandin was used, with the exception that CASPO is a preferred echinocandin among hematological patients in our hospital.

2.4 | Statistical analysis

The data were analyzed with descriptive statistics. Summary statistics for continuous or ordinal variables are expressed as medians with 25th and 75th percentiles or 95%CI as appropriate, and the analysis between groups was done by the Kruskal–Wallis test. Categorical variables were analyzed using Pearson's Chi-square test. Two-tailed P-values less than 0.05 were considered statistically significant. Analyses were performed using the SPSS software program for Windows (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.).

3 | RESULTS

During the 6-year study period, there were 13 302 patient admissions to our ICU and 367 patients (2.8%) received empiric echinocandin therapy; 210 (57%) MICA, 84 (23%) CASPO, and 73 (20%) ANI (Table 1). Twenty-five patients (7%) received two echinocandins. As a first-line therapy, 52% of patients had received fluconazole.

The median age of the patients was 60.7 years (Table 1). There were 231 men (62.9%) and 357 patients (97.3%) had an emergency admission. Their median BMI was 26.1 and 25.9% of the patients had a BMI higher than 30. The median APACHE II and SAPS II scores on admission were 19 and 42, respectively. Comorbidities were recorded in 207 patients (56%). Malignancies were recorded in 39 (11%) cases and leukemia or lymphoma in 54 cases (15%).

MICA patients had the lowest SAPS II scores on admission (Table 1). This was the only statistical difference ($P = .037$), while other severity scores or organ dysfunctions between the echinocandin groups did not differ statistically (Table 1). CASPO patients had the lowest median platelet and leucocyte levels on admission. Either leukemia or lymphoma was detected in 35.7% of patients. MICA patients had the highest frequency of chronic comorbidities (62%) and post-operative admissions (30%).

The foci of infections in the three groups are presented in Table 2. The spectrum of different foci was rather similar in the three groups with three exceptions: Twenty-six patients (7.1%) had a blood culture-positive infection; 16 with *Candida* species and 10 with bacterial species. Blood culture-positive infections were observed only in the CASPO group (13.1%) and MICA group (7.0%), while none was observed in the ANI group (Table 2). Intra-abdominal infections were observed most often in the MICA group and urinary tract infections in the CASPO group. The focus of the infection was unknown in only 12 cases (3.2%).

Table 3 shows *Candida* findings. Altogether, there were 135 positive infections in 112 patients (ANI 19, CAPSO 22, and MICA 71 patients). There were 16 positive blood cultures: 10 *Candida albicans* and 6 *Candida non-albicans* findings. Five of them (6.0%) were in the CASPO group and 11 (5.2%) in the MICA group, while none occurred in the ANI group (Table 3). All 10 *Candida albicans* strains were sensitive to echinocandins and fluconazole. Four of six non-albicans species were sensitive to echinocandins: one *Candida glabrata* strain was resistant to all three echinocandins and the other one was sensitive only to ANI and MICA. Four non-albicans strains were resistant to fluconazole (66.7%). Furthermore, there were 27 positive central line cultures and 92 deep site cultures—most often in the MICA group (n = 57). Altogether, there were 73 *Candida albicans* and 62 non-albicans findings. There were no significant differences in 30-day (26%, 32%, and 34%) or 365-day (42%, 41%, and 45%) mortalities in cases with culture-proven *Candida* infections among ANI, CASPO, and MICA groups. There were no differences between the groups regarding the SMR calculated according to the APACHE II score (ANI 0.645 [95%CI 0.209-1.505]; CASPO 0.855 [95% 0.344-1.762]; MICA 1.034 [95%CI 0.622-1.538]) or SAPS II score (ANI 0.675 [95%CI 0.219-1.575]; CASPO 0.837 [95%CI 0.337-1.725]; and MICA 0.986 [95% CI 0.631-1.466]) in cases with culture-proven *Candida* infections.

Renal replacement therapy (RRT) was needed in 25% of the patients and it varied from 24% to 27% in the three echinocandin groups (Table 4). The duration of RRT was longest in the CASPO group (Table 4). Noradrenalin treatment was least often needed in the CASPO group (Table 4). The resource utilization measured by TISS scores did not differ between the groups.

The total costs of all antifungal treatments during ICU stays did not differ between the three echinocandin groups (Table 5). The same holds true for fluconazole and echinocandin days. ICU and hospital length of stay or hospital, and 30-day and 1-year mortality did not differ between echinocandin groups (Table 5). The SMR values were equal by both APACHE II and SAPS II calculations. The SMR value was lowest in the ANI group with a wide confidence interval. During the study period, between 2009 and 2014, the cheapest echinocandin was usually used annually with the exception of CASPO for hematological patients.

4 | DISCUSSION

To the best of our knowledge, this retrospective non-interventional study is the first and one of the largest of its kind comparing real-life ICU data on the empiric use of three echinocandins (ANI, CASPO and MICA). We showed that ICU and hospital stay or mortality (hospital, 30-day, and 1-year) and the costs of empiric antifungal therapy did not differ between the three echinocandin groups.

Echinocandins are recommended as a first-line empiric treatment for critically ill patients in the ICU according to IDSA guidelines.[10]

TABLE 1 Summary of patient characteristics, ICU scores, clinical data, and comorbidities according to echinocandin group

	All (N = 367)	Anidulafungin (N = 73)	Caspofungin (N = 84)	Micafungin (N = 210)
Age (median)	60.7 [49.7, 70][b]	60.5 [47.9, 68.6]	59.8 [48.5, 68.6]	60. 2[49.5, 69.5]
Gender (male, %)	231 (63)	45 (62)	57 (68)	129 (61)
Body mass index, kg/m^2 (range)	26.1 [23.4, 30.2]	26.6 [22.7, 29.1]	25.8 [22.6, 30.2]	26.2 [23.6, 30.8]
BMI > 30 (%)	25.9	20.6	25.0	28.1
APACHE II adm	19 [14, 24]	21.5 [16, 24]	20 [15, 25]	18 [14, 23]
SAPS II	42 [33, 53]	46 [38, 57]	45 [36, 55]	41 [31, 53]
SOFA adm	6 [4, 9]	7 [5, 11]	6.5 [4.5, 10]	6 [4, 9]
SOFA max	10 [7, 14]	10 [7,14]	10 [7,14]	10 [7, 14]
CRP mg/mL adm	145 [75, 228]	133 [96, 208]	138 [64, 230]	158 [96, 228]
PCT µg/mL adm	2.4 [0.8, 12.8]	2.2 [0.9, 10.5]	2.5 [0.8, 14.2]	2.4 [0.7, 12.4]
Platelets, x 10^9/L adm	183 [102, 288]	204 [105, 313]	116 [40, 213]	197 [111, 297]
WBC, x 10^9/L adm	4.6 [9.8, 14.9]	10 [7.2, 13.6]	5.6 [1.2, 12.9]	10 [5.1, 15.7]
Fluconazole use (%)	191 (52)	39 (53)	36 (43)	116 (55)
Duration fluconazole treatment before echinocandin (days)	4.1 [1.8, 8.2]	3.8 [1.9, 7]	6.1 [1.5, 11.7]	4.1 [1.3, 7.4]
Echinocandin initiation since ICU admission (days)	1.1 [0.3, 6.2]	1.2 [0.5, 7.9]	0.9 [0.25, 3.2]	1.6 [0.3, 6.4]
Emergency admission (%)	357 (97)	72 (99)	82 (98)	203(97)
Operative admission (%)	91(25)	18 (25)	10 (12)	63 (30)
Comorbidities[a] (%)	207 (56.4)	38 (52.1)	39 (46.4)	130 (61.9)
Lymphoma (%)	24 (6.5)	3 (4)	10 (12)	11 (5.2)
Leukemia (%)	30 (8.2)	1 (1)	20 (24)	9 (4.3)
Malignancy (%)	39 (10.6)	9 (12)	6 (7)	24 (11)
Chronic heart failure (%)	16 (4.4)	5 (6.8)	2 (2.4)	9 (4.3)
Coronary heart disease (%)	57 (15.5)	15 (21)	9 (11)	33 (16)
Chronic renal disease (%)	34 (9.3)	6 (8.2)	3 (3.6)	16 (7.6)
Diabetes (%)	53 (14.4)	9 (12.3)	9 (11)	35 16.7)
COPD (%)	42 (11.4)	6 (8.2)	12 (14.3)	24 (11.4)
Cerebrovascular diseases (%)	32 (8.7)	6 (8.2)	8 (9.5)	18 (8.6)
Universal ASO (%)	13 (3.5)	5 (8.2)	1 (1.2)	7 (3.3)
Hypertension (%)	90 (24.5)	13 (18)	13 (16)	64 (31)
Epilepsy (%)	15 (4)	4 (5.5)	3 (3.6)	8 (3.8)

[a]The number represents patients with any comorbidities. Patients may have several comorbidities. Abbreviations: adm, on admission; APACHE II adm, acute physiology and chronic health evaluation II scores on admission; ASO, Arteriosclerosis obliterans; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; PTC, procalcitonin; SAPS II, simplified acute physiology score; SOFA adm, sequential organ failure assessment scores on admission; WBC, white blood cell.

[b]Parenthesis, Results presented as medians with 25th and 75th percentiles.

Furthermore, according to European guidelines, empirical treatment of patients with septic shock and suspected candidiasis should be started as soon as possible.[23] We gave empiric echinocandin therapy to patients with surgical intra-abdominal infections with a poor response to fluconazole treatment or to patients with uncontrolled sepsis and long-term, broad-spectrum antibiotic therapy with fluconazole. We did not use *Candida* scores, which have been shown to be unreliable and costly predictors of candidemia in ICU populations.[24,25]

This EMPIRICUS trial is one of the most interesting empiric studies among critically ill patients who acquired severe sepsis with *Candida* colonization.[25] In this multi-center, double-blinded study, the 28-day mortality in the empirical micafungin group was 30% and the placebo group 29.7%. However, in this study, neutropenic patients were excluded and only 5% of the patients had undergone abdominal surgery.

Our series also included these excluded patient groups. Thus, we consider that our real-life, although retrospective, patient

TABLE 2 Foci of infections of 367 patients on whom empiric echinocandin treatment was started during ICU stay between 2009 and 2014

Foci of infections	All (N = 367)	Anidulafungin (N = 73)	Caspofungin (N = 84)	Micafungin (N = 210)
Lung	155 (42)	30 (41)	32 (38.1)	93 (44.3)
Intra-abdominal	94 (26)	15 (21)	15 (17.9)	64 (31)
Blood[a]	26 (7.1)	0	11 (13.1)	15 (7.1)
Surgical site infection	19 (5.2)	5 (6.8)	2 (2.4)	12 (5.7)
Skin and soft tissue	17 (4.2)	5 (6.8)	3 (3.6)	9 (4.3)
Central catheter	14 (3.8)	5 (6. 8)	4 (4.8)	5 (2.4)
Endocarditis	9 (2.5)	3 (4.1)	0	6 (2.9)
Urinary	8 (2.2)	1 (1.4)	7 (8.3)	0
Neutropenic sepsis	2 (0.5)	0	2 (2.4)	0
Other	4 (1.1)	1 (1.4)	0	3 (1.4)
Unknown	12 (3.2)	3 (4.1)	1 (1.2)	8 (3.6)

[a]*Candida* blood cultures were positive in 16 cases, please see Table 3. Blood cultures yielded in two cases *Eshericia coli* and *Enterococcus faecium* and the rest one of each; *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Bacillus cereus*, *Klebsiella pneumoniae*, *Serratia marcenscens*, and *Bacteroides fragilis*.

TABLE 3 *Candida* findings of 367 patients with empiric echinocandin treatment

	All (N = 367)	Anidulafungin (N = 73)	Caspofungin (N = 84)	Micafungin (N = 210)
Blood, n (%)	16 (4.4)	0	5 (6.0)	11 (5.2)
C albicans	10 (2.7)	0	3 (3.6)	7 (3.3)
C non-albicans	6 (1.6)	0	2 (2.4)	4 (1.9)
Central catheter culture	27 (7.4)	7 (9.6)	6 (7.1)	14 (6.7)
C albicans	17 (4.6)	4 (5.5)	4 (4.8)	9 (4.3)
C non-albicans	10 (2.7)	3 (4.1)	2 (2.4)	5 (2.4)
Deep site culture	91 (24.8)	15 (20.5)	17 (20.2)	59 (28.1)
C albicans	46 (12.5)	6 (8.2)	11 (13.1)	29 (13.8)
C non-albicans	45 (12.3)	9 (12.3)	6 (7.1)	30 (14.3)

TABLE 4 Renal replacement therapy, mechanical ventilation, and noradrenalin use therapeutic intervention scores during ICU stay in three echinocandin groups shown as median with 25 and 75 percentiles or percents

	All (N = 367)	Anidulafungin (N = 73)	Caspofungin (N = 84)	Micafungin (N = 210)	*P*-value
RRT (%)	90 (25)	20 (27)	20 (24)	50 (24)	.82
RRT duration, hrs[a]	96.8 [31, 194.8]	27.8 [20.4, 119.8]	130.2 [41.4, 316.6]	106.1 [35.3, 207.1]	.039[b]
MV (%)	286 (78)	61 (84)	59 (70)	166 (79)	.11
MV duration, hrs[a]	106.7 [29, 256]	81.7 [18, 252.8]	110.5 [37.3, 281.6]	108.5 [30.8, 228.2]	.62
NA-treatment (%)	309 (84)	66 (90)	64 (76)	179 (85)	.042[b]
NA-duration, hrs[a]	62 [20.1, 153.7]	50.5 [14.5, 121.2]	54 [27.6, 149.5]	69 [23, 164]	.19
TISS max score	53 [44.5, 58.5]	53 [44.5, 58.5]	51 [39.2, 60]	52 [41.8, 61.3]	.62
Total TISS scores	286 [127, 664]	286 [127, 664]	284 [124, 711]	365 [180, 770]	.36

Abbreviations: RRT, renal replacement therapy; MV, mechanical ventilation; NA, noradrenaline.

[a]Total time in cases with treatment, TISS, Therapeutic interventions scoring system.

[b]Difference between ANI and CASPO.

TABLE 5 Echinocandin and fluconazole treatment during ICU stay, ICU, and hospital LOS and mortality in echinocandin group. Results shown as median with 25 and 75 percentiles, percents, or 95%CI

	All (N = 367)	Anidulafungin (N = 73)	Caspofungin (N = 84)	Micafungin (N = 210)	*P*-value
Total costs of all antifungal treatment, €	1786 [893, 3079]	1872 [940, 2813]	1799 [835, 3190]	1783 [768, 3134]	.62
Fluconazole treatment days	4 [2, 9]	4 [2, 7]	3 [1, 8]	5 [2, 10]	.30
Echinocandin treatment, days	3 [2,7]	3 [1, 5]	3 [2, 8]	4 [2, 8]	.086
ICU LOS, days	7.1 [3.0, 16.8]	6.4 [2.7, 16.3]	5.3 [2.6, 15.9]	8.1 [3.5, 18.1]	.26
Hospital LOS, days	30.4 [16.1, 45.2]	32.9 [14.3, 53.9]	30.3 [18.8, 42.1]	30.0 [15.0, 45.1]	.64
Hospital mortality (%)	81 (22)	18 (25)	17 (20)	46 (22)	.80
30-day mortality (%)	114 (32)	20 (27)	27 (32)	67 (32)	.75
365-day mortality (%)	156 (43)	24 (33)	37 (44)	95 (45)	.17
SMR (APACHE II)	0.90 (95%CI 0.74-1.08)	0.69 (95%CI 0.42- 1.07)	0.88 (95% 0.58- 1.28)	0.99 (95%CI 0.77-1.26)	-
SMR (SAPS II)	0.88 (95%CI 0.73-1.06)	0.67 (95%CI 0.41-1.04)	0.87 (95%CI 0.57 - 1.27)	0.97 (95%CI 0.75-1.24)	-

Abbreviations: LOS, length of stay; SMR, standardized mortality ratio.

population is rather suitable for the evaluation of empiric echinocandin treatment in an ICU setting. In our series, neither ICU nor hospital stay differed between echinocandin groups. Also, the resource utilization was similar in the three groups. The 30-day mortality, which varied from 27% to 32%, is in harmony with the literature.[25] In addition, 1-year mortality did not differ between the echinocandin groups and the figure of 43% is in concordance with the rate of 59% in earlier literature.[26-28] Furthermore, there were no significant differences in 30-day (26%, 32%, and 34%) mortalities in 112 patients with culture-proven *Candida* infections among our anidulafungin, caspofungin, and micafungin groups. According to a recent epidemiologic meta-analysis of candidaemia in Europe, pooled day 30 mortality rate in intensive care units was 37%.[29]

In this empiric echinocandin series, blood culture yielded *Candida* growth in 4.4% of the patients. The proportion of *C albicans* species (63%) is in harmony with a recent series of candidemia findings in Southern Finland between 2007 and 2017, where the proportion of *Candida albicans* was 60.4%.[30] In our series, all 10 *Candida albicans* species were sensitive both to echinocandins and fluconazole. However, four of six (67%) of non-albicans species were resistant to fluconazole. Currently, it has been shown that ineffective empirical treatment was associated with persistent candidemia in adult patients.[31] There are reports showing an increase in infections caused by non-albicans species,[26-28] while in our series both *Candida albicans* and non-albicans species were found equally often only in deep-site cultures. Furthermore, in blood cultures and central line specimens, *Candida albicans* was still more prevalent.

The accurate dosing of echinocandins without known echinocandin concentrations is a challenge in the ICU due to large interindividual variability.[32] Moreover, the concentrations of caspofungin and micafungin were clearly lower than among healthy volunteers. All three echinocandins require a higher than standard dose for obese or markedly obese patients.[15,33,34] In our series, the median BMI was identical in the three echinocandin groups and only 7.1% of the patients had a body weight higher than 115 kg. Also, renal replacement therapy may affect echinocandin concentrations among ICU patients. A quarter of the patients needed RRT and the proportion was equal among groups. Although the duration of RRT was the longest in the caspofungin group, there is no need for caspofungin dose adjustment during continuous RRT.[35] Very recently, it was reported that during echinocandin therapy, mean arterial pressure may decrease with increasing noradrenalin doses.[36] Whether this phenomenon was behind the significant difference of noradrenalin use in our echinocandin groups (anidulafungin 90% vs caspofungin 76%) remains unclear. Some statistical differences were probably coincidental concerning the SAPS II score, duration of renal replacement therapy, or noradrenalin use in the three echinocandin groups. The lowest SMR in the ANI group could be explained by the fact that there were no blood culture-positive bacterial or fungal infections compared to the CASPO (13%) and MICA (7%) groups.

The acquisition costs of echinocandins are high and comprise a remarkable part of ICU pharmacy budgets throughout the Western world.[37] Echinocandins comprised a 5.3-10.5% share of annual pharmacy expenses in our department between 2009 and 2014. In our series, the costs of antifungal treatments during ICU stays were rather identical, probably due to the policies of our hospital: the lowest price was the driver for echinocandin selection. We consider that most of the differences among study groups during this 6-year period were coincidental due to marketing decisions. The only exception was the use of CASPO, which is the preferred echinocandin among hematological patients in our hospital.

Although our patient population with the highest SOFA score of 10 represents a quite typical mixed ICU population, it is a retrospective single-center study and thus the generalization of our results should be cautiously interpreted. Due to the fact that during

the study period the cheapest echinocandin was used, there was a bias toward a particular echinocandin. For example, patients with anidulafungin were treated between years 2009 and 2011, while the patients in the micafungin group were treated between years 2011 and 2014. The different time period may have had an impact on the outcome results. Also, unbalanced patient groups would be the main confounding issues in this retrospective study. Recent studies have underscored the importance of measuring echinocandin concentrations to achieve optimal concentrations among an ICU population. These results were not available in this retrospective series. In this study, the cost of echinocandins included only the ICU period, not the use of echinocandins in the wards after the ICU stay. Due to the retrospective nature of this study, we cannot exclude whether factors other than echinocandin use determined clinical outcome, although the same team treated all ICU patients. For more specific comparisons of empiric use of echinocandins, prospective studies with concentration measurements will be needed.

5 | CONCLUSION

According to our retrospective non-interventional study of the empiric use of echinocandins, ICU and hospital stay, mortality rates (hospital, 30-day and 1-year), and resource utilization did not differ between patients receiving anidulafungin, caspofungin, or micafungin in a mixed adult ICU. Considering the findings of this research, it is practical to select the least expensive echinocandin for empiric treatment in critically ill patients.

ACKNOWLEDGEMENTS

The help of study nurse S. Sälkiö, RN, in retrieving the data from the electronic archives is highly appreciated.

CONFLICTS OF INTERESTS

None declared.

AUTHORS' CONTRIBUTIONS

TA-K, HS, and JK contributed substantially to the study design, acquisition, interpretation, and analysis of data and writing of the manuscript. PY, JJL, and SÄ made substantial contributions to analysis and interpretation of data and writing of the manuscript. SÄ calculated the expenses of echinocandin treatment. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

The study protocol was approved by the Ethics Committee of Oulu University Hospital. Because the study was epidemiological without any interventions, the requirement for informed consent was waived.

CONSENT TO PUBLISH

Not applicable.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this published article. It can also be requested from the corresponding author.

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How to cite this article: Ylipalosaari P, Ala-Kokko TI, Koskenkari J, Laurila JJ, Ämmälä S, Syrjälä H. Use and outcome of empiric echinocandins in critically ill patients. *Acta Anaesthesiol Scand*. 2021;65:944–951. https://doi.org/10.1111/aas.13783