Use and outcome of empiric echinocandins in critically ill patients

Pekka Ylipalosaari¹ | Tero I. Ala-Kokko² | Juha Koskenkari² | Jouko J. Laurila² | Sirpa Ämmälä³ | Hannu Syrjälä¹

¹Department of Infection Control, Oulu University Hospital, Medical Research Center Oulu, University of Oulu, Oulu, Finland
²Division of Intensive Care Medicine, Research Group of Surgery, Anesthesiology and Intensive Care Medicine, Oulu University Hospital, Medical Research Center Oulu, University of Oulu, Oulu, Finland
³Hospital Pharmacy, Oulu University Hospital, Oulu, Finland

Correspondence
Dr Pekka Ylipalosaari, Department of Infection Control, Oulu University Hospital, PO BOX 21, 90029 OUH, Finland.
Email: pekka.ylipalosaari@ppshp.fi

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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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Fungal infections are an increasing problem in intensive care, and contribute significantly to morbidity and mortality as well as costs.\textsuperscript{4} Prophylaxis with fluconazole in high-risk, critically ill patients has reduced the incidence of invasive fungal infections and mortality.\textsuperscript{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.\textsuperscript{6,7} The assay time of many blood culture independent methods requiring DNA extraction is only about 2 hours.\textsuperscript{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.\textsuperscript{9} According to recent guidelines, echinocandins (caspofungin, micafungin, and anidulafungin) are recommended for first-line empiric treatment for critically ill patients in the ICU.\textsuperscript{10} They have less severe side effects than amphotericin B, the gold standard of antifungal agents.\textsuperscript{11-13} The echinocandins are semisynthetic lipopeptides which inhibit the synthesis of the 1,3-beta-D-glucan component of the fungal cell wall.\textsuperscript{14} They have rather similar pharmacological and efficacy profiles, as well as few drug-drug interactions.\textsuperscript{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.\textsuperscript{16} Recent studies have not shown the superiority of caspofungin or micafungin over fluconazole prophylaxis for high-risk patients in the ICU.\textsuperscript{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.

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, 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).\textsuperscript{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.

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 theazole 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% CI 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
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 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]²⁶ | 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/m² (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 10⁹/L adm    | 183 [102, 288]| 204 [105, 313]         | 116 [40, 213]        | 197 [111, 297]       |
| WBC, x 10⁹/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)              |
| Comorbidities²⁶ (%)        | 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)              |

²³The 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.

²⁴Parenthesis, Results presented as medians with 25th and 75th percentiles.
### 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<sup>a</sup>           | 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)              |

*<sup>a</sup>Candida blood cultures were positive in 16 cases, please see Table 3. Blood cultures yielded in two cases Escherica coli and Enterococcs faecium and the rest one of each: Staphylococcus aureus, Staphylococcus epidermidis, Bacillus cereus, Klebsiella pneumoniae, Serratia marancellens, 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) |
|---------------------|---------------|------------------------|----------------------|----------------------|
| RRT (%)             | 90 (25)       | 20 (27)                | 20 (24)              | 50 (24)              | .82 |
| RRT duration, hrs<sup>a</sup> | 96.8 [31, 194.8] | 27.8 [20.4, 119.8]    | 130.2 [41.4, 316.6] | 106.1 [35.3, 207.1] | .039<sup>b</sup> |
| MV (%)              | 286 (78)      | 61 (84)                | 59 (70)              | 166 (79)             | .11 |
| MV duration, hrs<sup>a</sup> | 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<sup>b</sup> |
| NA-duration, hrs<sup>a</sup> | 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.

<sup>a</sup>Total time in cases with treatment, TISS, Therapeutic interventions scoring system.

<sup>b</sup>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%CI 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.
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.

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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.

ORCID

Pekka Ylipalosaari https://orcid.org/0000-0003-3829-1344
Hannu Syrjälä https://orcid.org/0000-0002-2872-2748

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