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REVIEW ARTICLE

Echinocandins Pharmacokinetics: A Comprehensive Review of Micafungin, Caspofungin, Anidulafungin, and Rezafungin Population Pharmacokinetic Models and Dose Optimization in Special Populations

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Abstract

In recent years, many population pharmacokinetic (popPK) models have been developed for echinocandins to better understand the pharmacokinetics (PK) of these antifungals. This comprehensive review aimed to summarize popPK models of echinocandins (micafungin, caspofungin, anidulafungin, and rezafungin), by focusing on dosage optimization to maximize the probability of attaining the PK/PD target proposed in special populations. A search in PubMed, Embase, Web of Science, and Scopus, supplemented by the bibliography of relevant articles, was conducted from inception to March 2024, including both observational and prospective trials. A total of 1126 articles were identified, 47 of them were included in the review (22 for micafungin, 13 for caspofungin, 9 for anidulafungin, and 3 for rezafungin). A two-compartment model was more frequently used to describe the PK parameters of echinocandin (78.7% of developed models), although more complex structural models with three and four compartments have also been developed. The covariates to estimate the PK parameters such as clearance (CL) and volume of distribution (V_d) differed between models. Weight total (WT) was the most frequently reported to be a significant predictor for both parameters, especially for estimating the CL in pediatrics. The PD parameter most widely reported assessing the drug exposure–efficacy relationship was the area under the concentration–time curve to minimum inhibitory concentration (MIC) ratio ($AUC_{0–24}$/MIC) with different targets proposed for each echinocandin. In certain populations such as patients that are critically ill, obese, receiving extracorporeal membrane oxygenation (ECMO) and/or continuous renal replacement therapy (CRRT), or pediatric patients and/or patients with cancer or that are immunocompromised, the fixed dosing strategies recommended in the drug prescribing information may not reach the PK/PD target. For these populations, different strategies have been proposed, such as a dosing regimen based on body weight or increasing the loading and/or maintenance dose. Despite echinocandins' favorable safety profile and predictable PK, certain groups at risk of suboptimal drug exposure can benefit from therapeutic drug monitoring (TDM) to prevent clinical failures. Numerous popPK models of echinocandins have been developed. However, an external validation of the suggested dosing regimens in conjunction with an analysis of population subgroups should be conducted before implementing a popPK model in clinical practice.

1 Introduction

Candidiasis, aspergillosis, and other invasive fungal infections (IFIs) represent a significant source of morbidity and mortality (attributable range of 10–49%) in hospitalized patients, contributing substantially to healthcare costs despite the increased availability of antifungal agents with improved pharmacokinetic/pharmacodynamic (PK/PD) properties and activity spectra [1, 2]. Invasive candidiasis (IC) is the most prevalent fungal disease among patients that are critically ill [3]. Despite the increasing options for antifungal treatment,

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Key Points

Echinocandins population pharmacokinetic (popPK) models conducted in special populations are useful for improving dosing regimens and reaching the desired PK/PD target.

Some covariates have been found to influence echinocandins pharmacokinetics, especially body weight, although the unexplained variability remains considerable, so further research is necessary to improve the predictive performance of these models.

Different strategies such as a dosing regimen based on body weight, increasing the maintenance, and/or the loading have been proposed to achieve echinocandins PK/PD target in special populations.

IC-related prognosis remains poor [4, 5]. An important advancement in the management of IFIs came with the introduction of echinocandins into the antifungal arsenal with caspofungin in 2001, followed by micafungin in 2005 and anidulafungin 2006. Echinocandins, in contrast to triazoles, show notable efficacy in the presence of biofilms, as well as a postantifungal effect, which allows the inhibition of fungal growth after the drug is stopped [6]. Echinocandins are usually well tolerated because of their unique mechanism of action, which involves inhibiting β-(1,3)-D-glucan synthase, an enzyme required for the synthesis of an essential component of the fungi cell wall, while sparing human cells. Moreover, they have low risk of adverse effects [5, 7].

The clinical use of echinocandins, particularly for treating candidemia and IC, has increased significantly in recent years [1, 8]. Most treatment guidelines recommend initial therapy with echinocandins for patients that are critically ill and those at high risk of infection for some *Candida* species, based on their high efficacy, favorable safety profile, broader spectrum compared with fluconazole, and limited drug interactions [5, 9]. The current dose recommendation for IFIs involves a fixed dose for adults: caspofungin: loading dose (LD) 70 mg followed by 50 mg/day or 70 mg daily if > 80 kg [10], micafungin 100–150 mg/day or 2–4 mg/kg/day if ≤ 40 kg [11]; anidulafungin: LD 200 mg followed by 100 mg/day [12]; and rezafungin: LD 400 mg followed by 200 mg/weekly [13]. However, recent studies have documented inadequate exposure to echinocandins in special populations, such as patients that are critically ill or obese, patients undergoing extracorporeal membrane oxygenation (ECMO) and/or continuous renal replacement therapy (CRRT), and pediatrics [14–24]. Identifying the main causes of pharmacokinetic variability is crucial for optimizing echinocandin dosing [18].

Echinocandin dosing and therapeutic drug monitoring (TDM) have not been extensively studied. However, recently, many population pharmacokinetic (popPK) models have been developed to better understand dosing in special populations. The population-based modeling method assesses both intra- and interindividual variability, allowing the determination of optimal dosing regimens by identifying and quantifying sources of PK variability and enhancing the understanding and optimization of clinical interventions [25]. This method has an advantage over classical PK studies in that the effects of covariates on the PK parameters can be derived through sparse sampling from each subject. This reduces the need for bloodwork and increases participant recruitment [25–27].

Echinocandins PK/PD studies have demonstrated concentration-dependent fungicidal effect where the antifungal activity is correlated to higher drug concentrations than the MIC for the organism [6]. Thus, antifungal dosage could be optimized based on PK/PD properties [8, 14, 15]. A thorough understanding of PK/PD relationships provides the basis for developing reliable and effective dosages and identifies circumstances in which a conventional fixed regimen could fail, providing resources to prevent them [18, 27, 28]. The PD target to evaluate the exposure–response relationship of echinocandins has been well established to be the $AUC_{0–24}$/MIC ratio [18, 22, 28–30]. These ratios vary between the different *Candida* species and the echinocandins used. Monte-Carlo simulations are used to determine the probability of target attainment (PTA), defined as the percentage of subjects who achieved the proposed PD exposure in each study [28, 31]. The likely success of treatment identified the PTA by comparing the PD exposure against a MIC distribution. Usually, a PTA of > 90% is considered optimal [15, 28, 32]. Since echinocandins are highly protein bound and their antifungal activity is concentration dependent, the $fAUC_{0–24}$/MIC ratio has been identified as more accurate predictor of PK/PD characteristics and may be of great interest, especially in patients that are hypoalbuminemic, such as many patients that are critically ill [18, 22, 28, 33].

To date, no recent reviews have focused on describing the popPK of echinocandins in different populations. This review synthesizes the published literature on popPK of echinocandins, describes the significant covariates affecting them, compiles the PD targets, and the strategies to achieve them in special populations.

2 Search Methodology

2.1 Literature Search Strategy

A literature search was conducted in MEDLINE (via PubMed), Embase, Web of Science, and Scopus databases

using the following combination of terms for each antibiotic: ("micafungin" OR "caspofungin" OR "anidulafungin" OR "rezafungin") AND ("pharmacokinetic model" OR "popPK" OR "population pharmacokinetics") without language restrictions to identify popPK studies of echinocandins in all types of populations from inception to 6 March 2024. The principal search was supplemented by inspecting the bibliography of relevant articles.

2.2 Inclusion and Exclusion Criteria

All articles should meet the following criteria: (1) observational studies or clinical trials describing popPK models of echinocandins (caspofungin, micafungin, anidulafungin, and rezafungin) in humans (adults, children, and neonates); (2) the study must report at least one PK parameter (e.g., elimination constant [k_e], half-life [$t_{1/2}$], clearance [CL], intercompartmental clearance [Q], central volume [V_c], or peripheral volume of distribution [V_p]) and use at least one type of popPK analysis (models using both parametric methods such as the nonlinear mixed-effects model [NLME] and the iterative two-stage [iterative standard Bayesian method, IT2B] and nonparametric methods were allowed); (3) the text must be in English, Spanish, French, or German.

The following was excluded: (1) studies describing only covariates influencing the PK parameters without equations; (2) reviews of already published popPK models, protocols, editorials, commentaries, and book chapters; (3) validation studies for already published popPK models; and (4) studies that did not use popPK modeling analyses (studies in vitro or in animals).

2.3 Data Extraction

One investigator reviewed the literature, assessing the titles and abstracts of the studies according to the screening criteria for possible inclusion using a standard data extraction form in Microsoft Excel (Microsoft Corporation, Redmond, WA). The following data from the studies were extracted: study duration in years, country, statistical modeling software, total number of samples and patients, population demographics, dose and frequency, PD parameter used and target, treatment intention, structural PK model, developed model for calculating the PK parameters CL, Q, volume of distribution (V_d), V_c, V_p, and the included covariates in each equation.

To describe the characteristics of the population included in each study, age, weight, and serum creatinine (SCr) levels expressed as mean ± standard deviation (SD) or median (range) were recorded.

3 Eligible Studies and Characteristics of Population Pharmacokinetic Models

3.1 Studies Included and Population Characteristics

A total of 1126 articles were identified. After removing duplicates, 589 relevant studies were screened. Finally, 59 were assessed for title and abstract review, and 47 of them were included in the review (22 for micafungin, 13 for caspofungin, 9 for anidulafungin, and 3 for rezafungin) (Fig. 1).

For the articles included the year of publication ranges across approximately 19 years (from 2004 to the end of 2023).

3.1.1 Micafungin

Micafungin was the antifungal agent for which most models have been described ($n = 22$). The years of study included from 1998 to 2016. A total of 17 studies were conducted on adults and 5 on the pediatric population, one of which combined adults and pediatric patients. Nonlinear mixed-effects modeling was the most widely used approach for describing micafungin PopPK models, with NONMEM being the most statistical modeling software used in 10 of the 22 models described (45.5%). The nonparametric adaptive grid (NPAG) algorithm for Pmetrics software was used in 8 out of 22 models (36.4%). Micafungin popPK was best described by a two-compartment approach (2-CMT) in 18 models and by a three-compartment approach (3-CMT) in 3 models. The study of Jullien et al. [34] had the largest population: 100 adults with 436 plasma concentrations, and the study of Hope et al. [24] had the largest pediatric population: 1919 samples in 229 patients. The percentage of males was higher than females in most studies. SCr levels were missing in some studies, especially in studies that included pediatric patients. Patients that were critically ill were the most widely studied population, with 12 of the 17 studies conducted on adults. The doses in adults ranged from 12.5 to 300 mg daily, with the dose of 100 mg/day being the most commonly used. In pediatrics, the doses ranged from 0.5 to 15 mg/kg/day. Treatment intention included prophylaxis, suspected and proven fungal infections.

The PD parameter most widely reported for assessing the drug exposure–efficacy relationship for micafungin, was the area under the concentration–time curve/MIC ratio ($AUC_{0–24}$/MIC). The target most frequently reported for non-*Candida parapsilosis* spp varied between > 3000 and > 5000. However, the target $AUC_{0–24}$/MIC > 285 for *C. parapsilosis* seems to be common in most studies. Some studies, such

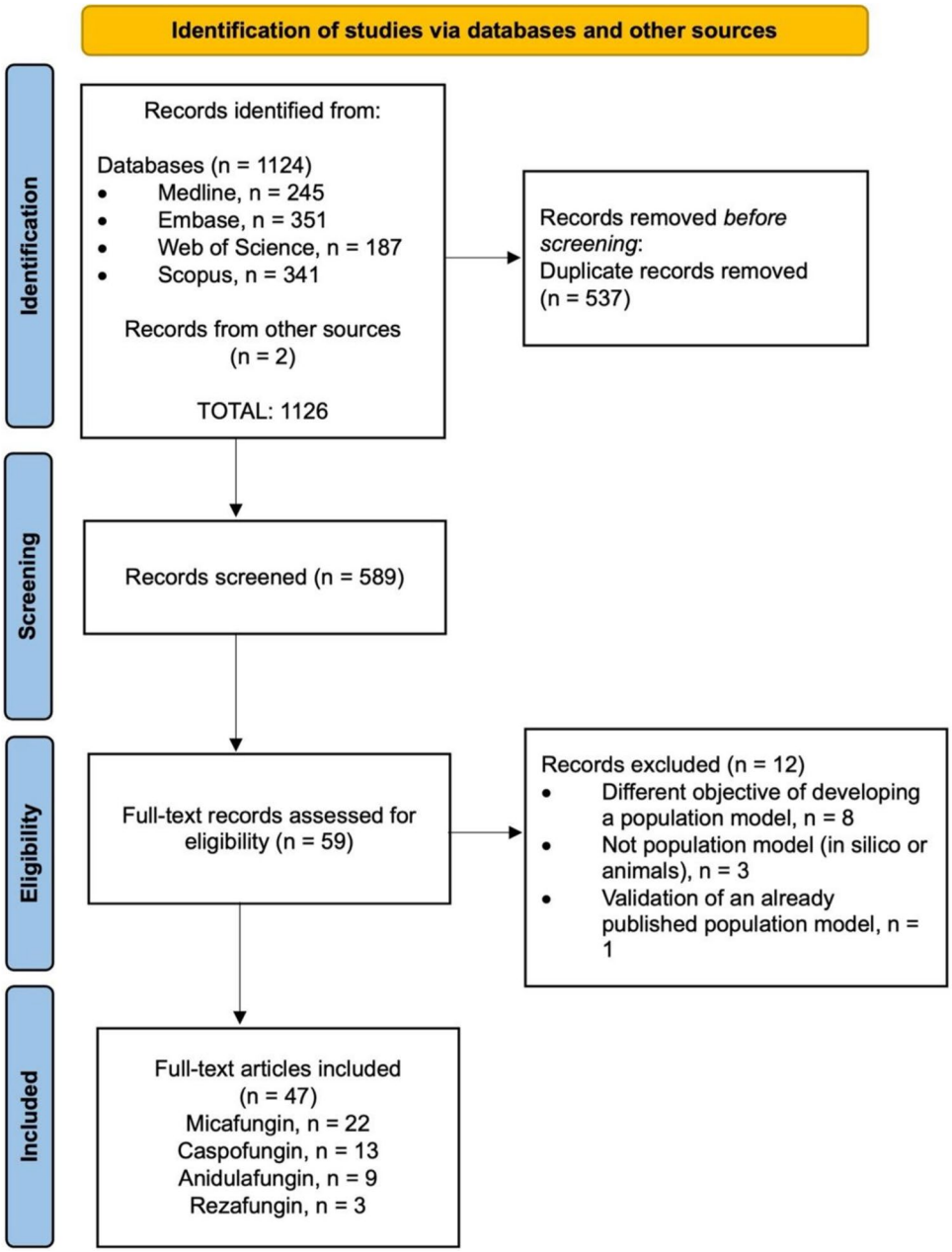

Fig. 1 Flow chart of the article selection process

as Gastine et al. [30] and Zhong et al. [35] have suggested different targets depending on the specific *Candida* species.

3.1.2 Caspofungin

A total of 13 models were described for caspofungin, 10 in adults and 3 in pediatrics. The studies were conducted between 1997 and 2021. NONMEM was the statistical modeling software most commonly used in 8 of the 13 models described (61.5%). Caspofungin popPK was best described using a 2-CMT approach in 11 models (84.6%). The study by Wu et al. [36] had the largest adult population with 58 patients (414 samples). In pediatrics, Yang et al. [37] included 48 patients with a total of 159 samples. Six studies [14, 15, 37–40] were conducted on the critically ill population including adults and children, and five on transplant recipients' patients [28, 32, 36, 41, 42]. An LD of 70 mg followed by 50 or 70 mg/day according to body weight was the most common regimen, although in the study of Würthwein G. et al. [43], it was used up to 200 mg/day. The most used PD parameter to evaluate the correlation between drug exposure and efficacy was the $AUC_{0–24}$/MIC ratio. According to Pressiat C. et al. for the fungicidal effect, an $AUC_{0–24}$/MIC > 865 for *C. albicans*; > 450 for *C. glabrata*; > 1185 for *C. parapsilosis* were most widely reported, which corresponds to a free drug target of $fAUC_{0–24}$/MIC > 25.9 for *C.*

albicans; > 13.5 for *C. glabrata*; > 35.5 for *C. parapsilosis.* [28]. Only one study evaluated the PD target in *Aspergillus* spp. infections, reporting a target of C_{max}/minimal effective concentration (MEC) of 10–20.

3.1.3 Anidulafungin

A total of nine models were described for anidulafungin for adults. The period over which the studies were conducted has not been reported in most of them. The statistical modeling software most commonly used was NONMEM, in four of the nine models developed (44.4%). Anidulafungin popPK was best described using a 2-CMT approach in eight of the nine models described (88.9%). Patients that were critically ill were again the most commonly studied population, in five of the nine studies included [18, 22, 27, 44, 45]. A LD of 200 mg followed by 100 mg/day was the most common regimen, although in some studies a lower MD of 50 mg/day was used [46, 47]. Different PD parameters to evaluate the correlation between drug exposure and efficacy have been described, such as $AUC_{0–24}$/MIC with a suggested but not clear threshold of 40 mg × h/L [47]; $fAUC_{0–24}$/MIC > 20.6 for *C. albicans*, > 7.0 for *C. glabrata*; > 7.6 for *C. parapsilosis* in the study of Luque et al. [18] and Kapralos et al. [22] or $AUC_{0–\tau} \geq 82$ h × mg/L for *C. glabrata* reported by Hall et al. [48].

3.1.4 Rezafungin

The population PK of rezafungin has only been described in three studies, as this echinocandin has recently been marketed. The popPK models developed are more complex than the other three echinocandins; 4-compartment (4–CMT) and 3-compartment models (3–CMT) have been used. Doses vary widely, including single- and multiple-dose studies, ranging from 50 to 1400 mg, although the regular dose is LD 400 mg and MD 200 mg/weekly. The PD target has not been clearly defined for humans in the popPK studies conducted.

Table 1 summarizes the characteristics of the population pharmacokinetic studies included in the review. The data for the variability of each popPK model as well as the antifungal dosing recommendation of the included studies are summarized in Supplementary Table 1.

3.2 Population Pharmacokinetic Analysis

3.2.1 Micafungin

Among the 17 studies described for micafungin in adults, CL estimates ranged from 0.69 to 1.56 L/h for the 2-CMT models and 1.09 to 1.61 L/h for the 3-CMT models. The V_c estimates ranged from 8.84 to 17.6 L, the V_p ranged from 2.77 to 12.6 L for the 2-CMT models, and the V_c from 5.85 to 12.85 L for the 3-CMT models. The V_p (3.86 L) and V_{pe} (4.82 L) were only reported in the study of Garbez et al. [31] for the 3-CMT models.

The frequency of covariates included in the popPK model ranged from none to three for CL. Weight total (WT) was the most frequently reported significant predictor of micafungin CL, especially in pediatric patients and was included in the equations developed. In other models, SOFA, albumin, bilirubin, transaminases (ALT and AST), platelet count, body surface area (BSA), and fat free mass (FFM) have been reported to influence CL. For V_d, the developed equations were simpler; in seven models, no covariates were found, and in other 5 [20, 34, 54, 55, 60] WT was used as a significant predictor. In other models, the FFM [31] and the lean body mass corrected (LBMc) were included [56].

3.2.2 Caspofungin

In the ten models developed for caspofungin in adults, the CL estimates ranged from 0.21 to 0.70 L/h for the 2-CMT models; only one 3-CMT [40] was developed for adults with a predicted CL of 0.78 L/h. The CL in pediatric patients cannot be compared because they are expressed in different units. The V_c estimates ranged from 2.21 to 18.6 L and the V_p from 2.87 to 49.20 L for the 2-CMT models, and for the 3-CMT models, the V_c was 9.36 and V_p and V_{pe} 4.87 L and 4.69 L, respectively.

The frequency of covariates included in the popPK model ranged from none to two for CL. Six models [15, 28, 29, 38, 39, 41] did not find any covariate to influence CL; WT was only reported in two popPK models [14, 43]; FFM in one [40], and BSA in two pediatric models [32, 37]. The covariates most frequently described to influence the V_d for caspofungin popPK models were WT in four of ten adult models [14, 15, 35, 41], FFM in one model [40], and BSA in two pediatric models [32, 37]. Five models did not include any covariates to estimate the V_d [28, 29, 36, 39, 41].

3.2.3 Anidulafungin

Among the nine popPK models described for anidulafungin in adults, CL estimates ranged from 0.78 to 1.05 L/h for the 2-CMT models. Only one 3-CMT was described for adults with a mean CL of 1.00 L/h [21]. The V_c estimates ranged from 0.17 to 29.48 L and the V_p from 14.42 to 48.70 L for the 2-CMT models and for the 3-CMT model, the V_c, Vp_2, and Vp_3 were 16.60 L for all of them.

The covariates included in the anidulafungin popPK models for estimating the CL ranged from one to three. The WT was included in four models [18, 21, 44, 46], in one model FFM was included [27] and in another one, the lean body weight (LBW) [48]. The covariate most frequently described to influence the V_d was WT [21, 46, 47]. Other reported

Table 1 Characteristics of the population pharmacokinetic studies included in the review

First author, publication year [ref.]	Years of study	Country	PK software	Type of patients	*N* samples/ patients	Gender M/F (%)	Age (in years) mean (SD) or median, [range]	Weight (in Kg) mean (SD) or median, [range]	SCr (in mg/dL) mean (SD) or median, [range]	Structural PK model	Dose/interval	Treatment intention	PD parameter used and target
Micafungin pharmacokinetic models													
Adults													
Maseda 2014 [51]	2012	Spain	NONMEM	Patients that are critically ill on CVVH	ND/10	80/20	73.5 [54–83]	70 [61–80]	ND	2–CMT	100 mg/day	Proven invasive candidiasis	AUC_{0-24}/MIC >285 *C. parapsilosis*; > 3000 *Candida* spp; >5000 non-*C. parapsilosis* spp
Grau 2015 [17]	2013–2014	Spain	NPAG (Pmetrics software)	Post-surgical patients that are critically ill with severe peritonitis	ND/10	60/40	72 [43–85]	65 [60.3–73.8]	1 [0.6–1.4]	3–CMT	100 mg/day	Suspected or Proven fungal IAI	AUC_{0-24}/MIC >285 *C. parapsilosis*; >3000 non-*C. parapsilosis* spp
García-de-Lorenzo 2016 [52]	2013–2015	Spain	NPAG (Pmetrics software)	Patients that are critically ill with burn injuries and patients with complicated IAI	ND/25 (15 Burn; 10 IAI)	Burn: 80/20 IAI: 60/40	Burn: 43 [32.0–49.5] IAI: 72 [54–77.8]	Burn: 80.0 [75.0–87.5] IAI: 65 [60.3–73.8]	Burn: 0.8 [0.6–1.1] IAI: 1.0 [0.6–1.5]	3–CMT	100–150 mg/day	Suspected or Proven fungal infection	AUC_{0-24}/MIC >285 *C. parapsilosis*; >3000 non-*C. parapsilosis* spp
Jullien 2017 [34]	ND	France	NONMEM	Patients that are critically ill with sepsis and mechanical ventilation	436/100	66/33	61.4 [29.9–92.7]	84.5 [48–141]	ND	2–CMT	100 mg/day	Suspected but not proven candidiasis	AUC_{0-24}/MIC ≥285 *C. parapsilosis*; >5000 non-*C. parapsilosis* spp
Martial 2017 [53]	ND	Netherlands	NONMEM	Patients that are critically ill	356/20	40/60	68 [20–84]	76.5 [50–134]	ND	2–CMT	100 mg/day	Suspected or Proven fungal infection	AUC_{0-24}/MIC >285 *C. parapsilosis*; >3000-12000 *Candida* spp; >5000-12000 non-*C. parapsilosis* spp

Table 1 (continued)

First author, publication year [ref.]	Years of study	Country	PK software	Type of patients	*N* samples/ patients	Gender M/F (%)	Age (in years) mean (SD) or median, [range]	Weight (in Kg) mean (SD) or median, [range]	SCr (in mg/dL) mean (SD) or median, [range]	Structural PK model	Dose/interval	Treatment intention	PD parameter used and target
Maseda 2018 [19]	ND	Spain	NPAG (Pmetrics software)	Patients that are obese, critically ill, and morbidly obese and critically ill	242/31 (10 critically ill non-obese, 10 non-critically ill obese, 11 critically ill morbidly obese)	29/71	58 [27–85]	95 [44–193]	1.0 [0.4–3.9]	2–CMT	100 mg/day (BMI ≤ 45 kg/m^2) and 150 mg/ day (BMI > 45 kg/m^2)	Empirical or proven fungal infection	AUC_{0-24}/MIC >285 *C. parapsilosis*; > 3000 *Candida* spp; >5000 non-*C. parapsilosis* spp
Gastine 2019 [30]	ND	Germany	NONMEM	Patients that are critically ill including renal failure supported by RRT	ND/36	67/33	65 [22–84]	94.5 [49.9–162]	1.1 [0.3–6.2]	2–CMT	100 mg/day	Suspected or Proven fungal infection	AUC_{0-24}/MIC >285 *C. parapsilosis*; >2420 *C. albicans*; >1283 *C. glabrata*
Tenorio-Cañamás 2019 [54]	2014–2015	Spain	NPAG (Pmetrics software)	Patients that are critically ill on CVVHD-HCO	ND/9	56/44	50 [28–80]	71 [55–200]	ND	2–CMT	100 mg/day	Suspected or Proven fungal infection	ND
Kapralos 2020 [23]	ND	Greece	NONMEM	Patients that are critically ill	210/14	50/50	61 (15)	85 (22)	1.3 (1.0)	2–CMT	100 mg/day	Suspected or Proven fungal infection and prophylaxis	AUC_{0-24}/MIC >285 *C. parapsilosis*; > 3000 *C. albicans*; >6000 *C. glabrata*
Garbez 2021 [31]	ND	France	NPAG (Pmetrics software)	Patients that are critically ill and septic with IAI	171/12	58/42	71 [32–85]	64.8 [52–110]	Day 1: 1.1 [0.6–2.2] Days 3–5: 0.9 [0.42–6.8]	3–CMT	100 mg/day	Suspected or Proven fungal infection	AUC_{0-24}/MIC >3000 all *Candida* spp
Garbez 2021 [16]	ND	France	NPAG (Pmetrics software)	Patients that are critically ill with septic shock undergoing CVVH or CVVHDF	18/8	88/12	72.3 [43.9–80.8]	94.8 [66–138]	1.6 [1.0–2.8]	2–CMT	100 mg/day	Proven fungal infection	AUC_{0-24}/MIC >3000 all *Candida* spp

Table 1 (continued)

First author, publication year [ref.]	Years of study	Country	PK software	Type of patients	*N* samples/ patients	Gender M/F (%)	Age (in years) mean (SD) or median, [range]	Weight (in Kg) mean (SD) or median, [range]	SCr (in mg/dL) mean (SD) or median, [range]	Structural PK model	Dose/interval	Treatment intention	PD parameter used and target
Zhong 2021 [35]	2017– 2018	China	NONMEM	Patients that are critically ill with sepsis	ND/32	66/34	60.1 [23.0–89.0]*	70.22 [55.0–90.0]*	1.5 [0.5–2.9]*	2–CMT	100–200 mg/day	Suspected or Proven fungal infection	AUC_{0-24}/MIC >285 *C. parapsilosis*; >3000 *C. krusei* and *C. tropicalis*; >5000 *C. albicans* and *C. glabrata*
Boonstra 2022 [56]	2012–2016	Netherlands	MW\Pharm	Patients that are critically ill	165/19	53/47	64 [57–73]	85 [65–98]	ND	2–CMT	100 mg/day	Proven fungal infection	AUC_{0-24}/MIC >3000 all *Candida* spp
Gumbo 2008 [49]	1998–1999	USA	Systat Software for Windows	Patients who underwent bone marrow or peripheral stem cell transplant	1128/62	32/68	ND	82.6 (19.3)	ND	2–CMT	12.5–200 mg/day	Prophylaxis	AUC_{0-24}/MIC
Ikawa 2009 [50]	ND	Japan	NONMEM	Patients with hematological malignancies	48/10	40/60	63.5 (16.2)	55.4 (10.3)	0.6 (0.4)	2–CMT	50–300 mg/day	Suspected fungal infections	$fAUC_{0-24}$/MIC
Wasmann 2019 [20]	2017	Netherlands	WinNonlin and NONMEM	Normal-weight adults and morbidly obese subjects (BMI > 40 kg/m^2)	223/24 (8 normal weight, 16 morbidly obese)	50/50	Normal weight: 31 [22–56] Obese: 48.5 [24–61]	Normal weight: 70.8 [61.5–81.5] Obese: 148.5 [112-184]	ND	2–CMT	100 mg/day (normal weight), 100–200 mg/day (obese)	Healthy volunteers and prophylaxis	AUC_{0-24}/MIC >5000 all *Candida* spp excluding *C. parapsilosis*
Alqahtani 2021 [55]	ND	Arabia Saudi	Monolix	Patients with and without cancer	133/19 (10 with cancer, 9 without cancer)	Cancer: 60/40 Without Cancer: 67/33	Cancer: 47.3 (12.3) Without Cancer: 51.1 (19.1)	Cancer: 63.4 (18.2) Without Cancer: 69.8 (15.7)	Cancer: 0.85 (0.49) Without Cancer: 0.72 (0.4)	2–CMT	100–150 mg/day	Empirical or confirmed fungal infection	AUC_{0-24}/MIC >285 *C. parapsilosis*; > 3000 non-*C. parapsilosis* spp
Pediatrics													
Hope 2007 [57]	ND	USA	NPAG and Big NPAG	Hematologic children	ND/72	ND	2–17	35.65 (18.66)	ND	2–CMT	0.5, 1.0, 1.5, 2.0, 3.0, and 4.0 mg/kg/day	Empirical therapy for neutropenia febrile patients	AUC_{0-24}

Table 1 (continued)

First author, publication year [ref.]	Years of study	Country	PK software	Type of patients	*N* samples/ patients	Gender M/F (%)	Age (in years) mean (SD) or median, [range]	Weight (in Kg) mean (SD) or median, [range]	SCr (in mg/dL) mean (SD) or median, [range]	Structural PK model	Dose/interval	Treatment intention	PD parameter used and target
Tabata 2006 [58]	1997–2004	Japan	NONMEM	Data obtained from seven previous studies: adult and pediatrics	1825/198 (82 healthy adults, 97 adult patients,19 pediatrics)	ND	All: 43.5 [0.7–78]* Adult: 47.4 [19–78] Children: 6.1 [0.7–15]*	All: 52.3 [7.0–80.6]* Adult: 55.6 [28.0–80.6]* Children: 22.0 [7.0–48]*	ND	2–CMT	2.5–150 mg/ day (adults: 25–150 mg/ day; pediatric: 1–6 mg/ kg/day)	Healthy subjects and proven fungal infection by *Aspergillus* or *Candida* spp.	ND
Hope 2010 [59]	ND	United Kingdom	Big NPAG	Neonates and young infants	ND/47	ND	ND	1.3 (0.5)	ND	2–CMT	0.75, 1.5, 3, 7, 10, and 15 mg/kg/day	Suspected or proven fungal infection	$AUC_{0–24}$/MIC > 1332
Hope 2015 [24]	ND	All around the world	NONMEM	Data obtained from six previous studies: children and adolescents; hematopoietic stem cell transplantation; febrile neutropenia; fungal infections caused by *Aspergillus* spp or *Candida* spp	1919/229	ND	4 mo to < 2 yrs: 1.0 (0.4) 2–5 yrs: 3.7 (1.2) 6–11 yrs: 9.0 (1.5) 12–16 yrs: 14.5 (1.5)	4 mo to < 2 yrs: 7.9 (1.7) 2–5 yrs: 15.3 (4.4) 6–11 yrs: 28.9 (9.0) 12–16 yrs: 54.4 (17.3)	4 mo to < 2 yrs: 28.2 (22.2) 2–5 yrs: 31.6 (15.1) 6–11 yrs: 47.2 (79.9) 12–16 yrs: 57.9 (31.7)	2–CMT	Data of six studies[1]	Suspected or proven fungal infection and prophylaxis	$AUC_{0–24}$ that were within the 10th and 90th percentile of the AUCs for adults receiving 100 mg/day (i.e., 75–139 g × h/mL)
Autmizguine 2016 [60]	ND	USA	Winonlin	Infants on ECMO	124/12	42/58	59 [0.0–574]	3.7 [2.9– 9.6]	0.5 [0.2– 1.6]	1–CMT	4 mg/kg/day (prophylaxis); 8 mg/kg/day suspected or confirmed fungal infection	Prophylaxis and proven fungal infection	Proven infection: AUC_{0-24}: 75–139 mg×h/L Prophylaxis: (50% of the therapeutic target): 37.5–69.5 mg×h/L

Table 1 (continued)

First author, publication year [ref.]	Years of study	Country	PK software	Type of patients	*N* samples/ patients	Gender M/F (%)	Age (in years) mean (SD) or median, [range]	Weight (in Kg) mean (SD) or median, [range]	SCr (in mg/dL) mean (SD) or median, [range]	Structural PK model	Dose/interval	Treatment intention	PD parameter used and target
Caspofungin pharmacokinetic models													
Adults													
Martial 2016 [39]	ND	Netherlands	NONMEM	Patients that are critically ill	419/21	62/38	71 [45–80]	75 [50–99]	ND	2–CMT	LD: 70 mg MD: 50 mg/ day if WT ≤ 80 kg; 70 mg/day if WT > 80 kg; 35 mg if Child-Pugh B or C	Prophylaxis or proven fungal infection	AUC_{0-24}/MIC >865 *C. albicans*
Roger 2017 [14]	ND	France	NPAG (Pmetrics software)	Patients that are critically ill undergoing CVVH or CVVHDF	12/9	78/22	62 [52–72]**	84 [75–93] **	ND	2–CMT	LD: 70 mg MD: 50 mg/ day if WT ≤ 80 kg; 70 mg/day if WT > 80 kg	Suspected or proven fungal infection	AUC_{0-24}/ MIC >865 *C. albicans*; >450 *C. glabrata*
Pérez-Pitarch 2018 [15]	ND	Spain	NONMEM	Patients that are critically ill on CVVHDF	105/12	50/50	73 [56–78] ***	75 [60–88] ***	0.8 [0.4–2.4] ***	2–CMT	LD: 70 mg MD: 50 mg/ day if WT ≤ 80 kg; 70 mg/day if WT > 80 kg	Suspected or proven fungal infection (candidiasis and aspergillosis)	AUC_{0-24}/ MIC >865 *C. albicans*; >450 *C. glabrata*; >1185 *C. parapsilosis* C_{max}/MEC: 10–20 *Aspergillus* spp
Märtson 2020 [38]	ND	Netherlands	NPAG (Pmetrics software)	Patients that are critically ill	219/15	55/45	56 [25–83]	78 [48–139]	0.83 [0.40–4.66]	2–CMT	LD: 70 mg MD: 50 mg/ day if WT ≤ 80 kg; 70 mg/day if WT > 80 kg[2]	Suspected or proven fungal infection	AUC_{0-24}/ MIC >865 *C. albicans*; >450 *C. glabrata*; >1185 *C. parapsilosis*
Garbez 2022 [40]	ND	France	NPAG (Pmetrics software)	Patients that are critically ill with septic shock and secondary peritonitis	159/11	45/55	67 [33–88]	87 [45–109]	ND	3–CMT	LD: 70 mg MD: 50 mg/ day if WT ≤ 80 kg; 70 mg/day if WT > 80 kg	Suspected or proven fungal infection	AUC_{0-24}/ MIC >865 *C. albicans*; >450 *C. glabrata*; >1185 *C. parapsilosis*

Table 1 (continued)

First author, publication year [ref.]	Years of study	Country	PK software	Type of patients	*N* samples/ patients	Gender M/F (%)	Age (in years) mean (SD) or median, [range]	Weight (in Kg) mean (SD) or median, [range]	SCr (in mg/dL) mean (SD) or median, [range]	Structural PK model	Dose/interval	Treatment intention	PD parameter used and target
Würthwein 2012 [41]	ND	Germany	NONMEM	Allogeneic hematopoietic stem cell recipients	458/36 (19 Only CAS, 17 LAMB and CAS)	Only CAS: 58/42 LAMB and CAS: 59/41	Only CAS: 43.4 [20.1–57.6] LAMB and CAS: 47.9 [20.1–61.4]	Only CAS: 71.2 [56.0–99.2] LAMB and CAS: 79.5 [53.6–99.1]	ND	2–CMT	LD: 70 mg MD: 50 mg/ day	Prophylaxis	AUC_{0-24}
Wang 2020 [42]	2017–2018	China	NONMEM	Patients with and without ECMO after lung transplantation	271/19 (12 ECMO, 7 non-ECMO)	ECMO: 75/25 Non-ECMO: 71/29	ECMO: 65 [60–67]** Non-ECMO: 59 [56–62]**	ECMO: 64 [59–69.3]** Non-ECMO: 65 [53–65]**	ND	2–CMT	50 mg/day	Prophylaxis	ND
Pressiat 2022 [28]	2017	France	MONOLIX	Patients receiving a liver transplant	395 (plasma and 50 peritoneal fluid)/20	45/55	45 [40.7–50]	72 [62–81]	1.5 [0.1–2.6]	2–CMT	LD:70 mg MD: 50 mg/day if WT ≤ 80 kg; 70 mg/day if WT > 80 kg	Prophylaxis	*f*AUC_{0-24}/ MIC > 25.9 *C. albicans*; >13.5 *C. glabrata*; >35.5 *C. parapsilosis*
Wu 2022 [36]	2019–2021	China	NONMEM	Heart transplant recipients and controls	414/58 (27 Heart transplant, 31 Control)	Heart transplant: 81/19 Control: 68/32	Heart transplant: 50 [20–73] Control: 58 [22–78]	Heart transplant: 59.5 [43.5–76] Control: 62.0 [48.0–100.0]	Heart transplant: 2.3 [0.2–7.1] Control: 2.1 [0.4–7.0]	2–CMT	LD: 70 mg MD: 50 mg/ day	Prophylaxis	AUC_{0-24}/ MIC >865 *C. albicans*; >450 *C. glabrata*; >1185 *C. parapsilosis*
Würthwein 2013 [43]	2006–2009	Germany	NONMEM	Patients that are immunocompromised	468/46	46/54	61 [18–74]	76 [43–104]	ND	2–CMT	70–200 mg / day	Suspected or proven aspergillosis	AUC_{0-24}
Pediatrics													
Yang 2019 [37]	2014–2016	France	NONMEM	Children that are critically ill	159/48	58/42	6.1 (2.7) 5.1 [2.1–11.8]	22.8 (8.7) 21.0 [11.8–47.5]	28.8 (10.2) 28.75 [14.0–67.0]	2–CMT	LD: 70 mg/m^2 MD:50 mg/m^2/ day	ND	MIC > 1 µg/L

Table 1 (continued)

First author, publication year [ref.]	Years of study	Country	PK software	Type of patients	*N* samples/ patients	Gender M/F (%)	Age (in years) mean (SD) or median, [range]	Weight (in Kg) mean (SD) or median, [range]	SCr (in mg/dL) mean (SD) or median, [range]	Structural PK model	Dose/interval	Treatment intention	PD parameter used and target
Niu 2020 [32]	2017–2019	China	Phoenix NLME and and R program	Children with allogeneic hematopoietic stem cell transplantation	139/48	65/35	6.58 (3.7) 6.2 [0.6–14]	21.7 (10.3) 20 [7.5–54]	0.5 (0.3) 0.3 [0.2–4.4]	1–CMT	LD: 70 mg MD: 50 mg/ day	Prophylaxis	Fungicidal target: AUC_{0-24}/MIC >865 *C. albicans*; >450 *C. glabrata*; >1185 *C. parapsilosis* Fungistatic target: AUC_{0-24}/ MIC >748 *C. albicans*; >96.2 *C. glabrata*; >559 *C. parapsilosis*
Gastine 2022 [29]	ND	USA	NONMEM	Children and adolescents	ND/48	55/45	Yrs: 6 [0–16] Mo: 81 [10–200]	21.5 [9.4–79.5]	ND	2–CMT	4 doses according to subgroup[3]	Prophylaxis	AUC_{0-24}/ MIC >865 *C. albicans*; >450 *C. glabrata*; >1185 *C. parapsilosis* *f*AUC_{0-24}/ MIC: 10–20
Anidulafungin pharmacokinetic models													
Adults													
Liu 2013 [44]	ND	Austria, Belgium, Germany, Greece, Netherlands, and Portugal	eNCA	Patients that are critically ill	ND/21	55/45	57 [39–78]	65 [48–106]	ND	2–CMT	LD: 200 mg MD:100 mg/ day	Proven invasive C or IC	AUC_{0-24}
Van Wanrooy 2015 [27]	2010–2011	Netherlands (obese patients)	MW\Pharm	Patients that are critically ill	ND/20	55/45	71 [60–75]	ND	ND	2–CMT	LD: 200 mg MD: 100 mg/ day	Proven IC	AUC_{0-24}

Table 1 (continued)

First author, publication year [ref.]	Years of study	Country	PK software	Type of patients	*N* samples/ patients	Gender M/F (%)	Age (in years) mean (SD) or median, [range]	Weight (in Kg) mean (SD) or median, [range]	SCr (in mg/dL) mean (SD) or median, [range]	Structural PK model	Dose/interval	Treatment intention	PD parameter used and target
Dupont 2017 [45]	ND	France	WinNonlin and Monolix	Patients that are critically ill	ND/14	43/57	62 [36–84]	ND	ND	2–CMT	LD: 200 mg MD: 100 mg/ day	Suspected or proven fungal IAI	C_{max}, C_{min}, AUC_{0-24}
Luque 2019 [18]	ND	Spain	NPAG (Pmetrics software)	Patients that are critically ill	ND/23	43/57	65 [28–81]	75 [54–168]	ND	2–CMT	LD: 200 mg MD: 100 mg/ day	Suspected or proven fungal infection	$fAUC_{0-24}$/MIC > 20 *C. albicans*, >7.0 *C. glabrata*
Kapralos 2021 [22]	ND	Greece	NONMEM	Patients that are critically ill	205/13	77/23	64.3 (14.3)	77.9 (11.3)	1.0 (0.8)	2–CMT	LD: 200 mg MD: 100 mg/ day	Suspected or proven IC and prophylaxis	$fAUC_{0-24}$/ MIC > 20.6 *C. albicans*, >7.0 *C. glabrata*; >7.6 *C. parapsilosis*
Hall 2023 [48]	ND	USA	Monolix	Healthy adults	ND/20	45/55	45 [21–78]	82.7 [42.4–208.3]	0.9 [0.6–1.1]	2–CMT	A single 100 mg dose	Healthy volunteers	$AUC_{0-\tau} \geq 82$ h × mg/L *C. glabrata*
Wasmann 2018 [21]	ND	Netherlands (obese patients)	NONMEM	Adults that are morbidly obese and normal weight	283 (195 normal-weight, 88 obese)/20 (12 normal-weight, 8 obese)	Normal weight: 83/17 Obese: 38/62	Normal weight: 24.5 [21–30] Obese: 43 [29–66]	Normal weight: 67.7 [61.5–93.6] Obese: 149.7 [124.1–166.5]	ND	3–CMT	LD: 200 mg MD: 100 mg/ day	Prophylaxis	AUC_{0-24} for normal-weight subjects (60-80kg): 99 mg × h/L (IQR, 91 to 108 mg × h/L)
Dowell 2004 [46]	ND	USA	NONMEM	Patients with serious fungal infections (IC, mucosal candidiasis, aspergillosis)	600/225	48/52	42 [18–88]	60 [31–154]	ND	2–CMT	LD: twice the MD MD: 50–100 mg/ day	Proven fungal infection	ND
Liu 2013 [47]	2001–2002 (2 studies) 3rd study ND	United States, South Africa, Thailand, and Argentina	NONMEM	Adult patients	741/235 (3 studies: 129 EC; 87 C/IC; 19 EC or OC)	47/53	40 [18–88]	59 [31–154]	ND	2–CMT	Data from 3 studies[4]	Proven IC, C, EC, or OC	AUC_{0-24}/MIC. No clear threshold, suggested AUC_{0-24}/ MIC > 40 mg × h/L

Table 1 (continued)

First author, publication year [ref.]	Years of study	Country	PK software	Type of patients	*N* samples/ patients	Gender M/F (%)	Age (in years) mean (SD) or median, [range]	Weight (in Kg) mean (SD) or median, [range]	SCr (in mg/dL) mean (SD) or median, [range]	Structural PK model	Dose/interval	Treatment intention	PD parameter used and target
Rezafungin pharmacokinetic models													
Adults													
Roepcke 2023 [33]	2016–2021	All around the world	NONMEM	Patients that are healthy adults and critically ill	2512/277 (94 healthy, 183 infected)	61/39	53.2 (15.5) 53.0 [20–89]	76.50 (19.5) 74.70 [34.0–154.5]	1.14 (1.01) 0.84 [0.1–7.1]	3–CMT	Data from 3 studies[6]	Healthy subjects and patients with confirmed C and/or IC	$fAUC_{0-168}$/ MIC****
Lakota 2018 [61]	2015	All around the world	Software program S-ADAPT (parametric)	Healthy adult	840/42	52/48	41.7 (9.0) 42.5 [22–54]	76.2 (11.1) 75.0 [57.1–102]	ND	4–CMT	Single dose of 50–400 mg and 100-400 mg/weekly	Healthy subjects	AUC_{0-24} and AUC_{0-24}/ MIC
Rubino 2021 [62]	2015–2021	All around the world	NONMEM	Adult patients with fungal infections	1518 (1102 healthy, 416 infected)/ 135 (66 healthy, 69 infected)	53/47	44.2 (10.3) 42.8 [20–88]	75.8 (14.3) 74.9 [34–102]	ND	4–CMT	Data from 4 studies[5]	Healthy subjects and patients with confirmed C and/or IC	$AUC_{0-\tau}$, C_{max}, C_{min}

AUC_{0-24} area under the curve over a 24 h dosing interval, *C* candidemia, *CASP* caspofungin, *CVVH* continuous venovenous hemofiltration, *CVVHDF* continuous venovenous hemodiafiltration, *CVVHD-HCO* continuous venovenous high cutoff membrane hemodialysis, *EC* esophageal candidiasis, *ECMO* extracorporeal membrane oxygenation, $fAUC_{0-24}$ free-drug area under the curve over a 24 h dosing interval, *IAI* intra-abdominal infection, *IC* invasive candidiasis, *IQR* interquartile range, *LAMB* liposomal amphotericin B, *LD* loading dose, *MEC* minimal effective concentration, *MD* maintenance dose, *MIC* minimum inhibitory concentration, *mo.* months, *NLME* nonlinear mixed-effects model, *NPAG* nonparametric adaptive grid, *OC* oropharyngeal candidiasis, *PD* pharmacodynamics, *PK* pharmacokinetic, *RRT* renal replacement therapy, *WT* current weight, *yrs* years, *1-CMT* one-compartment model, *2-CMT* two-compartment model, *3-CMT* three-compartment model, *4-CMT* four-compartment model

*Data are expressed as mean [range]

**Data are expressed as median [IQR]

***Data are expressed as median [2.5% and 97.5% percentile]

****PK/PD targets associated with net fungal stasis and $1 - \log_{10}$ drop in colony-forming units (CFU) reductions from baseline for *C. albicans* > 37.2, *C. glabrata* > 2.94, *C. parapsilosis* (not applicable), *C. auris* > 38.4, *C. tropicalis* > 148.9, and *C. dubliniensis* > 228.3

[1]Study 1: micafungin 3 mg/kg of body weight (weight ≥ 25 kg) or 4.5 mg/kg (weight < 25 kg) to a maximum of 150 mg in children (aged 2–11 years) and adolescents (aged 12–16 years). Study 2: micafungin 4.5 mg/kg for infants and toddlers (aged ≥ 4 months to 2 years). Study 3: micafungin 1.5 mg/kg (weight, < 25 kg) or 1 mg/kg (weight, ≥ 25 kg). Study 4: micafungin 0.5, 1, 1.5, 2, 3, or 4 mg/kg/day to a maximum of 200 mg/day. Study 5: micafungin 2 mg/kg/day if ≤ 40 kg or 100 mg/day if > 40 kg. Study 6: initial dosage of 1 mg/kg/day, with the possibility of dose escalation to 6 mg/kg/day

[2]Caspofungin 35 mg/day if WT ≤ 80 kg and moderate hepatic impairment (Child–Pugh score of 7 to 9) and 50 mg/day if WT > 80 kg and moderate hepatic impairment (Child–Pugh score of 7 to 9)

[3]Four subgroups designated as CAS I to IV: CAS I: 1 mg/kg/day; CAS II: 50 mg/m^2/day; CAS III: 70 mg/m^2/day; CAS I–III (pediatric patients 2–17 years old); CAS IV (3–23 months): 50 mg/m^2/day

[4]Study 1: LD: 100mg. MD: 50mg/day; Study 2: LD: twice the MD. MD: 50–100 mg/day; Study 3: LD:100mg. MD: 50mg/day

[5]Study 1: single- and multiple-dose studies, ranging from 50–1400 mg. Study 2: 100–400 mg/weekly. Study 3: single dose of 600 or 1400 mg. Study 4: LD: 400 mg; MD: 200–400 mg/weekly

[6]Study 1: single- and multiple-dose studies, ranging from 50–1400 mg. Study 2: LD: 400 mg; MD: 200–400 mg/weekly. Study 3: LD: 400 mg; MD: 200 mg/weekly

covariates were SOFA, Body mass index (BMI), LBW, and LBMc.

3.2.4 Rezafungin

Only three popPK models have been described for rezafungin. The CL estimates ranged from 0.19 to 0.33 L/h and the V_c from 8.94 to 17.70 L for the 3-CMT and 4-CMT models developed. The covariates affecting the CL and the V_d differed between models. For CL, the BSA, disease state, WT, albumin, and sex were reported, while for V_d, the BSA, disease state, WT, infection, and albumin were included in the different models.

Table 2 summarizes the popPK model equations and mean values of the PK parameters (CL and V_d).

3.3 Special Populations

3.3.1 Critically ill patients

The population of patients that are critically ill has been deeply studied in population PK studies for echinocandins. For micafungin, different popPK models have been developed. These models combined with an optimal sampling scheme, rapid identification of the *Candida* species and accurate susceptibility testing (MIC) provide an opportunity to achieve quick optimization of micafungin exposure and may guide early dose decision making [56]. The covariates included estimating the CL and V_d differed between models. WT has been mostly described but also SOFA, albumin, BSA, or ALT. To achieve the PK/PD targets, different approaches have been proposed in this population. In fungal peritonitis, the daily dose of 100 mg seems to be adequate to reach the PK/PD targets in plasma for *Candida* spp and, specifically, *C. parapsilosis* MICs of 0.008–0.016 and 0.125–0.25 mg/L, respectively [17]. In patients that are critically ill with severe burn injuries and patients with complicated intra-abdominal infections (IAI), 100 mg daily achieved the PK/PD targets in plasma for non-*C. parapsilosis* spp with MIC < 0.008 mg/L and *C. parapsilosis* with MIC < 0.064 mg/L, in both groups [52]. Nevertheless, the V_c was higher in patients with burns. In patients with sepsis and mechanical ventilation, 100 mg daily was associated with a very low probability of attaining the PK/PD target value in infections due to *C. albicans* or *C. glabrata* with MIC ≥ 0.015 mg/L, as well as in almost all cases of infection of *C. parapsilosis*. An increase in the dose should be considered in these cases [34]. In a cohort of Chinese patients that are septic, the recommended 100 mg daily had low clinical success for non-*C. albicans* infections; therefore, higher doses of at least 200 and 250 mg for MIC breakpoints of 0.032 and 0.064 mg/L for *C. glabrata* and *C. tropicalis*, respectively, should be considered. However, daily doses of 300 mg could not achieve MIC breakpoints of 0.125–0.25 mg/L for *C. krusei* and 1–2 mg/L for *C. parapsilosis* [35]. These results agree with Martial et al. [53] who stated that current micafungin dosing regimens are adequate to treat *Candida* infections with species up to 0.016 mg/L, but the dose should be increased to 200 mg in the case of MIC ≥ 0.032 mg/L. Kapralos et al. [23] proposed an alternative approach based on the use of a high LD. An LD of up to 300 mg for the treatment of IC in ICU patients may be needed, while an MD of up to 200 mg can be considered in empirical antifungal treatment.

For caspofungin, a weight-based dosing regimen supported by a popPK model has been proposed to reach the AUC target. An LD of 2 mg/kg, followed by 1.25 mg/kg as a MD, might be appropriate for achieving adequate exposure in ICU patients [38]. Martial et al. [53] suggested that the MD should not be reduced to 35 mg/day in ICU patients with moderate to severe hepatic dysfunction (classified as Child–Pugh B or C), contrary to what is indicated in the drug package insert. A MD of 70–100 mg in infections caused by pathogens with attenuated MIC > 0.125 mg/L, should be considered to achieve an optimal target attainment. For IAI treatment, due to the moderate penetration of caspofungin into the peritoneal cavity, in patients with FFM > 50 kg, an LD of 70 or 100 mg, with a MD of 70 mg, should be used to guarantee appropriate concentrations in the abdominal cavity for *C. albicans* and *C. glabrata*. While standard dosing regimens for patients with FFM < 50 kg for these species appear to be appropriate [40].

In the case of anidulafungin, a limited-sampling strategy may be useful for adequately estimating the exposure. The drug concentration can be adequately estimated from a single sample drawn 12 h after the start of the infusion either by linear regression or using a popPK model [27]. The PK of anidulafungin in ICU patients appeared to be comparable with the general population [44]. Another study reported that although drug exposure was comparable with that in healthy volunteers, elevated interindividual and significant interoccasion variability was found in patients that are critically ill [22]. In ICU patients with complicated IAI, the PK parameters were similar to healthy volunteers or other types of ICU patients. The standard dosage seems to be adequate in this population, although an increased V_d and a longer $t_{1/2}$ were observed [45]. Luque et al. [18] recommended a higher dose of anidulafungin for the treatment of *C. albicans* or *C. glabrata* infections in patients that are critically ill with high TBWs > 150 kg to avoid potential clinical failures.

3.3.2 Renal Replacement Therapies

In patients undergoing renal replacement, including continuous venovenous haemofiltration (CVVH), continuous venovenous hemodiafiltration (CVVHDF), continuous

venovenous high cutoff membrane hemodialysis (CVVHD-HCO), and slow low-efficient daily dialysis (SLEDD), the data obtained for micafungin revealed no removal of it or need for dose adjustment for those patients, obtaining an optimal PK/PD coverage using the standard doses of this antifungal [16, 31, 49, 52]. Garbez et al. [16] recommended an LD of 150 mg to achieve the PK/PD target for less susceptible *Candida* species from the first day of therapy. For caspofungin, the two studies [14, 15] including patients undergoing CRRT revealed different data. Roger et al. [14] showed that no dosing adjustment was necessary for patients undergoing either form of CRRT (CVVH or CVVHDF), although a higher than recommended LD of caspofungin, (i.e., 100 mg) is required to achieve optimal exposure in patients that are critically ill [14]. However, Pérez-Pitarch et al. [15] found that the standard caspofungin regimen was insufficient to reach the target for *C. albicans* and *C. parapsilosis* with MIC ≥ 0.1 mg/L, suggesting that the determination of MIC and dose escalation to 100 mg (LD) or 200 mg once daily will increase the probability of attaining the PK/PD target for *Candida* spp and *Aspergillus* spp. Previously published data demonstrated that caspofungin can be safely used at doses of up to 200 mg/day [63–65].

No popPK model has been developed to evaluate the effect of CRRT on anidulafungin. However, different studies have shown that the PKs of anidulafungin during CVVH resemble healthy adults and patients with fungal infections, recommending an LD of 200 mg and 100 mg on consecutive treatment days [66–69]. Similarly, for rezafungin the population analyzed did not include patients undergoing CRRT, although Jang et al. [70] analyzed the influence of CVVH on rezafungin, proving that the drug is not removed by membrane adsorption during CVVH; hence, no dosage adjustment is required for patients that are critically ill receiving CVVH. The covariates influencing CL and V_d in patients undergoing CRRT are not uniform. WT has been described as a significant covariate in some studies [14, 16, 51, 54] but not in all of them. Gastine et al. [30], reported SOFA and bilirubin as significant covariates for CL and SOFA for V_d.

3.3.3 Extracorporeal Membrane Oxygenation

Few studies have developed popPK models including patients undergoing extracorporeal membrane oxygenation (ECMO). For micafungin, Jullien et al. [34] included 11 patients undergoing ECMO and did not find any covariates to influence micafungin PK in ECMO. Gastine et al. [30] included six patients to develop a popPK model for micafungin and did not report any influence of ECMO on the PK parameters. Echinocandins have different logPs (micafungin: − 1.5; caspofungin 0.1 and anidulafungin 2.9), are soluble in water and, consequently, are not expected to interact with the organic material of the ECMO circuit, although echinocandins are also highly protein bound, and this condition has been associated with reductions in the V_d and CL during ECMO [8, 34]. Autmizguine et al. [60] studied the PK and safety of micafungin in infants supported by ECMO, describing a higher V_d and CL than previously published values for infants not on ECMO. A dose of 2.5 and 5 mg/kg/day for prophylaxis and treatment of IC was recommended for achieving a PK target of $AUC_{0–24}$: 37.5–69.5 mg × h/L for prophylaxis and $AUC_{0–24}$: 75–139 mg × h/L for proven infection. For caspofungin, Wang et al. [42] studied the population PK of caspofungin in patients with ECMO and reported no significant differences in the PK parameters (CL and V_d) and the concentrations of caspofungin among ECMO and non-ECMO patients [42]. The popPK models of anidulafungin did not include patients with ECMO. Anidulafungin is more lipophilic than other echinocandins (log P 2.9) and has less protein binding than the others (84%) [71]. Only one case report described similar maximum and trough of plasma anidulafungin concentrations in a patient that is critically ill on ECMO, suggesting that ECMO had little effect on the PK of anidulafungin and no dose adjustment is required [71, 72]. There is no available information on rezafungin in patients undergoing ECMO.

3.3.4 Patients that are Overweight and Obese

Dosing in patients that are critically ill and obese is challenging due to pathophysiological changes derived from obesity and/or critical illness. Moreover, the rates of obesity are increasing leading to more patients that are obese requiring antifungal therapy for serious infections [19, 20]. Two popPK models have been developed for micafungin in patients that are morbidly obese. In both models, WT was included as an influential covariate for CL but only in one (Wasmann et al.) for V_d [19, 21]. In both studies, higher doses of micafungin were required to reach the PK/PD target. Maseda et al. [19] suggested a dose of 150 mg daily to cover *C. albicans* and 200 mg daily to cover *C. glabrata* for patients weighing up to 115 kg and 200 mg daily for those surpassing such weight to cover *C. albicans*. Wasmann et al. [20] recommended 100 mg daily in patients weighing ≤ 125 kg infected by *Candida* spp with MIC of 0.016 mg/L, 200 mg daily in patients > 125 kg infected by *Candida* spp with MIC of 0.016 mg/L, and 300 mg daily for MIC of 0.032 mg/L and > 125 kg weight [20]. For caspofungin, the MD recommended in the prescribing information is already adjusted according to the patient's weight. However, Märtson et al. [38], suggested a weight-based dose regimen of 2 mg/kg LD and 1.25 mg/kg daily to be more appropriate for achieving adequate exposure of caspofungin in patients that are critically ill than the standard fixed-dose regimen,

as the registered dose might not be suitable for patients that are critically ill who were overweight (≥ 120 kg), over 80% of median weight (78 kg) and around 25% of lower weight (≤ 50 kg). In their model, the WT was only included as a significant covariate for the V_d [38]. Wasmann et al. [21] studied the PK of anidulafungin in obese and normal-weight adults. WT was identified as a descriptor for both CL and V_d, but the effect of weight on these parameters was limited. A MD of 100 mg daily reached the PK/PD target in more than 97% of subjects with a weight < 140 kg. In patients that are obese with a weight > 140kg, a 25% increase in LD and MD could be considered [21]. Liu et al. [44] used 150 mg of anidulafungin daily (50% increase over the standard dose) in a patient that is critically ill of 240 kg to achieve the PK/PD target. No data are available on the PK of rezafungin in patients with obesity.

3.3.5 Pediatric Patients

The pediatric and neonatal population has also been studied for the development of PK models of echinocandins. For micafungin, five models have been developed [24, 57–60], one of them includes children and adults [58]. All models included WT as a significant covariate for CL. However, only one model included WT for V_d [60]. The PD parameters and targets differ between models. Micafungin weight-based dosing (mg/kg) has been suggested for pediatric patients to provide the same plasma concentrations as adults since body weight was found to be the primary factor of variability [58]. Hope et al. [59] in neonates and young infants recommended a dosage of 10 mg/kg/day to reach the PK/PD target (AUC_{0-24}/MIC > 1332); for children and adolescents weighing up to 40 to 50 kg, dose regimens of 1, 2, and 3 mg/kg/day are appropriate for prevention of IC, treatment of IC, and treatment of esophageal candidiasis, respectively [24]. In children aged 2–17 years, WT has been considered and incorporated as a covariate to adequately describe micafungin PK. Based on the principles of scaling by body weight, lower-weight children may present higher weight-normalized CL. Consequently, a degree of dosage increase is required in smaller children to ensure comparable levels of drug exposure to those observed in larger children and adults [57]. In infants on ECMO, higher V_d and CL than infants not on ECMO have been reported, thus a dosage of 2.5 and 5 mg/kg/day for prophylaxis and treatment of IC, respectively, can be used [60].

For caspofungin, instead of WT, the BSA has been incorporated as a significant predictor for CL and V_d [32, 37]. The adjustment of caspofungin dosage based on BSA on children from 2 to 12 years of age seems to be most appropriate for pediatric use [37]. Niu et al. [32] showed that a 70 mg/m^2 LD and 50 mg/m^2 MD regimen can be recommended for a successful outcome against *C. albicans* and *C. glabrata*, although for *C. parapsilosis*, conventional doses may not be sufficient for reaching the fungistatic target and the MD can be increased to 60 mg/m^2. An extended dosing regimen of 200 mg/m^2 twice weekly, (maximal 200 mg total dose) in patients from 3 months to 17 years has been proposed to achieve PK/PD targets for treatment of IFIs [30]. No pediatric popPK models have been developed for anidulafungin and rezafungin.

3.3.6 Patients with Cancer and Patients That Are Immunocompromised

Echinocandins are highly used as empirical antifungal therapy in patients with cancer with neutropenic fever and prophylaxis of IC. In the case of micafungin, three popPK models including patients with cancer and patients that are immunocompromised have been developed. The estimated micafungin CL was significantly higher in patients with cancer than without cancer, suggesting a need for increased dosage, especially for *Candida* spp with high MICs in these patients. Patients without cancer achieved higher PK/PD targets compared with patients with cancer [55]. A study of micafungin used for prophylaxis in hematological patients described that if weight > 66.3 kg, larger doses may be needed to achieve similar exposures to those < 66.3 kg [49]. Ikawa et al. [50] rationalized the approved micafungin dosages for *Candida* spp infections (50 mg daily for prophylaxis and 100–150 mg daily for treatment) in adult patients with hematological malignancies. However, for *Aspergillus* spp infections, higher doses of 200–250 mg/day might be needed to reach favorable outcomes [50] .

The PK of caspofungin in patients that are immunocompromised with invasive aspergillosis has been studied, demonstrating no relevant changes in PKs when caspofungin was given at dosages of up to 200 mg to patients with invasive aspergillosis relative to the PKs in other populations receiving standard or high doses [43]. In allogeneic hematopoietic stem cell recipients, popPK models have been developed for caspofungin and liposomal amphotericin B (LAMB). Drug exposures in these patients were comparable to those in other populations, and no PK interactions were observed between the two compounds. The PK of caspofungin was not altered by the coadministration of LAMB and viceversa [41]. For anidulafungin and rezafungin, no popPK models have been described for hematologic and/or patients that are immunocompromised.

4 Discussion

In this literature review of 47 studies, numerous popPK models with different covariates that describe the PK

parameters for echinocandins have been identified. The multiple model properties (constants and functions) and covariates included in the popPK models reflect the differences between the populations used for developing the models based on age, comorbidities, and treatment intention. Micafungin was the antifungal for which more models have been developed, followed by caspofungin. The critically ill population has been the most studied for echinocandins, due to the importance of reaching effective concentrations in this group of patients. Another highly studied population is patients that are immunocompromised because of the use of echinocandins for fungal prophylaxis. Rezafungin is an echinocandin recently introduced into the market; hence, the studies to date are limited.

Most studies used the NLME modeling approach to estimate the PK parameters (32 out of 47 studies; 68%). However, other methods like the nonparametric and the iterative have also been employed. NONMEM modeling software was the most used, followed by NPAG (Pmetrics software). The PK of echinocandins seems to be better described using a two-compartment approach (78.7% of the developed models), although more complex structural models with three and four compartments have been used. Most studies described internal evaluation methods such as goodness-of-fit plots and/or bootstrap analysis to evaluate the performance of the popPK developed models, but the external evaluation was lacking in most of them (only 4 of the 47 studies included).

Echinocandins are generally administered in a fixed dosing strategy in clinical practice. However, based on safety and efficacy considerations, the weight-based dosing method may be more appropriate for achieving adequate exposure in certain populations such as patients that are critically ill, patients that are obese, and pediatric patients [5]. The WT could explain the PK variability for CL and V_d and has been the most frequently reported significant covariate included to describe both PK parameters.

The identification of the factors that affect PK variability is critical for the optimization of echinocandin dosing. The recommendation for TDM has been debated, mainly because of the predictable PK and good safety profile of echinocandins [8, 73]. Nevertheless, TDM is recommended in patients that are critically ill and obese for the three echinocandins (no data for rezafungin) and for caspofungin also if drug–drug interactions are expected, in moderate hepatic impairment (if product information for dose reduction is followed) and hypoalbuminemia [8]. However, dose adjustment alone can be considered without TDM if the patient does not respond to treatment, due to the excellent safety profile of echinocandins [5, 8].

Intermittent dosing has been proposed as a strategy to ensure echinocandins adequate exposure [74, 75]. The safety risks are low, as numerous clinical trials have demonstrated that high dosages of echinocandins are well tolerated. However, given that patients that are critically ill themselves are in an acute condition and require daily fluid therapy, the benefits of this dosage approach could not be fully elucidated in these patients. Possible increased rates of hepatic and cardiovascular toxicity are the major concern when using high doses [5].

In general, this review provides a comprehensive summary of all the published evidence to date related to popPK for echinocandins in different population groups. It also provides information on the PK/PD targets for each echinocandin and the different strategies proposed to achieve them. Observational studies and clinical trials conducted in different countries were included to integrate a large sample of populations from different racial backgrounds. Nevertheless, several limitations must be acknowledged when interpreting the results. First, this review is not a systematic review since the search, extraction, and interpretation of the results were conducted only by one investigator, and the quality of the studies included was not evaluated. Second, the biggest limitation of most of the popPK models included is that they lack external validation, which is essential to evaluate whether the models are generalizable outside the original population and for assessing the bias and the precision [76, 77]. The US Food and Drug Administration (FDA) considers external validation as the most stringent method for testing a developed model [78]. Third, it is important to note that a significant number of the studies featured retrospective data, highlighting the inherent limitations of this study design. Fourth, the number of samples and patients was small in some studies, which might have prevented the identification of other significant covariates that could predict variability in PK parameters. Fifth, the free $fAUC_{0-24}$/MIC parameter was determined in a few studies. This PD parameter would be of great interest to evaluate, especially in hypoalbuminemic patients, such as most patients that are critically ill, due to the high binding to plasma proteins that echinocandins exhibit.

5 Conclusions

Numerous popPK models for the main three echinocandins have been developed in different populations, especially patients that are critically ill, pediatric patients, and patients that are hematologic and/or immunocompromised. The covariates to estimate the PK parameters (CL and V_d) differed between models. WT was the most frequently reported significant predictor for both parameters, especially for estimating the CL in pediatrics.

Due to the significant heterogeneity of the popPK models and study populations, limited prospective studies and lack of

Table 2 Population pharmacokinetic model equations and mean values of the pharmacokinetic parameters

First author, year of publication [ref.]	Structural PK model	Variables used for CL estimation	CL and Q equations (L/h)	Mean CL (L/h)	Variables used for V_d estimation	V_d equation (L)	Mean V_d (L)
Micafungin pharmacokinetic models							
Adults							
Maseda 2014 [51]	2–CMT	WT	$CL = 0.90 \times (WT/70)^{0.75}$ $Q = 5.03$	CL: 0.90 Q: 5.03	None	V_c =12.5 V_p = 10.0	V_c: 12.5 V_p : 10.0
Grau 2015 [17]	3–CMT	WT	$CL = 1.27 \times (WT/70)^{0.75}$	CL: 1.27	Alb (g/dL)	$V_c = 9.26 \times (Alb/2.2)$	V_c: 9.26
García-de-Lorenzo 2016 [52]	3–CMT	ND	All patients: CL = 1.38 Burnt: CL = 1.61 IAI: CL = 1.09	All patients: CL: 1.38 Burnt: CL: 1.61 IAI: CL: 1.09	ND	All patients: V_c = 5.87 Burnt: V_c = 6.07 IAI: V_c = 5.85	All patients: V_c: 5.87 Burnt: V_c: 6.07 IAI: V_c: 5.85
Jullien 2017 [34]	2–CMT	WT, Alb (break point: 25), SOFA (break point: 10)	$CL = 1.34 \times (WT/84)^{0.59} \times 1.14$ (if Alb ≤ 25 g/L) × 0.75 (if SOFA ≥10) $Q = 4.67$	CL: 1.34 Q: 4.67	WT, Alb (break point: 25)	$V_c = 11.8 \times (WT/84)^{0.61}$ ×1.14 (if Alb ≤ 25 g/L) $V_p = 7.68 \times (WT/84)^{0.67}$ ×1.14 (if Alb ≤ 25 g/L)	V_c: 11.80 V_p: 7.68
Martial 2017 [53]	2–CMT	None	CL = 1.10 $Q = 0.363$	CL: 1.10 Q: 0.363	None	V_c = 17.6 V_p = 3.64	V_c: 17.6 V_p: 3.64
Maseda 2018 [19]	2–CMT	WT, Age	$CL = 0.80 \times (WT/70)^{0.75} \times (Age/60)^{0.75}$	CL: 0.80	None	V_c = 16.34	V_c: 16.34
Gastine 2019 [30]	2–CMT	SOFA (break point: 10), Bilirrubin (break point: 4 mg/dl)	ND	CL: 1.56 Q: 14.4	SOFA (break point: 10)	ND	V_c: 16.2 V_p: 13.8
Tenorio-Cañamás 2019 [54]	2–CMT	WT	$CL = 0.86 \times (WT/86)$	CL: 0.86	WT	$V_c = 6.06 \times (WT/70)^{0.75}$	V_c: 6.06
Kapralos 2020 [23]	2–CMT	None	CL = 1.31 $Q = 2.89$	CL: 1.31 Q: 2.89	None	V_c = 14.2 V_p = 12.6	V_c: 14.2 V_p: 12.6
Garbez 2021 [31]	3–CMT	FFM	$CL = 1.18 \times (FFM/52.5)^{1.25}$ $Q = 5.89$ $Q_{pe} = 0.04$	CL: 1.18 Q: 5.89 Q_{pe}: 0.04	FFM	$V_c = 12.85 \times (FFM/52.5)^{0.66}$	V_c: 12.85 V_p: 3.86 V_{pe}: 4.82
Garbez 2021 [16]	2–CMT	None	CL = 0.96	CL: 0.96	None	V_c = 14.8	V_c: 14.8
Zhong 2021 [35]	2–CMT	ALT	$CL = 0.761 \times e^{((ALT/43) \times (-0.268))}$	CL: 0.761 Q: 4.72	SOFA (break point: 10)	V_c = 6.7 $V_p = 10.2 \times e^{(\theta \times (-1.08))}$ θ = 0 if SOFA < 10; θ = 1 if SOFA ≥ 10	V_c: 6.7 V_p: 10.2
Boonstra 2022 [56]	2–CMT	BSA	ND	ND	LBMc	ND	ND
Gumbo 2008 [49]	2–CMT	WT (break point: 66.3 kg)	ND	CL: 1.165	None	V_c = 10.43	V_c: 10.43
Ikawa 2009 [50]	2–CMT	ND	CL = 0.762 $Q = 7.02$	CL: 0.762 Q: 7.02	ND	V_c = 9.25 V_p = 8.86	V_c: 9.25 V_p: 8.86

Table 2 (continued)

First author, year of publication [ref.]	Structural PK model	Variables used for CL estimation	CL and Q equations (L/h)	Mean CL (L/h)	Variables used for V_d estimation	V_d equation (L)	Mean V_d (L)
Wasmann 2019 [20]	2–CMT	WT	CL = 0.69 × (WT/70)$^{0.74}$ Q = 7.15	CL: 0.69 Q: 7.15	WT	V_c = 5.84 × (WT/70)$^{1.17}$ V_p = 6.96 × (WT/70)$^{0.71}$	V_c: 5.84 V_p: 6.96
Alqahtani 2021 [55]	2–CMT	AST, ALT, WT	ND	Patients with cancer: CL: 1.2; Q: 0.144 Patients without cancer: CL: 0.6; Q = 0.188	BMI, WT, bilirubin, Alb	ND	Patients with cancer: V_c: 10.7; V_p: 3.5 Patients without cancer: V_c: 12; V_p: 2.77
Pediatrics							
Hope 2007 [57]	2–CMT	WT in the linear and allometric model	ND	CL: standard model: 0.635 Linear model: 0.480 Allometric model: 1.082[3]	ND	ND	V_c: standard model: 5.848 Linear model: 5.181 Allometric model: 13.616[4]
Tabata 2006 [58]	2–CMT	WT (in children <16 years), PLT	CL = 13.0 + 0.228 × (WT – 52.370) × FIX + 0.0345 × (PLT – 21.6) FIX = 0 if age < 16 years old	CL: 0.78 Q =5.79	None	V_c = 11.2 V_{ss} = 20.6	V_c: 11.2 V_{ss}: 20.6
Hope 2010 [59]	2–CMT	WT	ND	CL: 1.080[3]	ND	ND	V_c: 10.3[4]
Hope 2015 [24]	2–CMT	WT, AST, Bilirubin	CL = 0.356 × (WT/21.5)$^{0.787}$ × (AST/50)$^{-0.0601}$ × (bilirubin/12)$^{-0.0492}$ Q = 5.54	CL: 0.356 Q =5.54	None	V_c = 1.21 V_p = 4.62	V_c: 1.21 V_p: 4.62
Autmizguine 2016 [60]	1–CMT	Age, WT, Alb	ND	CL: 0.041 L/kg/h	Age, WT	ND	V_d: 0,.64
Caspofungin pharmacokinetic models							
Adults							
Martial 2016 [39]	2–CMT	None	CL = 0.55 Q = 0.71	CL: 0.55 Q =0.71	None	V_c = 8.9 V_p = 4.98	V_c : 8.9 V_p: 5.0
Roger 2017 [14]	2–CMT	WT	CL = 0.64 × (WT/80)	CL: 0.64	WT	V_c = 9.35 × (WT/80)0.75	V_c : 9.35
Pérez-Pitarch 2018 [15]	2–CMT	None	CL = 0.59 Q = 3.2	CL: 0.59 Q =3.2	WT, Protein concentration (g/dL)	V_c = 6.46 × (WT/75) × [0.767 × (protein – 5.6)]	V_c : 6.46
Märtson 2020 [38]	2–CMT	None	CL = 0.7	CL: 0.7	WT	V_c = 7.71 × (WT/78)	V_c : 7.71
Garbez 2022 [40]	3–CMT	FFM	CL = 0.78 × (FFM/52.5)0.98 Q = 1.95 Qpe = 0.10	CL: 0.78 Q = 1.95 Qpe: 0.10	FFM	V_c = 9.36 × (FFM/52.5)1.08 V_p = 4.87 V_{pe} = 4.69	V_c : 9.36 V_p: 4.87 V_{pe}: 4.69

Table 2 (continued)

First author, year of publication [ref.]	Structural PK model	Variables used for CL estimation	CL and Q equations (L/h)	Mean CL (L/h)	Variables used for V_d estimation	V_d equation (L)	Mean V_d (L)
Würthwein 2012 [41]	2–CMT	None	Only CAS: CL = 0.462 Q = 1.25 LAMB and CAS: CL: 0.637 Q = 2.27	Only CAS: CL: 0.462 Q = 1.25 LAMB and CAS: CL: 0.637 Q = 2.27	None	Only CAS: V_c = 8.33 V_p = 3.59 LAMB and CAS: V_c = 18.6 V_p = 49.2	Only CAS: V_c: 8.33 V_p: 3.59 LAMB and CAS: V_c: 18.6 V_p: 49.2
Wang 2020 [42]	2–CMT	OPT on Cl; SOFA on Q	CL = 0.21 × (OPT/5)1.30 Q = 0.84 × (SOFA/7)1.98	CL: 0.21 (ECMO: 0.27; non-ECMO: 0.31) Q = 0.84	SEX, OPT	V_c = (2.21 + SEX × 0.62) × (OPT/5)0.93 SEX = 1 if male; SEX = 0 if female V_p = 2.87	V_c: 2.21 V_p: 2.87 ECMO: V_c: 3.22; V_p: 2.97; Non-ECMO: V_c: 3.0; V_p: 2.57
Pressiat 2022 [28]	2–CMT	None	CL = 0.38 Q = 2.58	CL: 0.38 Q = 2.58	None	V_c = 6.24 V_p = 6.44	V_c: 6.24 V_p: 6.44
Wu 2022 [36]	2–CMT	Alb	CL = 0.385 × (Alb/37)$^{-1.01}$ Q = 2.85	CL: 0.385 (Heart transplants: 0.35; Control: 0.45) Q = 2.85	None	V_c = 4.27 V_p = 6.01	V_c: 4.27 V_p: 6.01 Heart transplants: V_c: 3.14 V_p: 4.98; Control: V_c: 5.27 V_p: 6.31
Würthwein 2013 [43]	2–CMT	WT	CL = 0.411 × (WT/80)$^{0.0102}$ Q = 0.843	CL: 0.411 Q = 0.843	WT	V_c = 5.85 × (WT/80)$^{0.0102}$ V_p = 6.53	V_c: 5.85 V_p: 6.53
Pediatrics							
Yang 2019 [37]	2–CMT	BSA	CL = 0.165 × (BSA/0.79)$^{1.3}$ Q = 0.351	CL: 0.165 Q: 0.351	BSA	V_c = 1.730 × (BSA/0.79)$^{1.5}$ V_p = 0.943	V_c: 1.730 V_p: 0.943
Niu 2020 [32]	1–CMT	BSA, AST	CL = 0.14 × (BSA/0.79)$^{0.89}$ × (lnAST/3.38)$^{-0.23}$	CL: 0.14	BSA	V_c = 1.36 × (BSA/0.79)	V_c: 1.36
Gastine 2022 [29]	2–CMT	None	ND	CL: 0.793 Q: 1.203	None	V_c = 9.36 V_p = 4.87	V_c: 9.36 V_p: 4.87
Anidulafungin pharmacokinetic models							
Adults							
Liu 2013 [44]	2–CMT	ND	ND	CL: 1.3	ND	ND	V_{ss}: 38.8
Van Wanrooy, 2015 [27]	2–CMT	FFM	ND	CL: 1.397 Q: 7.947	LBMc	ND	ND
Dupont 2017 [45]	2–CMT	ND	CL = 0.87 Q = 18.2	CL: 0.87		V_c = 22.3 V_p= 48.7	V_c: 22.3 V_p: 48.7 V_{ss}: 72.8

Table 2 (continued)

First author, year of publication [ref.]	Structural PK model	Variables used for CL estimation	CL and Q equations (L/h)	Mean CL (L/h)	Variables used for V_d estimation	V_d equation (L)	Mean V_d (L)
Luque 2019 [18]	2–CMT	WT	$CL^3 = 0.852 \times (WT/70)^{0.75}$	CL: 0.852^3	None	$V_c = 18.413$	V_c: 18.41
Kapralos 2021 [22]	2–CMT	SOFA, BMI	$CL = 0.778 \times (SOFA/12)^{-0.924}$ $Q = 4.4$	CL: 0.778 Q: 4.4	SOFA, BMI	$V_c = 10.2 \times (BMI/25)^{2.74}$ $V_p = 21.1$	V_c: 10.2 V_p: 21.1
Hall 2023 [48]	2–CMT	LBW	$CL = 1.05 \times (LBW/55)^{0.76}$ $Q = 2.81 \times (LBW/55)^{1.39}$	CL: 1.05 Q: 2.81	LBW	$V_c = 29.48 \times (LBW/55)^{0.58}$ $V_p = 14.42 \times (LBW/55)^{1.34}$	V_c: 29.48 V_p: 14.42
Wasmann 2018 [21]	3–CMT	WT	$CL = 0.996 \times (WT/70)^{0.322}$ $Q_2 = 0.153$ $Q_3 = 14.1$	CL: 0.996 Q_2: 0.153 Q_3: 14.1	WT	$V_c = 16.6 \times (WT/70)^{0.631}$ $Vp_2 = Vp_3 = 16.6$	$V_c = V_{p2} = V_{p3} = 16.6$
Dowell 2004 [46]	2–CMT	WT, Gender, Study (type of fungal infection)	$CL = 0.768 + 0.00417 \times (WT - 60) + 0.166 \times$ Gender $+ 0.278 \times$ Study. Gender = 1 if male; Gender = 0 if female. Study = 1 for patients included in the study of IC, including C; Study = 0 for all other studies Q = 20.3	CL: 0.946 Q: 20.3	WT	$V_c = 0.215 \times WT$ $V_p = 19.6$ $V_{ss} = V_c + V_p$	V_c: 9.97 V_p: 20.3 V_{ss}: 33.4
Liu 2013 [47]	2–CMT	WT, Gender, Study (type of fungal infection)	$CL = 0.777 + (WT - 60) \times 0.00461 +$ Gender $\times 0.183 +$ Study $\times 0.256$ Gender = 1 if male; Gender = 0 if female. Study = 1 for patients included in the study of IC, including C; Study = 0 for all other studies $Q = 21.6$ SEX = 1 if male; SEX = 0 if female	CL: 0.777 Q: 21.6	WT	$V_c = 0.170 \times WT$ $V_p = 23.5$ $V_{ss} = V_c + V_p$	V_c: 0.170 V_p: 23.5 V_{ss}: 34.6

Table 2 (continued)

First author, year of publication [ref.]	Structural PK model	Variables used for CL estimation	CL and Q equations (L/h)	Mean CL (L/h)	Variables used for V_d estimation	V_d equation (L)	Mean V_d (L)
Rezafungin pharmacokinetic models							
Adults							
Roepcke 2023 [33]	3–CMT	BSA, Disease state (Ihealthy)	$CL = 0.328 \times (BSA/1.9)^{0.882} \times (1 + (-0.276 \times Ihealthy))$ (Ihealthy = 0 if no; Ihealthy = 1 if yes) $Q_2 = 0.236$ $Q_3 = 12.4$	CL: 0.328 Q_2: 0.236 Q_3: 12.4	BSA, Disease state (Ihealthy) on V_c; BSA, Alb on V_p	$V_c = 17.7 \times (BSA/1.9)^{1.56} \times (1 + (-0.222 \times Ihealthy))$ $V^{p23} = 19.1 \times (BSA/1.9)^{1.17} \times (Alb/3.2)^{-0.708}$	V_c: 17.7 V_{p23}: 19.1
Lakota 2018 [61]	4–CMT	WT	$CL = 0.187 \times (WT/75)^{0.75}$ $Q_2 = 24.3 \times (WT/75)^{0.75}$ $Q_3 = 0.908 \times (WT/75)^{0.75}$ $Q_4 = 0.0736 \times (WT/75)^{0.75}$	CL: 0.188 Q_2: 24.3 Q_3: 0.908 Q_4: 0.0736	WT	$V_c = 8.94 \times (WT/75)$ $Vp_2 = 8.88 \times (WT/75)$ $Vp_3 = 12.5 \times (WT/75)$ $Vp_4 = 27.7 \times (WT/75)$	V_c: 8.94 V_{p2}: 8.88 V_{p3}:12.5 V_{p4}: 27.7
Rubino 2021 [62]	4–CMT	Alb, Sex	$CL = 0.254 \times (1 - 0.133 \times SEXF) \times (Alb/4.2)^{-0.844}$ SEXF = 1 if female, SEXF = 0 if males $Q_2 = 18.2$ $Q_3 = 0.541$ $Q_4 = 0.0743$	CL: 0.254 Q_2: 18.2 Q_3: 0.541 Q_4: 0.0743	BSA, Infected on V_c; Alb, BSA on V_{p2}; Infected, BSA on V_{p3}	$V_c = [(11.1 + 7.54 \times (BSA - 1.83)] \times (1 + 0.478 \times infected)$ Infected = 1; Healthy = 0 $V_{p2} = 14.6 \times (Alb/4.2)^{-0.829} \times (BSA/1.83)^{1.14}$ $V_{p3} = 6.69 \times (1 + 1.69 \times infected) \times (BSA/1.83)^{2.47}$ $V_{p4} = 13.6$	V_c: 11.1 V_{p2}: 14.6 V_{p3}: 6.69 V_{p4}: 13.6

Alb albumin, *ALT* alanine transaminase, *AST* aspartate transaminase, *BMI* body mass index, *BSA* body surface area, *CAS* caspofungin, *CL* clearance, *FFM* fat free mass, *IAI* intra-abdominal infection, *Ihealthy* indicator variable for healthy subjects who are not infected of candidemia and/or invasive candidiasis and have normal liver function, *infected* patients with a systemic fungal infection, *LAMB* liposomal amphotericin B, *LBMc* lean body mass corrected, *LBW* lean body weight, *OPT* operative time, *PLT* platelet counts, *PK* pharmacokinetic, *Q* intercompartmental clearance, Q_{pe} intercompartment clearance between the central and peritoneal compartments, Q_2, Q_3, *and* Q_4 intercompartmental clearances between the central and each of the two peripheral compartments, *SOFA* Sequential Organ Failure Assessment, V_c central compartment volume of distribution, V_p volume of distribution of peripheral compartment, V_{pe} volume of distribution of the peritoneal compartment, V_{p2}, V_{p3}, *and* V_{p4} volume of distribution of peripheral compartments, V_{p23} peripheral volume 2 and 3, single shared parameter for V_2 and V_3, *Vss* volume of distribution at steady state, *WT* current weight, *1–CMT* one-compartment model, *2–CMT* two-compartment model, *3–CMT* three-compartment model, *4–CMT* four-compartment model

[1]Units in L/h/1.85 m^2

[2]L/kg LBMc

[3]L/h/70 kg

[4]L/70 kg

[5]L/h/m^2

[6]L/m^2

[7]L/h/56 kg FFM

external validation of most models, a single universal popPK model cannot be recommended for dosing all echinocandins. Before clinical application, it is advised to carefully select a popPK model that reflects the PK variability of the target population and conduct external validation to assess the popPK model's predictive performance.

Special attention should be paid to patients that are critically ill, obese, on ECMO and/or CRRT, pediatric patients, patients with cancer, and/or patients that are immunocompromised since multiple studies of the three main echinocandins (micafungin, caspofungin, and anidulafungin) showed that conventional doses do not achieve the PK/PD targets. In these groups, different strategies have been proposed, such as a dosing regimen based on body weight or increasing the LD and/or the MD. Despite the predictable PK and good safety profile of echinocandins, certain populations at risk of suboptimal drug exposure can benefit from TDM to avoid potential clinical failures.

Further research should include the characterization of the PK profile in larger cohorts, especially for rezafungin, the external validation of the popPK models developed, and the validation of PD thresholds for all echinocandins, especially anidulafungin and rezafungin.

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Author contributions M.A.F. contributed to the conception and design of the study, data search, extraction, and interpretation and to the drafting and revision of the manuscript.

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