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REVIEW ARTICLE

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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 $AUC_{0\text{-}24\ h}$, C_{max} and C_{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 $AUC_{0\text{-}24\ h}$ than those who received anidulafungin and micafungin. The C_{max} of critically ill patients who received caspofungin and micafungin was similar to healthy volunteers. However, the C_{max} in critically ill patients who received anidulafungin was lower than in healthy volunteers. The C_{min} and $T_{1/2}$ of critically ill patients who received caspofungin were larger than in healthy volunteers. The V_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

1 | WHAT IS KNOWN AND OBJECTIVE

Echinocandins are the newest addition to the antifungal agents.[1] Currently, anidulafungin, caspofungin and micafungin are three echinocandin drugs licensed for the treatment of invasive fungal infections, and their clinical use is widespread.[2] Echinocandins are the first-line treatment for candidemia or invasive candidiasis, and have better safety and tolerability profiles.[3,4] 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.[5] 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.[3]

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.[6] 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.[7,8] All echinocandins display linear pharmacokinetics after intravenous administration.[7] 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.[9] Caspofungin undergoes hepatic metabolism via peptide hydrolysis and N-acetylation, and its metabolites are then eliminated in both urine and faeces.[10] Micafungin, however, is degraded by the arylsulfatase and catechol-O-methyltransferase enzymes in the liver, and its metabolites are eliminated in faeces.[11]

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 C_{max}), which can result in sub-optimal efficacy, especially for infections with less susceptible stains (such as *Candida albicans* or *Candida glabrata* strains).[12-15] 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.

2 | 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.

2.1 | 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. All data gathered was analysed after achievement of steady-state pharmacokinetics. Our primary outcomes are $AUC_{0\text{-}24\ h}$ (mg·min/mL), C_{max} and C_{min} (24 hours). Secondary outcomes include $T_{1/2}$, total clearance (CL) and volume of distribution (V_d).

2.2 | Trial searching and study screening

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.

2.3 | 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,

age, sex and BMI; clinical characteristics: diagnosis, kidney function, sepsis, artificial internal organ, continuous renal replacement and hypoproteinemia; interventions: type of study drugs, dosage, frequency and combination with other medication; and outcome data.

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.[12,15-30] The study screening process was presented in Figure 1.

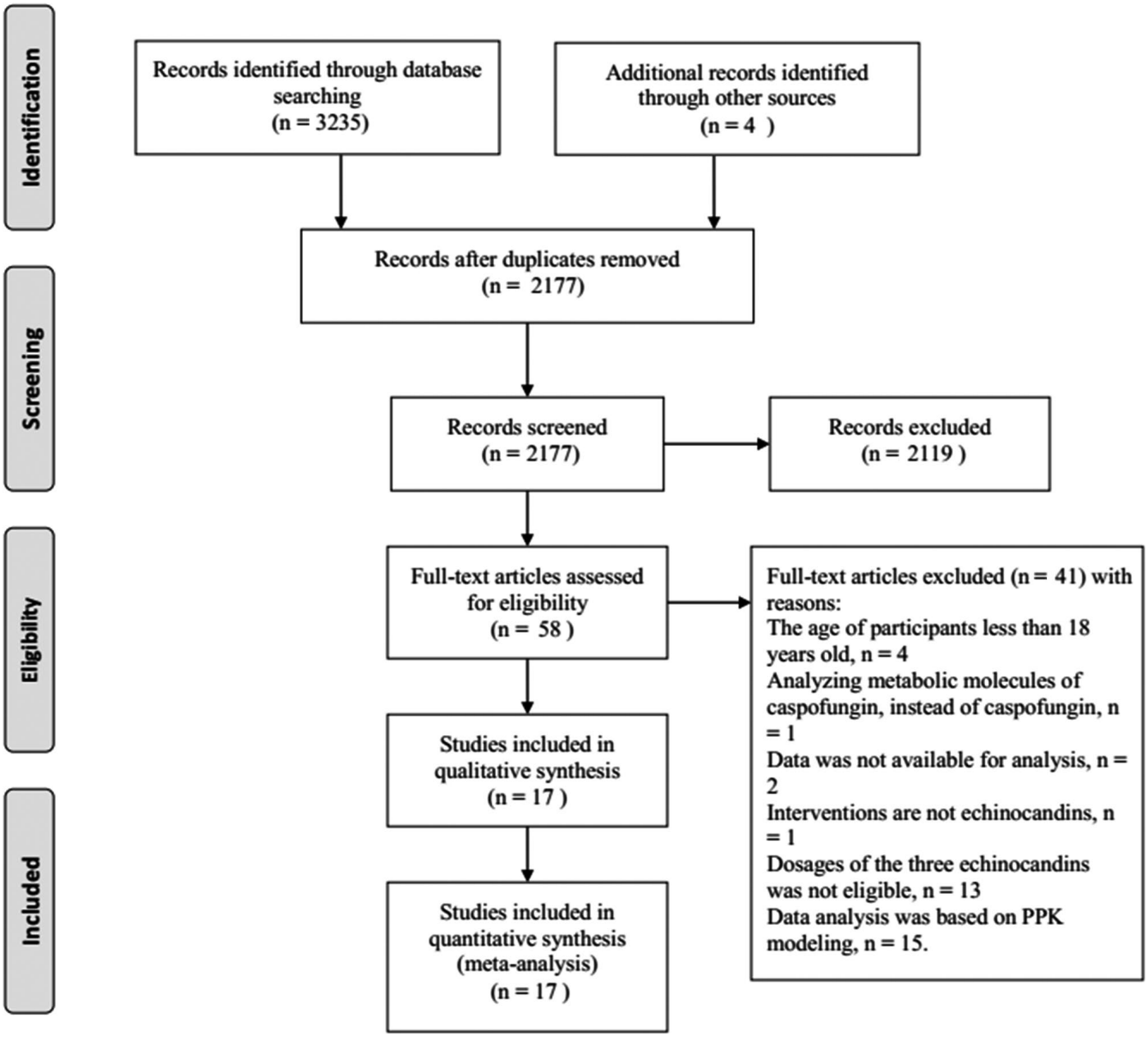

FIGURE 1 Study screening flow diagram

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 ($AUC_{0\text{-}24\,h}$)

Sixteen studies[12,15-24,26-30] 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 $AUC_{0\text{-}24\,h}$ 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 $AUC_{0\text{-}24\,h}$ at steady-state with healthy volunteers (Figure 2); when receiving micafungin 100 mg per day, critically ill patients had lower $AUC_{0\text{-}24\,h}$ at steady-state than healthy volunteers (Figure 2). However, critically ill patients who received micafungin 150 mg per day had similar $AUC_{0\text{-}24\,h}$ 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 1 followed by 100 mg/d maintenance therapy, the steady-state C_{min} in critically ill patients was similar with healthy volunteers (Figure 4). When caspofungin was administered at a loading dose of 70 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 (T1/2)

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 studies[12,19-23,26,29] 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 studies [12,18,21,23,26,29] 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 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 $AUC_{0\text{-}24\,h}$ in critically ill patients who received anidulafungin and micafungin was somewhat lower than that in healthy volunteers; the $AUC_{0\text{-}24\,h}$ in critically ill patients who received caspofungin was similar to or even

TABLE 1 General characteristics of studies included in the meta-analysis

Study ID First author Year	No. of subjects	Age (years)	Disease Status	Diagnosis-details	Echinocandins	Dosages/ Frequency	Outcomes	Measurement timepoints
Aguilar 2014[16]	12	≥18	Critically ill	acute renal failure (Receiving CVVHDF)	anidulafungin	LD: 200 mg; MD: 100 mg QD	$AUC_{0\text{-}24\ h}$, C_{max}, C_{min}, $T_{1/2}$	Day 3
Aguilar 2017[17]	12	56-78	Critically ill	Receiving CVVHDF	caspofungin	LD: 70 mg; MD: 50 mg QD	$AUC_{0\text{-}24\ h}$, C_{max}, C_{min}, V_d, $T_{1/2,}$ CL	Day 3 or later
Bruggemann 2017[12]	23	28-88	Critically ill	Invasive Fungal Infections	anidulafungin	LD: 200 mg; MD: 100 mg QD	$AUC_{0\text{-}24\ h}$, C_{max}, C_{min}, V_d, $T_{1/2,}$ CL	Day 3, 7
Crandon 2009[18]	20	≥18	Healthy volunteer	–	anidulafungin	LD: 200 mg; MD: 100 mg QD	$AUC_{0\text{-}24\ h}$, C_{max}, V_d, $T_{1/2,}$ CL	Day 3
Dowell 2005a[19]	12	18-50	Healthy volunteer	–	anidulafungin	LD: 200 mg; MD: 100 mg QD	$AUC_{0\text{-}24\ h}$, C_{max}, C_{min}, CL	Day 4, 8
Dowell 2005b[20]	18	20-40	Healthy volunteer	–	anidulafungin	LD: 200 mg; MD: 100 mg QD	$AUC_{0\text{-}24\ h}$, C_{max}, V_d, $T_{1/2,}$ CL	Day 4
Dowell 2007[21]	35	20-49	Healthy volunteer	–	anidulafungin	LD: 200 mg; MD: 100 mg QD	$AUC_{0\text{-}24\ h}$, C_{max}, C_{min}, V_d, $T_{1/2,}$ CL	Day 10
Dupont 2017[22]	14	48-70	Critically ill	suspected yeast IAI	anidulafungin	LD: 200 mg; MD: 100 mg QD	$AUC_{0\text{-}24\ h}$, C_{max}, C_{min}, V_d, $T_{1/2,}$ CL	Day 1 ~ 5
Hebert 2005[11,23]	28	≥ 18	Healthy volunteer	–	micafungin	100 mg QD	$AUC_{0\text{-}24\ h}$, V_d, $T_{1/2,}$ CL	Day 7, 9, 24
Keirns 2007[24]	35	18-50	Healthy volunteer	–	micafungin	150 mg QD	$AUC_{0\text{-}24\ h}$, C_{max}	Day 20, 24
Leitner 2011[25]	10	46-89	Critically ill	acute renal failure (Receiving CVVHDF)	anidulafungin	LD: 200 mg; MD: 100 mg QD	$AUC_{0\text{-}24\ h}$, V_d, $T_{1/2,}$ CL	Day 3
Lempers 2015[15]	20	20-84	Critically ill	suspected or proven fungal infection	micafungin	100 mg QD	$AUC_{0\text{-}24\ h}$, C_{max}, C_{min}, V_d, $T_{1/2,}$ CL	Day 3(±1) and 7
Liu 2013[26]	21	39-78	Critically ill	invasive candidiasis	anidulafungin	LD: 200 mg; MD: 100 mg QD	$AUC_{0\text{-}24\ h}$, C_{max}, C_{min}, V_d, CL	Day 3 ~ 8
Muilwijk 2014[27]	21	45-80	critically ill	N/A	caspofungin	LD: 70 mg; MD: 50 mg QD	$AUC_{0\text{-}24\ h}$, C_{max}, C_{min}, V_d, $T_{1/2,}$ CL	Day 3(±1) and day 7(±1)
Stone 2002[28]	8	21-39	Healthy volunteer	–	caspofungin	LD: 70 mg; MD: 50 mg QD	$AUC_{0\text{-}24\ h}$, C_{max}, C_{min}, $T_{1/2,}$ CL	Day 14
Undre 2012a[29]	74	19-68	Critically ill	HIV and esophageal candidiasis	micafungin	100 or 150 mg QD	$AUC_{0\text{-}24\ h}$, C_{max}, V_d, $T_{1/2,}$ CL	Day 1 and at end of therapy
Undre 2012b[30]	20	18-84	Critically ill	invasive candidiasis	micafungin	100 mg QD	$AUC_{0\text{-}24\ h}$, $T_{1/2}$	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.

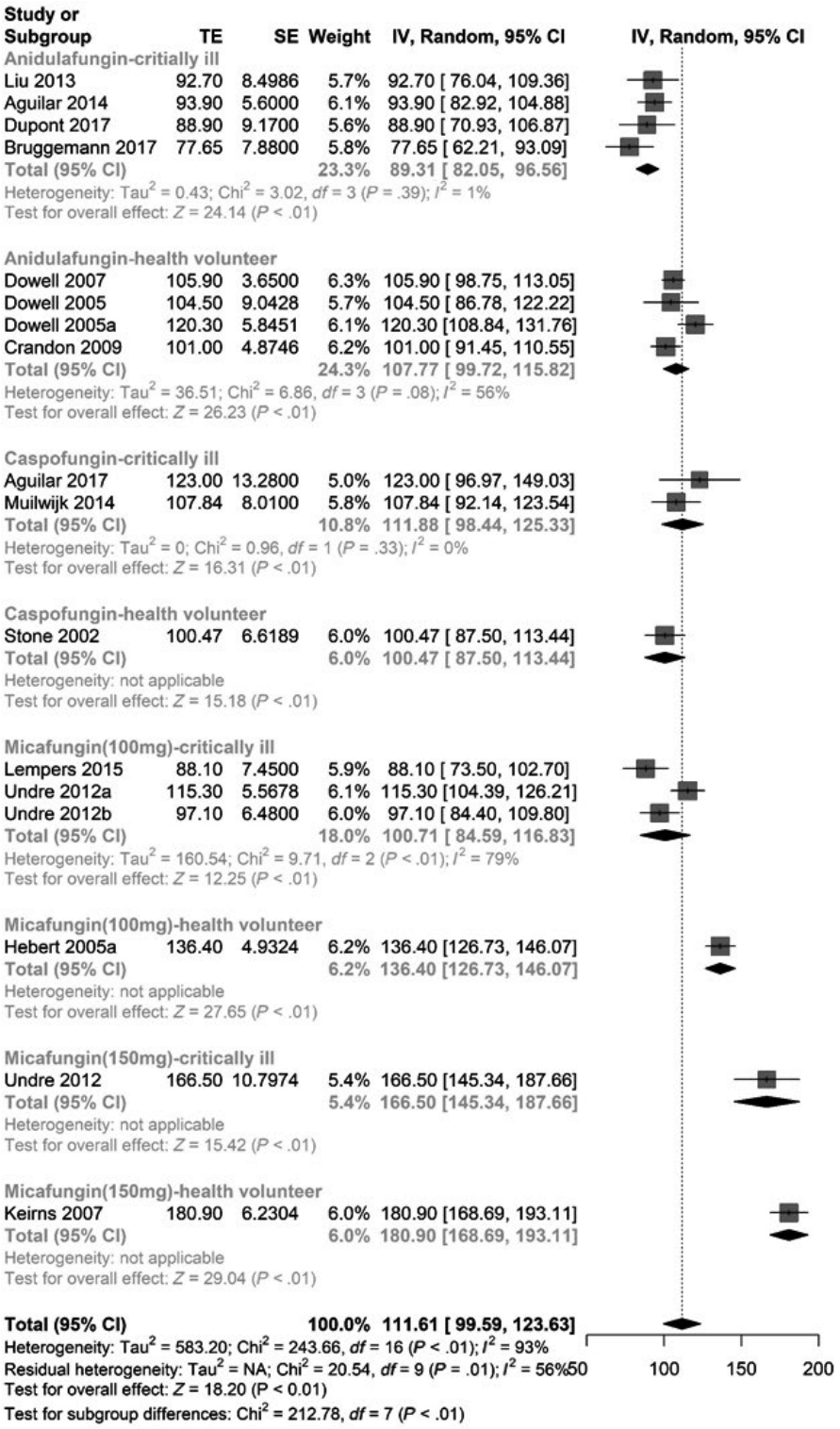

FIGURE 2 Meta-analysis of $AUC_{0\text{-}24\,h}$ of different types of echinocandins in critically ill-patients steady state

higher than that of healthy volunteers; (b) the C_{max} in critically ill patients who received anidulafungin was lower than that in healthy volunteers; however, C_{max} in critically ill patients who received caspofungin and micafungin was similar to healthy volunteers; (c) the C_{min} in critically ill patients who received anidulafungin was similar to healthy volunteers; the C_{min} in critically ill patients who received caspofungin was somewhat higher than that in healthy volunteers. Whether C_{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

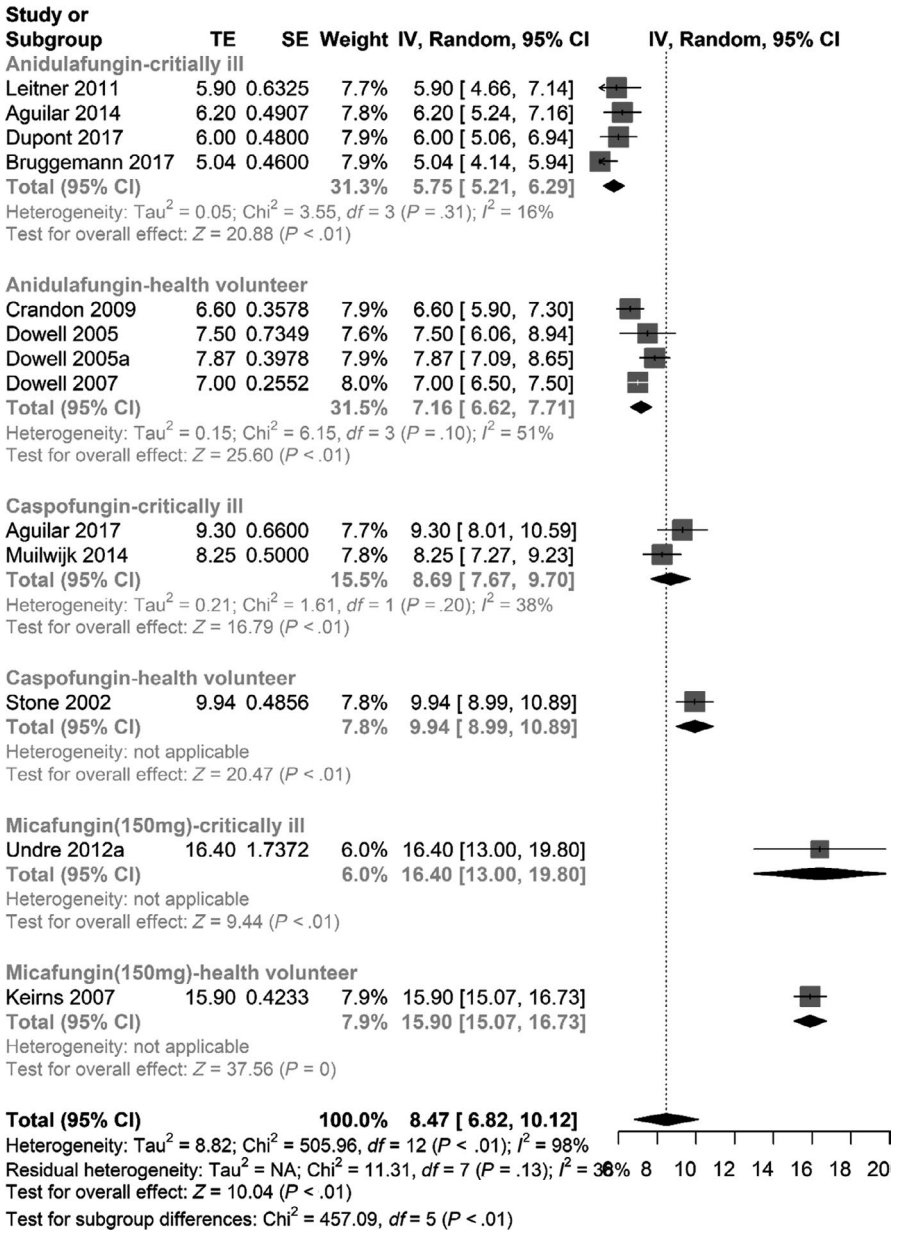

FIGURE 3 Meta-analysis of C_{max} of different types of echinocandins in critically ill-patients steady state

mainly related to the ratio of $AUC_{0\text{-}24}$ to the MIC of the microorganism ($AUC_{0\text{-}24}$/MIC ratio).[31] Consequently, $AUC_{0\text{-}24}$/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.[32] 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 $AUC_{0\text{-}24}$/MIC ratios.[12-15] The aforementioned data revealed that $AUC_{0\text{-}24\ h}$ in critically ill patients who received anidulafungin or micafungin was lower than that in healthy volunteers, but $AUC_{0\text{-}24\ h}$ in critically ill patients who received caspofungin was similar to or even higher than that in healthy volunteers. Consistently with the characteristics of $AUC_{0\text{-}24\ h,}$ 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 $AUC_{0\text{-}24\ h}$ 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%.[33] The three echinocandins drugs are highly bound to plasma protein before absorption (99% in anidulafungin, 96.5% in caspofungin and 99% in micafungin).[34,35] 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.[33] Different from the other two echinocandins drugs, the absorption of caspofungin requires the lowest protein binding ratio, which partially explains the stability

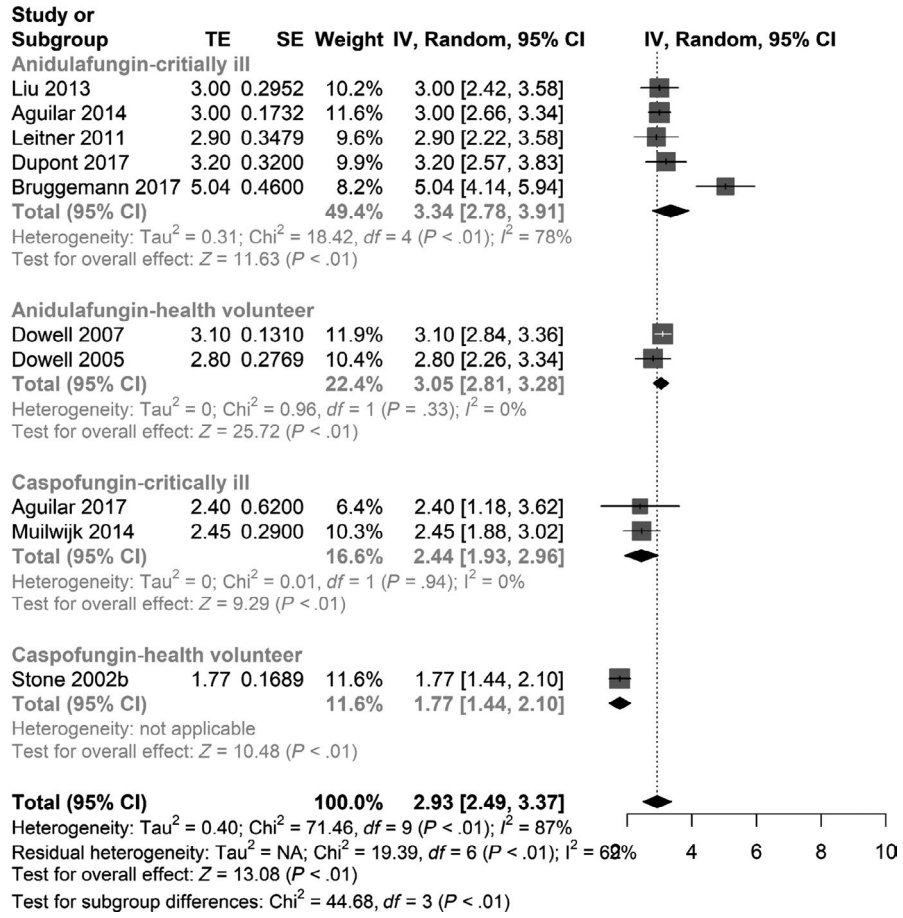

FIGURE 4 Meta-analysis of C_{min} of different types of echinocandins in critically ill-patients steady state

Population	Anidulafungin	Caspofungin	Micafungin	
V_d of different types of echinocandins (Mean, 95%Confidence Interval, L)				
Dosage	200/100 mg[a] steady state	70/50 mg[b] at steady state	100 mg/d at steady state	150 mg/day at steady state
Critical ill patients	41.24 (34.83-47.64)	N/C	259.00 (234.46-283.54)[c]	N/C
Healthy volunteers	32.59 (28.35-36.83)		215.00 (204.26-225.74)[c]	
$T_{1/2}$ of different types of echinocandins (Mean, 95%Confidence Interval, h)				
Critical ill patients	31.24 (13.21-49.26)	18.41 (16.07-20.74)	14.79 (12.86-16.72)	N/C
Healthy volunteers	30.46 (11.45-49.47)	10.58 (9.8-11.36)	16.40 (15.44-17.36)	
CL of different types of echinocandins (Mean, 95%Confidence Interval, L/h for Anidulafungin, mL/h/kg for Micafungin)				
Critical ill patients	1.28 (1.12-1.44)	N/C	12.20 (10.84-13.56)[c]	N/C
Healthy volunteers	0.96 (0.85-1.06)		10.40 (9.62-11.18)[c]	

TABLE 2 Vd, $T_{1/2\ and}$ CL of different types of echinocandins

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.[36] For micafungin, aqueous solubility is nearly 10 times larger than caspofungin.[2] Hence, fluid shift and aqueous solubility of micafungin exert a larger pharmacokinetic effect on micafungin in critical patients appearing as increase in Vd and decrease in $AUC_{0\text{-}24\,h}$.

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 C_{min} in critically ill patients than the target concentration of 1 μg/mL is used as an indication of efficacious concentrations.[28] 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*.[37] 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.[38] 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 50mg 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.

5 | WHAT IS NEW AND LIMITATIONS

This study has certain strengths: firstly, the search strategy was developed by a professional information specialist; in addition, we searched both electronic databases and the references of relevant systematic reviews. These actions allowed us to collect as many relevant trials as possible; secondly, the study screening and data extraction process were conducted independently by two researchers to minimize bias. Up to now, we have not discovered a systematic review and meta-analysis analysing the PK/PD variability of echinocandins in critically ill patients and this article is the first systematic review and meta-analysis conducted on this topic. Sinnollareddy et al reviewed the PK of antifungal agents in a number of disease states, including critically illness. Only a small portion of this article reviewed the PK of echinocandins without analysing the PK/PD variability, and only 6 studies were included with limited data available.[39] Muilwijk et al published an expert review which provided up-to-date information on PK data of anidulafungin, caspofungin and micafungin in special patient populations. Only a small portion of this article summarized PK data in critically ill patients from relatively few studies.[40] Bellmann et al's review summarized published PK data on systemically administered antifungals. This article summarized PK data in critically ill patients briefly based on published literature.[41] Hahn et al discussed changes in the PK of antibiotic, antiviral, antituberculosis and antifungal agents administered to adult patients on ECMO. The target population included was that ECMO patients not, 'critically ill patients'.[42]

Our study also has some limitations, for instance, the pharmacokinetic data for primary outcomes are insufficient to detect a clear difference between the groups. As all included studies were single-arm cohort studies, heterogeneity between populations was significant. Due to insufficient data, we failed to detect variability in some pharmacokinetic parameters, for instance, V_d and CL for caspofungin.

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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REFERENCES

1. Chen SCA, Slavin MA, Sorrell TC. Echinocandin antifungal drugs in fungal infections. *Drugs*. 2011;71:11-41.
2. Patil A, Majumdar S. Echinocandins in antifungal pharmacotherapy. *J Pharm Pharmacol*. 2017;69:1635-1660.
3. Pappas PG, Kauffman CA, Andes DR, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the infectious diseases society of America. *Clin Infect Dis*. 2016;62:e1-e50.
4. Cornely OA, Bassetti M, Calandra T, et al. EESCMID* guideline for the diagnosis and management of Candida diseases 2012: non-neutropenic adult patients. *Clin Microbiol Infect*. 2012;18:19-37.
5. Liu J, Balasubramanian M. 1,3-beta-Glucan synthase: a useful target for antifungal drugs. *Curr Drug Targets Infect Disord*. 2001;1:159-169.
6. Eschenauer G, DePestel DD, Carver PL. Comparison of echinocandin antifungals. *Ther Clin Risk Manag*. 2007;3:71-97.
7. Denning DW. Echinocandin antifungal drugs. *Lancet*. 2003;362:1142-1151.
8. Felton T, Troke PF, Hope WW. Tissue penetration of antifungal agents. *Clin Microbiol Rev*. 2014;27:68-88.
9. Damle BD, Dowell JA, Walsky RL, et al. In vitro and in vivo studies to characterize the clerarance mechanism and potential cytochrome P450 interactions of anidulafungin. *Antimicrob Agents Chemother*. 2009;53:1149-1156.
10. Sandhu P, Xu X, Bondiskey PJ, et al. Disposition of caspofugin, a novel antifugal agent, in mice, rats, rabbits, and monkeys. *Antimicrob Agents Chemother*. 2004;48:1272-1280.
11. Hebert MF, Smith HE, Marbury TC, et al. Pharmacokinetics of micafungin in healthy volunteers, volunteers with moderate liver disease, and volunteers with renal dysfunction. *J Clin Pharmacol*. 2005;45:1145-1152.
12. Bruggemann RJ, Middel-Baars V, de Lange DW, et al. Pharmacokinetics of anidulafungin in critically ill intensive care unit patients with suspected or proven invasive fungal infections. *Antimicrob Agents Chemother*. 2017;61:e01894-e01916.
13. Martial LC, Bruggemann RJ, Schouten JA, et al. Dose reduction of caspofungin in intensive care unit patients with child Pugh B will result in suboptimal exposure. *Clin Pharmacokinet*. 2016;55:723-733.
14. Van der Elst KC, Veringa A, Zijlstra JG, et al. Low caspofungin exposure in patients in intensive care units. *Antimicrob Agents Chemother*. 2017;61:e01582-e01616.
15. Lempers VJ, Schouten JA, Hunfeld NG, et al. Altered micafungin pharmacokinetics in intensive care unit patients. *Antimicrob Agents Chemother*. 2015;59:4403-4409.
16. Aguilar G, Azanza JR, Carbonell JA, et al. Anidulafungin dosing in critically ill patients with continuous venovenous haemodiafiltration. *J Antimicrob Chemother*. 2014;69:1620-1623.
17. Aguilar G, Ferriols R, Lozano A, et al. Optimal doses of caspofungin during continuous venovenous hemodiafiltration in critically ill patients. *Crit Care*. 2017;21:1594-1599.
18. Crandon JL, Banevicius MA, Fang AF, et al. Bronchopulmonary disposition of intravenous voriconazole and anidulafungin given in combination to healthy adults. *Antimicrob Agents Chemother*. 2009;53:5102-5107.
19. Dowell J, Schranz J, Baruch A, et al. Safety and pharmacokinetics of coadministered voriconazole and anidulafungin. *J Clin Pharmacol*. 2005;45:1373-1382.
20. Dowell J, Stogniew M, Krause D, et al. Assessment of the safety and pharmacokinetics of anidulafungin when administered with cyclosporine. *J Clin Pharmacol*. 2005;45:227-233.
21. Dowell JA, Stogniew M, Krause D, et al. Lack of pharmacokinetic interaction between anidulafungin and tacrolimus. *J Clin Pharmacol*. 2007;47:305-314.
22. Dupont H, Massias L, Jung B, et al. Pharmacokinetic study of anidulafungin in ICU patients with intra-abdominal candidiasis. *J Antimicrob Chemother*. 2017;72:1429-1432.
23. Hebert M, Blough D, Townsend R, et al. Concomitant tacrolimus and micafungin pharmacokinetics in healthy volunteers. *J Clin Pharmacol*. 2005;45:1018-1024.
24. Keirns J, Sawamoto T, Holum M, et al. Steady-state pharmacokinetics of micafungin and voriconazole after separate and concomitant dosing in healthy adults. *Antimicrob Agents Chemother*. 2007;51:787-790.
25. Leitner JM, Meyer B, Fuhrmann V, et al. Multiple-dose pharmacokinetics of anidulafungin during continuous venovenous haemofiltration. *J Antimicrob Chemother*. 2011;66:880-884.
26. Liu P, Ruhnke M, Meersseman W, et al. Pharmacokinetics of anidulafungin in critically ill patients with candidemia/invasive candidiasis. *Antimicrob Agents Chemother*. 2013;57:1672-1676.
27. Muilwijk EW, Schouten JA, van Leeuwen HJ, et al. Pharmacokinetics of caspofungin in ICU patients. *J Antimicrob Chemother*. 2014;69:3294-3299.
28. Stone J, Holland S, Wickersham P, et al. Single- and multiple-dose pharmacokinetics of caspofungin in healthy men. *Antimicrob Agents Chemother*. 2002;46:739-745.
29. Undre N, Stevenson P, Baraldi E. Pharmacokinetics of micafungin in HIV positive patients with confirmed esophageal candidiasis. *Eur J Drug Metab Pharmacokinet*. 2012;37:31-38.
30. Undre NA, Stevenson P, Kuse ER, et al. Pharmacokinetics of micafungin in adult patients with invasive candidiasis and candidemia. *Open J Med Microbiol*. 2012;2:84-90.
31. Andes DR, Reynolds DK, Wart SAV, et al. Clinical pharmacodynamic index identification for micafungin in esophageal candidiasis: dosing strategy optimization. *Antimicrob Agents Chemother*. 2013;57:5714-5716.
32. Smith BS, Yogaratnam D, Levasseur-Franklin KE, et al. Introduction to drug pharmacokinetics in the critically ill patient. *Chest*. 2012;141:1327-1336.
33. Ulldemolins M, Roberts JA, Rello J, et al. The effects of hypoalbuminaemia on optimizing antibacterial dosing in critically ill patients. *Clin Pharmacokinet*. 2011;50:99-110.
34. Stan CD, Tuchiluş C, Stan CI. Echinocandins–new antifungal agents. *Rev Med Chir Soc Med Nat Iasi*. 2014;118:528-536.
35. Song JC, Stevens DA. Caspofungin: pharmacodynamics, pharmacokinetics, clinical uses and treatment outcomes. *Crit Rev Microbiol*. 2016;42:813-846.
36. Roberts JA, Aziz MHA, Lipman J, et al. Challenges and potential solutions-individualised antibiotic dosing at the bedside for critically Ill patients: a structured review. *Lancet Infect Dis*. 2014;14:498-509.
37. Jullien V, Azoulay E, Schwebel C, et al. Population pharmacokinetics of micafungin in ICU patients with sepsis and mechanical ventilation. *J Antimicrob Chemother*. 2017;72:181-189.

38. Yang Q, Wang T, Xie J, et al. Pharmacokinetic/pharmacodynamic adequacy of echinocandins against Candida spp. in intensive care unit patients and general patient populations. *Int J Antimicrob Agents*. 2016;47:397-402.
39. Sinnollareddy M, Peake SL, Roberts MS, et al. Using pharmacokinetics and pharmacodynamics to optimise dosing of antifungal agents in critically ill patients: a systematic review. *Int J Antimicrob Agents*. 2012;39(1):1-10.
40. Muilwijk EW, Lempers VJ, Burger DM, et al. Impact of special patient populations on the pharmacokinetics of echinocandins. *Expert Rev Anti Infect Ther*. 2015;13(6):799-815.
41. Bellmann R, Smuszkiewicz P. Pharmacokinetics of antifungal drugs: practical implications for optimized treatment of patients. *Infection*. 2017;45(6):737-779.
42. Hahn J, Choi JH, Chang MJ. Pharmacokinetic changes of antibiotic, antiviral, antituberculosis and antifungal agents during extracorporeal membrane oxygenation in critically ill adult patients. *J Clin Pharm Ther*. 2017;42(6):661-671.

SUPPORTING INFORMATION

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

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