Pharmacokinetic/pharmacodynamics variability of echinocandins in critically ill patients: A systematic review and meta-analysis

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Abstract
What is known and objective: Anidulafungin, caspofungin and micafungin are three widely used echinocandin drugs licensed for the treatment of invasive fungal infections, and their clinical use is widespread. To evaluate pharmacokinetic/pharmacodynamics variability of echinocandins in critically ill patients by comparing the differences in pharmacokinetic parameters between critically ill patients and healthy volunteers or general patients.

Methods: MEDLINE, EMBASE, The Cochrane Library and Pubmed were searched from inception until 6 September 2018. Studies investigating the pharmacokinetic parameters of echinocandins in critically ill patients, healthy volunteers or general patients were included. Our primary outcomes included AUC\textsubscript{0-24 h}, C\textsubscript{max} and C\textsubscript{min} (24 hours). Two reviewers independently reviewed all titles, abstracts and text, and extracted data. We applied R software (R 2017) to conduct meta-analysis.

Results and discussion: Of 3235 articles screened, 17 studies were included in the data synthesis. Descriptive data from single-arm studies show that critically ill patients who received caspofungin had more stable AUC\textsubscript{0-24 h} than those who received anidulafungin and micafungin. The C\textsubscript{max} of critically ill patients who received caspofungin and micafungin was similar to healthy volunteers. However, the C\textsubscript{max} in critically ill patients who received anidulafungin was lower than in healthy volunteers. The C\textsubscript{min} and T\textsubscript{1/2} of critically ill patients who received caspofungin were larger than in healthy volunteers. The V\textsubscript{d} and CL of critically ill patients receiving anidulafungin and micafungin were larger than in healthy volunteers.

What is new and conclusion: This systematic review provides an analysis of the pharmacokinetic/pharmacodynamics variability of echinocandins in critically ill patients. Based on the limited data available, caspofungin has less pharmacokinetic/pharmacodynamics variability than anidulafungin and micafungin.

KEYWORDS
critically ill patients, echinocandins, pharmacokinetic/pharmacodynamics variability
WHAT IS KNOWN AND OBJECTIVE

Echinocandins are the newest addition to the antifungal agents. Currently, anidulafungin, caspofungin and micafungin are three echinocandin drugs licensed for the treatment of invasive fungal infections, and their clinical use is widespread. Echinocandins are the first-line treatment for candidemia or invasive candidiasis, and have better safety and tolerability profiles. Echinocandins inhibit 1, 3-β-D-glucan synthase, being selective and non-competitive inhibitors of the essential components of the fungal cell wall biosynthesis, making it easy to lysate. As the enzyme is not present in the cell wall of mammalian cells, the echinocandins do not elicit their activity on these cells, which explains the very few side effects and adverse events associated with echinocandin therapy compared with other mainstay antifungal agents, such as amphotericin B and the azole class of antifungal drugs.

As a class, the echinocandins possess many pharmacokinetic similarities. Due to their high molecular weight, all three echinocandins exhibit poor oral bioavailability, and hence, they are administered as intravenous formulations. They all have high protein binding (>90%), which contributes to their long half-lives. They distribute well in tissues including lung, liver and spleen. However, they do not penetrate into the brain, cerebrospinal fluid and eyes (except for micafungin, which penetrates into the eye) due to their high molecular weight and extensive tissue protein binding. All echinocandins display linear pharmacokinetics after intravenous administration. Anidulafungin undergoes slow metabolic degradation over a period of time under physiological conditions to form a ring-opened chemical moiety that is then degraded by hydrolysis and N-acetylation and eliminated primarily in the faeces. Caspofungin undergoes hepatic metabolism via peptide hydrolysis and N-acetylation, and its metabolites are then eliminated in both urine and faeces. Micafungin, however, is degraded by the arylsulfatase and catechol-O-methyltransferase enzymes in the liver, and its metabolites are eliminated in faeces.

For anidulafungin, the recommend standard dose is 200 mg on day 1 (loading dose) and 100 mg once daily on subsequent days (maintenance dose). For caspofungin, the standard dose is 70 mg as a single loading dose, followed by a maintenance dose of 50 mg, or 70 mg once daily. For micafungin, the standard dose is 100 mg once daily for the treatment of invasive candidiasis, 150 mg for the treatment of oesophageal candidiasis and 50 mg once daily for candida prophylaxis. More recently, several pharmacokinetics studies in critically ill patients revealed that standard dosages of echinocandins were frequently associated with lower drug exposure (AUC and Cmax), which can result in sub-optimal efficacy, especially for infections with less susceptible strains (such as Candida albicans or Candida glabrata strains). Thus, based on their data, the standard dose may be insufficient for critically ill patients, suggesting that the dose of echinocandins should be adjusted according to their pharmacokinetic variability. This approach needs to be confirmed with a larger data set. Therefore, the purpose of this systematic review is to evaluate the pharmacokinetic/pharmacodynamic (PK/PD) variability of echinocandins in critically ill patients.

METHODS

The systematic review and meta-analysis were conducted in alliance with the Cochrane Handbook of Interventional Reviews and reported in accordance with PRISMA standard.

Inclusion and exclusion criteria

Phase II studies were included in this systematic review. Critically ill patients, or general patients (referring to other non-critically ill patients) or healthy volunteers (aged above 18 years old, without limitations placed with regard to weight and sex), with a diagnosis defined by original studies were included in this study. Any study which applies anidulafungin at a loading dose of 200 mg on day 1 followed by 100 mg/day maintenance therapy, or caspofungin at a loading dose of 70 mg on day 1 followed by 50 mg/day maintenance therapy, or micafungin 100 mg or 150 mg per day was included in this systematic review. The steady-state PK/PD of these three drugs in critically ill patients was compared with those in healthy control.

Data extraction and management

We undertook an electronic search on 6 September 2018, in MEDLINE via Ovid SP, The Cochrane Library, EMBASE via Ovid SP and Pubmed. The search strategy was developed by an information specialist and presented in Appendix S1. There was no limitation placed with respect to language, document type and publication status. We also inspected the references of relevant systematic reviews to identify additional study.

Two reviewers screened the search results. Disagreements were resolved by discussion with assistance from a third party if necessary. A PRISMA flow diagram was constructed to show the full study selection process.

Data extraction and management

Data from each study were extracted independently by two separate reviewers using a standardized data extraction form. Any disagreements were resolved by discussion, with assistance from a third party if necessary. We extracted all relevant characteristics of included studies, including: general study characteristics: first author, title and publication year; population characteristics: sample size,
2.4 | Data synthesis

We applied R software (R 2017) to conduct the meta-analysis. Then, we combined outcome data derived from controlled studies and single-arm studies separately. We used a random-effects model for all meta-analysis. We considered and fully discussed the clinical and methodological heterogeneity. We investigated the statistical heterogeneity based on $I^2$ and chi-square statistics. An $I^2$ estimate greater than or equal to 50% accompanied by a statistically significant chi-square statistic was interpreted as evidence of substantial levels of heterogeneity. Where a substantial heterogeneity was found, we would explore potential sources.

3 | RESULTS

3.1 | Study screening

The trial search identified 3235 references and 2177 references were left after removing duplicates. In addition, we screened 4 references from relevant systematic reviews. Finally, 17 articles were eligible for meta-analysis.\textsuperscript{12,15-30} The study screening process was presented in Figure 1.
3.2 | Characteristics and quality of included studies

We included 17 studies with 383 participants. The study sample size ranged from 8 to 74. All critically ill patients were diagnosed with invasive fungal infections or suspected with invasive fungal infections with BMI ranging from 16.2 to 51.3. Four studies 12,15,26,27 included patients with hypoproteinemia. Two studies 15,27 reported the liver function of included participants with mild to severe level of liver dysfunction. Four studies 15,25-27 included some patients with kidney dysfunctions. Six studies 12,15-17,25,27 included mixed population with or without continuous renal replacement. Other studies did not report the above information (Table 1). All studies were rated as high risk of bias, as the included studies were single-arm studies.

3.3 | Estimate of effect

3.3.1 | Area under the drug concentration-time curve from 0 to 24 h (AUC_{0-24h})

Sixteen studies12,15-24,26-30 reported this outcome. The result showed that when receiving anidulafungin (a loading dose of 200 mg on day 1 followed by 100 mg/d maintenance therapy), critically ill patients had a somewhat lower AUC_{0-24h} at steady-state than healthy volunteers (Figure 2); when receiving caspofungin (a loading dose of 70 mg on day 1 followed by 50 mg/day maintenance therapy), critically ill patients had similar AUC_{0-24h} at steady-state with healthy volunteers (Figure 2); when receiving micafungin 100 mg per day, critically ill patients had slightly larger CL at steady-state than healthy volunteers (Figure 2). However, critically ill patients who received micafungin 150 mg per day had similar AUC_{0-24h} at steady-state with healthy volunteers.

3.4 | Maximum concentration (C_{max})

Thirteen studies 12,16-22,24,25,27-29 reported this outcome. The results showed that when receiving anidulafungin, critically ill patients had a somewhat lower C_{max} at steady-state than healthy volunteers (Figure 3). When receiving caspofungin (a loading dose of 70 mg on day 1 followed by 50 mg/d maintenance therapy), critically ill patients had similar steady-state C_{max} to healthy volunteers (Figure 3). When receiving micafungin 150 mg per day, critically ill patients had similar steady-state C_{max} with healthy volunteers (Figure 3).

3.5 | Minimum concentration (C_{min})

Ten studies 12,16,17,20-22,25-28 reported this outcome. The results showed that when anidulafungin was administered at a loading dose of 200 mg on day one and followed by 50mg per day at maintenance therapy, steady-state C_{min} in critically ill patients was somewhat larger than healthy volunteers (Figure 4). The data on micafungin steady-state C_{min} in critically ill patients were not yet available due to variation in management of medication, measurement time points and calculation models.

3.6 | Half-life (T_{1/2})

Eleven studies 12,15,17,18,20,22-23,27-30 reported this outcome. The results showed that when anidulafungin was administered at a loading dose of 200 mg on day 1 followed by 100 mg/d maintenance therapy, the steady-state T_{1/2} in critically ill patients was similar with healthy volunteers. When caspofungin was administered at a loading dose of 70 mg on day 1 followed by 50 mg/d maintenance therapy, the steady-state T_{1/2} in critically ill patients was somewhat longer than healthy volunteers. When micafungin was administered at the dose of 100 mg daily, steady-state T_{1/2} of critically ill patients was similarly with healthy volunteers. The available T_{1/2} data were summarized in Table 2.

3.7 | Total clearance

Eight studies12,19-23,26,29 reported this outcome. The results showed that when receiving anidulafungin, critically ill patients had larger CL at steady-state than healthy volunteers. When receiving micafungin at 100 mg per day, critically ill patients had slightly larger CL at steady-state than healthy volunteers. The data on caspofungin and micafungin (150 mg per day) steady-state CL were not yet available due to variation in management of medication, measurement time points and calculation models. The available CL data were summarized in Table 2.

3.8 | Volume of distribution

Six studies12,18,21,23,26,29 reported this outcome. The results showed that when receiving anidulafungin, critically ill patients had a much larger steady-state V_d at steady-state than healthy volunteers. When receiving micafungin at 100 mg per day, critically ill patients had larger V_d at steady-state with healthy volunteers. The available steady-state V_d data were summarized in Table 2.

4 | DISCUSSION

Very low quality of evidence showed that compared with the pharmacokinetics of echinocandins in healthy volunteers, (a) the AUC_{0-24h} in critically ill patients who received anidulafungin and micafungin was somewhat lower than that in healthy volunteers; the AUC_{0-24h} in critically ill patients who received caspofungin was similar to or even
| Study ID | First author Year | No. of subjects | Age (years) | Disease Status | Diagnosis-details | Echinocandins | Dosages/Frequency | Outcomes | Measurement timepoints |
|----------|--------------------|----------------|-------------|----------------|-------------------|---------------|------------------|----------|-----------------------|
| Aguilar 2014 | 12 | ≥18 | Critically ill | acute renal failure (Receiving CVVHDF) | anidulafungin | LD: 200 mg; MD: 100 mg QD | AUC₀-2₄₉.₉, Cₘₐₓ, Cₘᵢₙ, T₁/₂ | Day 3 |
| Aguilar 2017 | 12 | 56-78 | Critically ill | Receiving CVVHDF | caspofungin | LD: 70 mg; MD: 50 mg QD | AUC₀-2₄₉.₉, Cₘₐₓ, Cₘᵢₙ, V₉, T₁/₂, CL | Day 3 or later |
| Bruggemann 2017 | 23 | 28-88 | Critically ill | Invasive Fungal Infections | anidulafungin | LD: 200 mg; MD: 100 mg QD | AUC₀-2₄₉.₉, Cₘₐₓ, Cₘᵢₙ, V₉, T₁/₂, CL | Day 3, 7 |
| Crandon 2009 | 20 | ≥18 | Healthy volunteer | – | anidulafungin | LD: 200 mg; MD: 100 mg QD | AUC₀-2₄₉.₉, Cₘₐₓ, Cₘᵢₙ, V₉, T₁/₂, CL | Day 3 |
| Dowell 2005a | 12 | 18-50 | Healthy volunteer | – | anidulafungin | LD: 200 mg; MD: 100 mg QD | AUC₀-2₄₉.₉, Cₘₐₓ, Cₘᵢₙ, V₉, T₁/₂, CL | Day 4, 8 |
| Dowell 2005b | 18 | 20-40 | Healthy volunteer | – | anidulafungin | LD: 200 mg; MD: 100 mg QD | AUC₀-2₄₉.₉, Cₘₐₓ, Cₘᵢₙ, V₉, T₁/₂, CL | Day 4 |
| Dowell 2007 | 35 | 20-49 | Healthy volunteer | – | anidulafungin | LD: 200 mg; MD: 100 mg QD | AUC₀-2₄₉.₉, Cₘₐₓ, Cₘᵢₙ, V₉, T₁/₂, CL | Day 10 |
| Dupont 2017 | 14 | 48-70 | Critically ill | suspected yeast IAI | anidulafungin | LD: 200 mg; MD: 100 mg QD | AUC₀-2₄₉.₉, Cₘₐₓ, Cₘᵢₙ, V₉, T₁/₂, CL | Day 1 ~ 5 |
| Hebert 2005 | 28 | ≥18 | Healthy volunteer | – | micafungin | 100 mg QD | AUC₀-2₄₉.₉, V₉, T₁/₂, CL | Day 7, 9, 24 |
| Keim 2007 | 35 | 18-50 | Healthy volunteer | – | micafungin | 150 mg QD | AUC₀-2₄₉.₉, Cₘₙ | Day 20, 24 |
| Leitner 2011 | 10 | 46-89 | Critically ill | acute renal failure (Receiving CVVHDF) | anidulafungin | LD: 200 mg; MD: 100 mg QD | AUC₀-2₄₉.₉, V₉, T₁/₂, CL | Day 3 |
| Lempers 2015 | 20 | 20-84 | Critically ill | suspected or proven fungal infection | micafungin | 100 mg QD | AUC₀-2₄₉.₉, Cₘₐₓ, Cₘᵢₙ, V₉, T₁/₂, CL | Day 3(±1) and 7 |
| Liu 2013 | 21 | 39-78 | Critically ill | invasive candidiasis | anidulafungin | LD: 200 mg; MD: 100 mg QD | AUC₀-2₄₉.₉, Cₘₐₓ, Cₘᵢₙ, V₉, CL | Day 3 ~ 8 |
| Mulwijk 2014 | 21 | 45-80 | critically ill | N/A | caspofungin | LD: 70 mg; MD: 50 mg QD | AUC₀-2₄₉.₉, Cₘₐₓ, Cₘᵢₙ, V₉, T₁/₂, CL | Day 3(±1) and day 7(±1) |
| Stone 2002 | 8 | 21-39 | Healthy volunteer | – | caspofungin | LD: 70 mg; MD: 50 mg QD | AUC₀-2₄₉.₉, Cₘₐₓ, Cₘᵢₙ, T₁/₂, CL | Day 14 |
| Undre 2012a | 74 | 19-68 | Critically ill | HIV and esophageal candidiasis | micafungin | 100 or 150 mg QD | AUC₀-2₄₉.₉, V₉, T₁/₂, CL | Day 1 and at end of therapy |
| Undre 2012b | 20 | 18-84 | Critically ill | invasive candidiasis | micafungin | 100 mg QD | AUC₀-2₄₉.₉, T₁/₂ | Day 1 and at end of therapy |

Abbreviations: CVVHDF, continuous venovenous haemodiafiltration; HIV, human immunodeficiency virus; IAI, intra-abdominal infection; LD, loading dose; MD, maintenance dose.
higher than that of healthy volunteers; (b) the $C_{\text{max}}$ in critically ill patients who received anidulafungin was lower than that in healthy volunteers; however, $C_{\text{max}}$ in critically ill patients who received caspofungin and micafungin was similar to healthy volunteers; (c) the $C_{\text{min}}$ in critically ill patients who received anidulafungin was similar to healthy volunteers; the $C_{\text{min}}$ in critically ill patients who received caspofungin was somewhat higher than that in healthy volunteers. Whether $C_{\text{min}}$ in critically ill patients who received micafungin is different from that in healthy volunteers remains unclear due to incomparable data; and (d) The $T_{1/2}$ in critically ill patients who received anidulafungin or micafungin was similar to healthy volunteers; the $T_{1/2}$ in critically ill patients who received caspofungin was somewhat longer than that in healthy volunteers.

Echinocandins exhibited concentration-dependent effects on *Candida* species, and preclinical studies supported the administration of large, infrequent doses. The efficacy of echinocandins is

| Study or Subgroup | TE  | SE  | Weight | IV, Random, 95% CI | IV, Random, 95% CI |
|-------------------|-----|-----|--------|-------------------|-------------------|
| Anidulafungin-critically ill | | | | | |
| Liu 2013          | 92.70 | 8.4986 | 5.7% | 92.70 [76.04, 109.38] | |
| Aguilar 2014      | 93.90 | 5.6000 | 6.1% | 93.90 [82.92, 104.88] | |
| Dupont 2017       | 88.90 | 9.1700 | 5.6% | 88.90 [70.93, 106.87] | |
| Brugemann 2017    | 77.65 | 7.8600 | 5.8% | 77.65 [62.21, 93.06] | |
| Total (95% CI)    |       |       |       | 23.3% [8.06, 98.85] | |
| Heterogeneity: Tau$^2$ = 0.43; Chi$^2$ = 3.02, df = 3 ($P = .39$); $I^2$ = 1% | | | | | |
| Test for overall effect: $Z = 24.14$ ($P < .01$) | | | | | |

| Anidulafungin-health volunteer | | | | | |
| Dowill 2007                  | 105.90 | 3.6500 | 6.3% | 105.90 [98.75, 113.05] | |
| Dowill 2005                  | 104.50 | 9.0428 | 5.7% | 104.50 [88.78, 122.22] | |
| Dowill 2005a                 | 120.30 | 5.8451 | 6.1% | 120.30 [108.84, 131.76] | |
| Grandon 2009                | 101.00 | 4.8746 | 6.2% | 101.00 [91.45, 110.55] | |
| Total (95% CI)              |       |       |       | 24.3% [99.72, 115.82] | |
| Heterogeneity: Tau$^2$ = 36.51; Chi$^2$ = 6.86, df = 3 ($P = .08$); $I^2$ = 56% | | | | | |
| Test for overall effect: $Z = 28.23$ ($P < .01$) | | | | | |

| Caspofungin-critically ill | | | | | |
| Aguilar 2017              | 123.00 | 13.2800 | 5.0% | 123.00 [98.97, 149.03] | |
| Muijewke 2014             | 107.84 | 8.0100 | 5.8% | 107.84 [92.14, 123.54] | |
| Total (95% CI)            |       |       |       | 10.8% [88.44, 128.33] | |
| Heterogeneity: Tau$^2$ = 0; Chi$^2$ = 0.96, df = 1 ($P = .33$); $I^2$ = 0% | | | | | |
| Test for overall effect: $Z = 19.31$ ($P < .01$) | | | | | |

| Caspofungin-health volunteer | | | | | |
| Stone 2002                  | 100.47 | 6.5189 | 6.0% | 100.47 [87.50, 113.44] | |
| Total (95% CI)              |       |       |       | 6.0% [87.50, 113.44] | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: $Z = 15.18$ ($P < .01$) | | | | | |

| Micafungin(100mg)-critically ill | | | | | |
| Lempers 2015                 | 88.10 | 7.4500 | 5.9% | 88.10 [73.50, 102.70] | |
| Undre 2012a                   | 115.30 | 5.5678 | 6.1% | 115.30 [104.39, 126.21] | |
| Undre 2012b                   | 97.10 | 6.4800 | 6.0% | 97.10 [84.40, 109.80] | |
| Total (95% CI)               |       |       |       | 18.0% [84.59, 116.93] | |
| Heterogeneity: Tau$^2$ = 160.54; Chi$^2$ = 9.71, df = 2 ($P < .01$); $I^2$ = 79% | | | | | |
| Test for overall effect: $Z = 12.25$ ($P < .01$) | | | | | |

| Micafungin(100mg)-health volunteer | | | | | |
| Hebart 2005a                  | 138.40 | 4.9324 | 6.2% | 138.40 [126.73, 146.07] | |
| Total (95% CI)               |       |       |       | 6.2% [126.73, 146.07] | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: $Z = 27.65$ ($P < .01$) | | | | | |

| Micafungin(150mg)-critically ill | | | | | |
| Undre 2012                   | 165.50 | 10.7974 | 5.4% | 165.50 [145.24, 187.68] | |
| Total (95% CI)              |       |       |       | 6.4% [145.34, 187.66] | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: $Z = 15.42$ ($P < .01$) | | | | | |

| Micafungin(150mg)-health volunteer | | | | | |
| Kaima 2007                   | 180.90 | 6.2304 | 6.0% | 180.90 [168.69, 193.11] | |
| Total (95% CI)              |       |       |       | 6.0% [168.69, 193.11] | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: $Z = 29.04$ ($P < .01$) | | | | | |

| Total (95% CI) | 100.00 | 111.61 [99.59, 123.83] |
| Heterogeneity: Tau$^2$ = 583.20; Chi$^2$ = 24.02, df = 16 ($P < .01$); $I^2$ = 93% | | | |
| Residual heterogeneity: Tau$^2$ = NA; Chi$^2$ = 20.54, df = 9 ($P = .01$); $I^2$ = 89%50 | | | |
| Test for overall effect: $Z = 18.20$ ($P < .01$) | | | |
| Test for subgroup differences: Chi$^2$ = 212.78, df = 7 ($P < .01$) | | | |

FIGURE 2. Meta-analysis of AUC$_{0-24h}$ of different types of echinocandins in critically ill-patients steady state.
mainly related to the ratio of AUC$_{0-24}$ to the MIC of the microorganism (AUC$_{0-24}$/MIC ratio). Consequently, AUC$_{0-24}$/MIC ratio of echinocandins is considered as the PK/PD index target to predict efficacy. In critically ill patients, pathophysiological or iatrogenic conditions may result in variations in extracellular volume and drug pharmacokinetics. These physiological changes may affect the distribution, metabolism and elimination of echinocandins. Therefore, dose adjustments should be mandatory. Recently, clinical studies in critical patients showed that standard dosages of echinocandins in critical patients were frequently associated with lower drug exposure, which can result in sub-therapeutic AUC$_{0-24}$/MIC ratios. The aforementioned data revealed that AUC$_{0-24}$ in critically ill patients who received anidulafungin or micafungin was lower than that in healthy volunteers, but AUC$_{0-24}$ in critically ill patients who received caspofungin was similar to or even higher than that in healthy volunteers. Consistently with the characteristics of AUC$_{0-24}$, the T$_{1/2}$ in critically ill patients who received anidulafungin or micafungin was also similar to that in healthy volunteers, but the T$_{1/2}$ in critically ill patients who received caspofungin was longer than that in healthy volunteers. Several factors could explain the differences on AUC$_{0-24}$ variability between the three echinocandins drugs. One of the factors is the influence of hypoalbuminaemia. Hypoalbuminaemia is very common in critically ill patients, with reported incidences as high as 40%-50%.

The three echinocandins drugs are highly bound to plasma protein before absorption (99% in anidulafungin, 96.5% in caspofungin and 99% in micafungin). In patients with hypoalbuminaemia, the unbound proportion of highly protein-bound drugs will increase because of the decrease in available binding sites. As a result, it will lead to the increasing elimination of drugs due to the increases in CL of unbound proportion. Different from the other two echinocandins drugs, the absorption of caspofungin requires the lowest protein binding ratio, which partially explains the stability.
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FIGURE 4 Meta-analysis of $C_{\text{min}}$ of different types of echinocandins in critically ill-patients steady state

| Study or Subgroup | TE   | SE  | Weight IV, Random, 95% CI | IV, Random, 95% CI |
|-------------------|------|-----|--------------------------|------------------|
|                    |      |     |                          |                  |
| Anidulafungin-critically ill |
| Liu 2013          | 3.00 | 0.2952 | 10.2% | 3.00 [2.42, 3.58] |
| Aguiar 2014       | 3.00 | 0.1732 | 11.6% | 3.00 [2.66, 3.34] |
| Leitner 2011      | 2.90 | 0.3479 | 9.8%  | 2.90 [2.22, 3.58] |
| Dupont 2017       | 3.20 | 0.3200 | 9.0%  | 3.20 [2.57, 3.83] |
| Brugemann 2017    | 5.04 | 0.4600 | 8.2%  | 5.04 [4.14, 5.94] |
| Total (95% CI)    |      |      | 49.4% | 3.34 [2.78, 3.91] |
| Heterogeneity: Tau$^2$ = 0.31; Chi$^2$ = 18.42, df = 4 ($P < .01$); $I^2$ = 78% |
| Test for overall effect: Z = 11.63 ($P < .01$) |

Anidulafungin-health volunteer

| Study or Subgroup | TE   | SE  | Weight IV, Random, 95% CI | IV, Random, 95% CI |
|-------------------|------|-----|--------------------------|------------------|
| Dowell 2007       | 3.10 | 0.1310 | 11.9% | 3.10 [2.84, 3.36] |
| Dowell 2005       | 2.80 | 0.2769 | 10.4% | 2.80 [2.26, 3.34] |
| Total (95% CI)    |      |      | 22.4% | 3.05 [2.81, 3.28] |
| Heterogeneity: Tau$^2$ = 0; Chi$^2$ = 0.96, df = 1 ($P = .33$); $I^2$ = 0% |
| Test for overall effect: Z = 25.72 ($P < .01$) |

Caspofungin-critically ill

| Study or Subgroup | TE   | SE  | Weight IV, Random, 95% CI | IV, Random, 95% CI |
|-------------------|------|-----|--------------------------|------------------|
| Aguiar 2017       | 2.40 | 0.6200 | 6.4%  | 2.40 [1.18, 3.62] |
| Mulijk 2017       | 2.45 | 0.2900 | 10.3% | 2.45 [1.86, 3.02] |
| Total (95% CI)    |      |      | 16.8% | 2.44 [1.93, 2.96] |
| Heterogeneity: Tau$^2$ = 0; Chi$^2$ = 0.01, df = 1 ($P = .94$); $I^2$ = 0% |
| Test for overall effect: Z = 9.29 ($P < .01$) |

Caspofungin-health volunteer

| Study or Subgroup | TE   | SE  | Weight IV, Random, 95% CI | IV, Random, 95% CI |
|-------------------|------|-----|--------------------------|------------------|
| Stone 2002b       | 1.77 | 0.1689 | 11.6% | 1.77 [1.44, 2.10] |
| Total (95% CI)    |      |      | 11.6% | 1.77 [1.44, 2.10] |
| Heterogeneity: not applicable |
| Test for overall effect: Z = 10.48 ($P < .01$) |

V$_d$ of different types of echinocandins (Mean, 95%Confidence Interval, L)

| Population         | Anidulafungin | Caspofungin | Micafungin |
|--------------------|---------------|-------------|------------|
| Dosage             | 200/100 mg$^a$ | 70/50 mg$^a$ | 100 mg/d at |
|                    | steady state  | steady state | steady state |
| Critical ill patients | 41.24        | N/C         | 259.00     |
|                    | (34.83-47.64) |             | (234.46-283.54)$^c$ |
| Healthy volunteers | 32.59         | N/C         | 215.00     |
|                    | (28.35-36.83) |             | (204.26-225.74)$^c$ |

T$_{1/2}$ of different types of echinocandins (Mean, 95%Confidence Interval, h)

| Population         | Anidulafungin | Caspofungin | Micafungin |
|--------------------|---------------|-------------|------------|
| Critical ill patients | 31.24        | 18.41       | 14.79      |
|                    | (13.21-49.26) | (16.07-20.74) | N/C        |
| Healthy volunteers | 30.46         | 10.58       | 16.40      |
|                    | (11.45-49.47) | (9.8-11.36) | (15.44-17.36) |

CL of different types of echinocandins (Mean, 95%Confidence Interval, mL/h/kg for Anidulafungin, mL/h for Micafungin)

| Population         | Anidulafungin | Caspofungin | Micafungin |
|--------------------|---------------|-------------|------------|
| Critical ill patients | 1.28         | N/C         | 12.20      |
|                    | (1.12-1.44)   |             | (10.84-13.56)$^c$ |
| Healthy volunteers | 0.96          | N/C         | 10.40      |
|                    | (0.85-1.06)   |             | (9.62-11.18)$^c$ |

Note: N/C: no comparable data.

$^a$A loading dose of 200 mg on day 1 followed by 100 mg/d maintenance therapy.

$^b$A loading dose of 70 mg on day 1 followed by 50 mg/d maintenance therapy.

$^c$The unit for these values are mL/h/kg.
of its pharmacokinetic effect in critically ill patients and healthy volunteers. Critically ill patients frequently demonstrate a systemic inflammatory response syndrome, which ultimately leads to fluid shift and fluid overload. For hydrophilic drugs, these processes may lead to a large increase in Vd. In contrast, Vd for lipophilic drugs is often not significantly influenced by such fluid shift. For micafungin, aqueous solubility is nearly 10 times larger than caspofungin. Hence, fluid shift and aqueous solubility of micafungin exert a larger pharmacokinetic effect on micafungin in critical patients appearing as an increase in Vd and decrease in AUC₀₋₂₄h.

These findings prove that caspofungin, when being administered at a 70 mg loading dose on day 1, followed by 50 mg, is sufficient for most critically ill patients. Furthermore, a higher Cₘᵢₐₓ in critically ill patients than the target concentration of 1 μg/mL is used as an indication of efficacious concentrations. The present study assessed the recommended dosing regimens of echinocandins in critically ill patients, general patients and healthy volunteers. Micafungin 100 mg dose is associated with a very low probability of attaining the target AUC/MIC value in the case of infection due to C albicans or C glabrata with MIC ≤0.015 μg/mL, as well as in almost all cases of infection due to Candida parapsilosis. Previous research showed that for C albicans, cumulative fraction of response (CFR) for caspofungin (70/50 mg), micafungin (100 mg) and anidulafungin (200/100 mg) were 95.8%, 13.5% and 50.5% in ICU patients and 96.3%, 42.4% and 61.6% in general patients, respectively; for C glabrata, CFRs were 99.4%, 90.6% and 44.6% in ICU patients and 99.5%, 97.1% and 59.8% in general patients. For C parapsilosis, CFRs of echinocandins for standard regimens were <70%; only caspofungin 100 mg daily achieved the target CFR. Therefore, the recommended dosing regimen of caspofungin is an appropriate choice as it is associated with higher probability of achieving the target PK/PD in critical patients. As a result, we can speculate the suitability of caspofungin at a loading dose of 70 mg on day one and followed by 50 mg daily dose for critical individual. These findings also suggest that anidulafungin being administrated at a loading dose of 200 mg on day 1 followed by 100 mg daily or 100 mg micafungin daily may reveal inadequate antifungal treatment.

As all included studies were single-arm cohort studies, all studies were rated as high risk of bias. These biases also affected the quality of meta-analyses. Besides these, small total sample size and unexplainable heterogeneity between studies also impacted the quality of evidence body. For pharmacokinetic parameters, the difference in pathology and physiology conditions of participants, different pharmacokinetic modelling applied in included studies, and the indirectness on interpreting results may also affect our confidence on these findings.

6 | CONCLUSION

Descriptive data from single-arm studies show that when comparing with healthy volunteers, critically ill patients who received caspofungin have less pharmacokinetic/pharmacodynamics variability than those who received anidulafungin and micafungin. Further controlled studies with larger sample size to compare pharmacokinetic/pharmacodynamics variability in critically ill patients are recommended.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

All authors conceived, designed, and planned the study, interpreted the results, provided substantive suggestions for drafting manuscript and critically reviewed subsequent iterations of the manuscript. All reviewed and approved final version of the paper, and ensured for
all aspects of the work that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

ETHICAL APPROVAL
This article does not contain any studies with human participants or animals performed by any of the authors.

DATA AVAILABILITY STATEMENT
Data available on request from the authors.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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