Current Fungal Infection Reports (2019) 13:21–32
https://doi.org/10.1007/s12281-019-0335-3

PHARMACOLOGY AND PHARMACODYNAMICS OF ANTIFUNGAL AGENTS (N BEYDA, SECTION EDITOR)

Dosing Antifungals in Obesity: a Literature Review

Jarrett R. Amsden[1,2] · Douglas Slain[3]

Published online: 6 February 2019

Abstract

Purpose of Review To summarize the available evidence regarding antifungal dosing in obese adults as well as to provide meaningful guidance on the dosing of each antifungal agent in obese patients.

Recent Findings The pharmacokinetic evidence regarding dosing antifungal agents in obesity is limited. Fluconazole's volume of distribution (VD) is influenced by BMI. Therapeutic drug monitoring (TDM) studies provide some insights into dosing voriconazole in obesity, but not with posaconazole. Isavuconazole seems to be unaffected by weight. The available data for echinocandins suggests that increased doses are likely necessary in obese patients. TDM may be beneficial, particularly for azoles when available in a timely manner.

Summary Fluconazole and voriconazole dosing should be based on total body weight and adjusted body weight, respectively. Posaconazole may have reduced exposures in obese patients, but data on its new dosage forms is lacking. Isavuconazole appears unaffected by weight. Echinocandin doses likely need to be increased in obese patients, but the exact weight and dosages remain elusive.

Keywords Obesity · Antifungals · Fluconazole · Voriconazole · Posaconazole · Isavuconazole · Caspofungin · Micafungin · Anidulafungin · Echinocandin · Triazole antifungal

Introduction

It is well known that obesity is a worldwide problem. In 2015–2016, obesity affected 39.8% of adults and 18.5% of children 2–19 years of age in the USA, and the overall incidence of obesity has continued to rise over the past decade [1]. Obesity is associated with many health conditions including an increased risk of infections [2]. The purpose of this review is to summarize the quantity and quality of the evidence regarding dosing antifungal agents in obesity since our last review [3] and to provide meaningful guidance on dosing of antifungal agents in obese patients. It should be noted that no significant new information was discovered for itraconazole, amphotericin B, and flucytosine, and these agents were not included in this review. Details regarding these agents can be found in our prior review in this journal [3].

This article is part of the Topical Collection on *Pharmacology and Pharmacodynamics of Antifungal Agents*

✉ Jarrett R. Amsden
jamsden@butler.edu

Douglas Slain
dslain@hsc.wvu.edu

[1] College of Pharmacy and Health Sciences, Butler University, 4600 Sunset Avenue, Indianapolis, IN 46208, USA

[2] Community Health Network, Community North Hospital, 7250 Clearvista Drive, Indianapolis, IN 46259, USA

[3] Schools of Pharmacy & Medicine, West Virginia University, 1124 Health Sciences North, Morgantown, WV 26506-9520, USA

Triazoles (Azoles)

Class Review

Azole antifungals are considered first-line treatments for invasive fungal infections [4, 5]. Azoles are weak bases and are predominantly lipophilic with limited water solubility. The exception is fluconazole, which is hydrophilic and water soluble [6]. Due to their lipophilicity, itraconazole, voriconazole, and posaconazole need a solubilizing agent to produce oral solutions and intravenous dosage forms [7–10]. Isavuconazole is also lipophilic and insoluble in water; however, it is formulated as the highly water-soluble prodrug isavuconazonium sulfate, which does not require a solubilizing agent [11, 12]. Despite these similarities, itraconazole, voriconazole, posaconazole, and isavuconazole display diverse pharmacokinetic profiles

[6, 13]. Fluconazole differs from these agents in that it has high bioavailability in addition to having low protein binding and minimal hepatic metabolism which results in dose-dependent linear pharmacokinetics [6]. Pharmacodynamically, azoles display concentration-dependent activity with free area under the concentration time curve (AUC) to minimum inhibitory concentrations (MIC) ratios (*f*AUC/MIC) > 25–50 being associated with efficacy in invasive fungal infections [14]. With fluconazole, increasing the dose results in predictable increases in AUC and thus does not warrant routine TDM. The other azoles and perhaps isavuconazole have less predictable pharmacokinetics, but these agents have high correlations between their AUC values and trough concentrations (C_{min}) which allows for TDM [8, 15–19]. With this, itraconazole, voriconazole, and posaconazole have established C_{min} goals for both prophylaxis and treatment [20]. The relationship of isavuconazole C_{min} and clinical efficacy and safety has not been established. Therefore, the role of isavuconazole TDM is unclear. Despite the exposure-response relationships with the aforementioned azoles, it should be noted that TDM is only valuable in select situations and with timely drug concentrations [20]. The following sections are intended to summarize the new data regarding the effects of obesity on azole and echinocandins pharmacokinetics as well as to provide dosing recommendations for each agent (Fig. 1).

Fluconazole

Since 2011, there have only been two published studies on fluconazole in obesity (Table 1) [21, 22••]. The first of these studies is a single case report in a morbidly obese male (272 kg, BMI 84 kg/m^2). The patient received a 1200-mg (12 mg/kg) loading dose and then 600 mg (6 mg/kg) daily based upon lean body weight (LBW) [23]. The resultant AUC was 184.75 mg h/L and was sufficient to produce an AUC/MIC > 25 for *Candida* isolates with a MIC ≤ 4 mg/L. The volumes of distribution (VD) were 0.6 L/kg based upon total body weight (TBW), 1.61 L/kg lean body weight (LBW), and 1.06 L/kg using adjusted body weight (AdjBW). The authors concluded that fluconazole should be dosed based upon LBW; however, the VD using TBW or AdjBW is comparable to volunteers/patients and similar to ICU patients [21, 24]. Thus, this data suggests that fluconazole does distribute into excess fat in obese patients, but not completely. Alobaid et al. conducted a population pharmacokinetic study (Table 1) that included six obese and four morbidly obese and 11 non-obese patients (Table 1) [22••]. Their analyses demonstrated that fluconazole's VD correlated with BMI while total clearance (CL) correlated with a measured creatinine clearance (CrCl). Their results also demonstrated that doses ≥ 400 mg are needed to achieve AUC/MIC ratio > 25 for organisms with an MIC ≤ 2 mg/L. However, fluconazole doses > 800 mg may be needed for patients with a BMI ≥ 40 kg/m^2 when higher AUC/MIC ratios are needed. The authors concluded that loading doses of 12 mg/kg (TBW) followed by maintenance doses of ≥ 6 mg/kg/day (TBW) are necessary to maintain AUC/MIC ratios > 100 for fluconazole susceptible organisms in patients with a BMI of 30 kg/m^2.

Voriconazole

Since 2011, there have been nine studies related to voriconazole dosing in obesity (Table 1). Three (33%) of the nine studies were pharmacokinetic studies in obese patients. Two studies were single case reports [25, 26], and the third study was a two-way crossover study in obese healthy volunteers [27•]. The aforementioned studies account for a total of 10 patients [25, 26, 27•]. The remaining six (67%) studies used TDM to determine the safety and/or efficacy of voriconazole in obese patients (Table 2) [28–32, 33••].

Pharmacokinetic Studies

Voriconazole pharmacokinetic data in obesity are sparse. In a two-way crossover study, the pharmacokinetics of voriconazole were evaluated in eight obese (BMI ≥ 35 kg/m^2) healthy volunteers given oral maintenance doses of either 200 mg or 300 mg BID, both after receiving a 400-mg PO BID loading

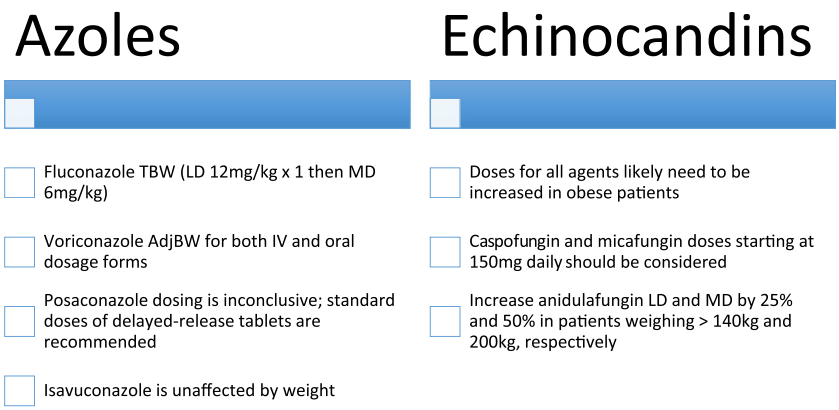

Fig. 1 Azole and echinocandins summary recommendations. TBW, total body weight; LD, loading doses; MD, maintenance doses; mg, milligrams; kg, kilograms; AdjBW, adjusted body weight; IV, intravenous

Table 1 Pharmacokinetic (PK) studies of antifungals in obese patients

Drug	First author [citation]	Subjects (*n*)	Study design	Dosing	C_{max} (mg/L)	C_{min} (mg/L)	$T_{1/2}$ (hr)	$AUC_{0-\tau}$	Cl (L/hr)	Vss or Vc (L)	Comments
Fluconazole (FCZ)	Lopez ND et al. [21]	1	Case report	LD 1200 mg IV × 1 dose; MD: 600 mg IV daily	9.64	5.98	34.8	0–24 184.75	3.25	163.32 (0.6 L/kg TBW; 1.06 L/kg AdjBW; 1.61 L/kg LBW)	Patient concurrently on CVVH; Dose recommendation was LBW, but VD fits better with TBW or AdjBW
	Alobaid AS et al. [22••]	21 6 (BMI ≥30–<40 kg/m^2) 4 (BMI ≥40 kg/m^2)	Population PK/PD	NR	NR	NR	NR	NR	0.95 ± 0.48	15.1 ± 78.07	VD correlated best with BMI; CL correlated with measured CrCl; numerically; CCG-IBW was most similar to measured CrCl; recommendation is to dose on TBW
Voriconazole (VCZ)	Pai MP et al. [27•]	8	Healthy volunteer; cross-over PK study	LD 400 mg PO q12 hr × 2 doses; MD 200 mg PO q12 hr; MD 300 mg PO q12 hr	2.36; 4.16	0.81; 1.76	NR	14.6; 29.2	13.4; 10.1	163; 118	Recommendation to dose on LBW; AdjBW could also be considered
	Dickmeyer NJ et al. [25]	1	Case report	LD 6 mg/kg (AdjBW) PO q12hr × 2 doses; MD 4 mg/kg (AdjBW) PO q12hr	NR	NR	NR	41.85	NR	NR	
	Moriyama B et al. [26]	1	Case report	LD 4.9 mg/kg (TBW) IV q12hr × 2 doses; MD 4 mg/kg (AdjBW) IV q12hr	NR	6.2	29.3	86.1	3.9	157	Patient was a CYP450 2C19*2/2 poor metabolizer
Caspofungin	Ferriols-Lisart R et al. [68]	1	Case report	100 mg IV daily	5.97	1.76	NR	140.4	NR	NR	BMI 50 kg/m2; AUC/MIC ratio 1123 (MIC = 0.125 mg/L)
	Hall RG et al. [65•]	18	Population PK/PD	70 mg (single dose)	NR	NR	NR	NR	0.508 ± 11.94*	6.28 (15.53)*	Weight increases caspofungin CL and VD and reduces exposure at a non-linear rate
Micafungin	Maseda M et al. [73••]	31; 10 non-obese ICU; 10 obese non-ICU; 11 morbidly obese ICU	Population PK/PD	100–150 mg IV daily	NR	NR	NR	NR	0.08 ± 0.49	16.34 ± 5.87	Doses of 150 mg daily in patients ≤ 115 kg; doses of ≥ 200 mg daily for *C. glabrata* of and patients ≤ 115 kg
	Hall RG et al. [66]	36; 12 BMI < 25 kg/m^2; 12 BMI 25–40 kg/m^2; 12 BMI > 40 kg/m^2	Population PK/PD	100 mg (single dose)	NR	NR	NR	NR	1.39 ± 0.419	8.05 ± 2.94	Micafungin CL increases with weight > 66–155 kg
Anidulafungin	Wasmann RE et al. [62••]	20; 12 normal weight and 8 obese	Population PK/PD	100 mg (single dose)	NR	NR	NR	NR	12.5 ± 50.3*	10 ± 39*	25% increase in loading and maintenance doses for patients > 140 kg
	Lempers VJ et al. [81••]	8 obese patients	Pre-bariatric procedure PK study	100 mg (single dose)	3.2	NR	23.7	54.1	1.4	46.9	AUC was negatively correlated with TBW and BSA; increase LD and MD doses by 50%

n total number of patients, C_{max} maximum concentration, C_{min} minimum concentration, $T_{1/2}$ half-life, *hr* hour(s), *AUC* area under the concentration time curve, *mg* milligrams, *L* liters, *Cl* clearance, *VDss* total volume of distribution at steady state, *VDc* volume of distribution in the central compartment; *LD* loading dose, *MD* maintenance dose, *IV* intravenous, *PO* oral, *kg* kilograms, *CVVH* continuous veno-venous hemofiltration, *TBW* total body weight, *AdjBW* adjusted body weight, *LBW* lean body weight, *BMI* body mass index, *PD* pharmacodynamics, *NR* not reported, *CrCl* creatinine clearance, *CCG* Cockcroft and Gault, *CYP450* cytochrome P450, *2C19*2/2* CYP450 enzyme subtype with *2/2 indicating a poor metabolizer phenotype, *MIC* minimum inhibitory concentration, *ICU* intensive care unit, *BSA* body surface area

*Mean ± % relative standard error (RSE)

dose [27•]. The pharmacokinetics of voriconazole in obese patients compared to historical non-obese patients was similar between groups receiving 300 mg BID. In obese patients receiving 200 mg BID, voriconazole CL was decreased by 50% with proportional increase in AUC; however, the total VD was similar between groups (Table 1). Further analysis demonstrated that voriconazole $AUC_{0–12}$ in obese patients was more correlated with LBW_{2005} ($r^2 = 0.42$) followed by AdjBW ($r^2 = 0.38$) and IBW ($r^2 = 0.31$). TBW had little correlation to voriconazole $AUC_{0–12}$ ($r^2 = 0.14$). In a single obese stem cell transplant patient (BMI 84.5 kg/m^2), given intravenous voriconazole (6 mg/kg loading dose followed by a maintenance dose of 4 mg/kg BID) using an AdjBW resulted in similar AUCs to non-obese patients with similar disease processes and the aforementioned pharmacokinetic study [25, 27•]. An additional case report describing voriconazole (4 mg/kg AdjBW) pharmacokinetics in an obese (BMI ≥ 35 kg/m^2) patient, who was a CYP2C19 poor metabolizer, demonstrated 2- to 3-fold increases in both AUC and C_{min} compared to their target goals (Table 1). The influence of obesity on voriconazole pharmacokinetics is hard to evaluate given the patients' CYP2C19 poor metabolizer status; however, similar increases in AUC and C_{min} are consistent with the increases seen in other voriconazole pharmacokinetics studies in CYP2C19 poor metabolizers [34]. Removing the CYP2C19 poor metabolizer influence, the resultant AUC value is similar to those previous discussed [25, 26, 27•].

Therapeutic Drug Monitoring Studies

Of the six studies that used TDM to describe the effects of obesity on voriconazole serum concentrations, two (33%) did not find weight as a significant covariate [29, 30]. Koselke et al. compared voriconazole concentrations in obese patients who were dosed based upon TBW, AdjBW, or IBW [28]. Their findings demonstrated that when patients received voriconazole dosed on TBW, they had significantly higher mean/median concentrations (Table 2). Additionally, voriconazole dosing based on TBW resulted in fewer patients with initial concentrations in their therapeutic range (2–5.5 mg/L) and more patients with supratherapeutic concentrations. The use of an AdjBW resulted in a higher number of patients reaching their target range with fewer patients having supratherapeutic concentrations compared to dosing based upon TBW or IBW (Table 2). The use of IBW resulted in slightly more subtherapeutic levels compared to TBW and AdjBW and interestingly more supratherapeutic concentrations than AdjBW [28]. Another study compared voriconazole concentrations in obese patients (which also included overweight patients (BMI ≥ 25 kg/m^2)) to non-obese patients [31]. Patients were treated with intravenous or oral voriconazole. Their work revealed a significant difference in median voriconazole concentrations with intravenous dosing, but not with oral dosing (Table 2). This finding could be due to the differences in how intravenous and oral voriconazole are dosed, but median doses were not significantly different across weight groups. The sample size in each group was small which may have contributed to the lack of significance as the median numeric doses were 200 mg higher in overweight and obese patients [31]. Sebaaly et al. conducted a retrospective review of voriconazole TDM in obese (BMI ≥ 30 kg/m^2) vs non-obese patients [32]. They did not find a significant difference in voriconazole serum concentrations between groups (Table 2); however, obese patients had numerically higher voriconazole mean doses and serum concentrations with wider interquartile ranges compared to non-obese patients [32]. The most recent study compared voriconazole serum concentrations between obese (BMI ≥ 35 kg/m^2) and non-obese patients; however, obese patients had their voriconazole dose based upon AdjBW while non-obese patients were dosed on TBW [33••]. Additionally, all patients were initially dosed at 6 mg/kg/dose twice daily and then further adjusted based upon TDM. Their results did not find a significant difference in patients reaching therapeutic (2–5 mg/L), subtherapeutic (< 2 mg/L), or supratherapeutic levels (> 5 mg/L) voriconazole concentrations between groups (Table 2). In fact, a higher percentage of obese patients had reached therapeutic concentrations (Table 2). Lastly, the median daily voriconazole dose to maintain a therapeutic maintenance dose was 8.5 mg/kg in obese patients compared to 8.6 mg/kg in non-obese patients based upon AdjBW and TBW, respectively [33••].

Posaconazole

The pharmacokinetics of posaconazole (any dosage form) has not been directly studied in obese patients. However, 21 studies evaluated weight (in kilograms, BMI, or BSA) as a covariate that may influence posaconazole concentrations via TDM studies with conflicting results [15, 35–54].

Oral Suspension

The effect of weight on posaconazole oral suspension (OS) concentrations was evaluated in 12 (57%) studies [15, 35, 37, 39, 44, 46, 48–52, 54]. Nine (75%) out of the 12 studies did not find weight as a significant covariate [15, 37, 39, 48–52, 54]. Three (25%) studies found a correlation between weight and posaconazole concentrations and will be further discussed [35, 44, 46•]. Shields et al., demonstrated that overweight patients had 47% lower mean posaconazole concentrations compared to non-overweight patients; however, weight was not a significant variable in their regression analysis ($p = 0.12$) [35]. Vehreschild and colleagues [46•] used population pharmacokinetic modeling which demonstrated that weight increased the apparent volume of distribution (VD/F) 33.4 L

Table 2 Therapeutic Drug Monitoring (TDM) Studies in Obese Patients

Drug	First author [citation]	Subjects (*n*)	Dosing	Route	Weight used for dosing	Levels used for analysis	Mean or median concentration (mg/L)	% therapeutic (2–5 mg/L)	% subtherapeutic (≤ 2 mg/L)	% supra-therapeutic (> 5 mg/L)	Comments
Voriconazole (VCZ)	Koselke E et al. [28]	42 (TBW *n* = 21; AdjBW *n* = 10; IBW *n* = 11	MD 4 mg/kg/dose	IV or PO	TBW; AdjBW; IBW	C_{min}	TBW = 6.2; AdjBW = 3.3; IBW = 3.95 ($p = 0.0009$)*	TBW = 29; AdjBW = 80; IBW = 45 ($p = 0.0599$)*^	TBW = 5; AdjBW = 20; IBW = 27 ($p = 0.1822$)*	TBW = 67; AdjBW = 0; IBW = 27 ($p < 0.0001$)	BW did not correlate with toxicities
	Mitsani D et al. [29]	93	LD 6 mg/kg IV q12hr × 2 doses; MD 200 mg PO BID	PO	NR	C_{min}	NR	NR	NR	NR	Only 25% of patients had a BMI > 30 kg/m^2; age correlated to increased C_{min}; C_{min} correlated AST changes
	Pascual A et al. [30]	55	LD 6 mg/kg IV q12hr × 2 doses; MD 4 mg/kg IV q12hr or MD 400 mg PO BID × 2 doses; MD 200 mg PO BID	IV or PO	TBW	All conc	NR	NR	NR	NR	BW did not impact VCZ PK or toxicities
	Davies-Vorbrodt S et al. [31]	92	NR (median dose 4 mg/kg/dose)	IV or PO	TBW	All conc	IV conc, obese 6.4 vs 2.8 non-obese ($p = 0.04$); PO conc obese 2.8 vs 2.0 non-obese ($p = 0.18$)	NR	NR	NR	Obese includes BMI ≥ 25 kg/m^2
	Sebaaly JC et al. [32]	88 (obese 21; non-obese 67)	NR (median dose was 3.9 mg/kg/dose per group)	IV or PO	TBW	All conc	Mean conc, obese 4.7 vs 4.3 non-obese ($p = 0.718$)	Obese 48 vs non-obese 55 ($p = 0.542$#)	NR	Obese 33 vs non-obese 25 ($p = 0.475$)#	80% of conc were C_{min}; IQR was wider for obese patients compared to non-obese patients ($p = 0.77$)
	Richards PG et al. [33••]	138 (obese 44; non-obese 94)$	6 mg/kg q12hr	IV or PO	Obese: AdjBW; non-obese: TBW	C_{min}	NR	50 obese vs 37 non-obese ($p = 0.095$)	5 obese vs 15 non-obese ($p = 0.077$)	45 obese vs 48 non-obese ($p = 0.6$)	MD to maintain target concentrations were 8.5 mg/kg/day (obese) vs 8.6 mg/kg/day (non-obese) (p = NS)

n total number of patients, % percentage, C_{min} minimum concentration, *mg* milligrams, *L* liters, *TBW* total body weight, *AdjBW* adjusted body weight, *IBW* ideal body weight, *BW* body weight (generic), *MD* maintenance dose, *LD* loading dose, *kg* kilograms, *IV* intravenous, *PO* oral, *BID* two times per day, *NR* not reported, *BMI* body mass index, *AST* aspartate aminotransferase, *conc* concentrations, *PK* pharmacokinetics, *IQR* interquartile range

**p* values comparing obese groups

^ Therapeutic concentrations defined as 2–5.5 mg/L

Therapeutic concentrations defined as 1–5.5 mg/L

$ BMI ≥ 35 kg/m^2

per kilogram in those > 77 kg, thus resulting in an expected lower posaconazole exposure in these patients [46•]. Lastly, Stelzer et al. [44] found that a BMI < 25 kg/m^2 was an independent predictor of a subtherapeutic posaconazole concentration. This result should be interpreted with caution as 82% of patients had a BMI < 25 kg/m^2 and no patient had a BMI ≥ 30 kg/m^2 [44]. A fourth study of 11 patients undergoing gastric bypass given a single dose of posaconazole OS (400 mg as a single dose with a mean BMI 40.4 kg/m^2) had concentrations measured pre- and post-procedure [55]. Their results showed comparable posaconazole pharmacokinetics pre-procedure; however, post-procedure exposures were decreased by ~ 50% despite patients having a lower BMI in this period [55, 56]. This suggests that the Roux-en-Y gastric bypass has a significant effect on posaconazole OS absorption that is more influential than weight [55].

Delayed-release Tablets

Weight was analyzed as a covariate in 11 posaconazole delayed-release (DR) TDM studies [36–42, 44, 45, 47, 53•]. Nine (82%) did not find weight to be an influential variable on posaconazole serum concentrations [36–41, 44, 45, 47], while two (18%) studies did [42, 53•]. The latter two studies will be discussed in further detail. van Iersel and colleagues constructed a posaconazole population pharmacokinetic model from several DR tablet formulation studies that included a total of 335 patients [42]. The model demonstrated that weight (> 72.5 kg) negatively affected posaconazole bioavailability. Despite these findings, over 90% of patients taking the DR tablets (irrespective of weight) achieved a posaconazole concentration > 0.5 mg/L. Further modeling demonstrated that even patients weighing > 172.4 kg would achieve a posaconazole concentration > 0.5 mg/L 66% of the time [42]. Miceli et al. [53•] evaluated posaconazole C_{min} in 28 patients undergoing chemotherapy or receiving a stem cell transplant. In their cohort, they determined that patients ≥ 90 kg had significantly lower posaconazole C_{min} compared to those weighing less than 90 kg (0.76 ± 0.09 vs 1.32 ± 0.14; $p = 0.002$). Similarly, patients with a BMI ≥ 30 kg/m^2 vs patients with BMI < 30 kg/m^2 had lower mean posaconazole C_{min} (0.89 ± 0.13 vs 1.29 ± 0.14; $p = 0.05$) [53•].

Intravenous

Only 2 (9.5%) studies evaluated the effect of weight on the pharmacokinetics of intravenous posaconazole with conflicting results [41, 43]. Sime and colleagues studied the pharmacokinetics of ICU patients receiving a single dose of intravenous posaconazole [43]. Their analysis included only one patient with a BMI > 37 kg/m^2. This patient had the lowest C_{max} concentration (6.8 mg/L) and the highest VD (989.9 L) among the eight patients analyzed. Despite these parameters, the patients C_{min} was similar to others in the study (2.2 mg/L, range 0.92–8.25 mg/L) [43].

Isavuconazole

Isavuconazole is the newest member of the triazole antifungal agents. Isavuconazole is unique in that it is delivered as a prodrug (isavuconazonium sulfate), which is rapidly converted to the active isavuconazole. The contribution of isavuconazonium to the pharmacokinetics is negligible and will not be discussed further. The intravenous and oral formulations produce similar pharmacokinetics and will be discussed together [12]. Similar to posaconazole, isavuconazole pharmacokinetics have not been formally studied in obese patients. Thus, the data presented in this section is derived from three studies that found weight to influence isavuconazole pharmacokinetics [57–59]. Desai and colleagues conducted a single-dose isavuconazole population pharmacokinetic study in healthy subjects with mild to moderate liver disease compared to healthy subjects without liver disease [57]. Their model demonstrated that increased BMI led to an increase in isavuconazole peripheral VD. Despite the correlation, BMI did not affect overall isavuconazole exposure. In a second population pharmacokinetic analysis, Kovanda et al. demonstrated that both increased weight and BMI increased isavuconazole CL while only weight increased the central compartment VD [58•]. When weight was included into the model, it had no impact. This finding suggests that the correlation of weight is not significant to isavuconazole pharmacokinetics. Lastly, intravenous isavuconazole (200 mg three times per day for 2 days followed by 200 mg daily) pharmacokinetics were studied in 26 solid organ transplant patients [59]. The results of this study revealed that patients with a BMI ≥ 18.5 kg/m^2 had a 48% lower $AUC_{0–24}$ compared to patients with a BMI < 18.5 kg/m^2 (51.8 vs 100.5 mg h/L; $p = 0.024$). However, the AUC in patients with a BMI ≥ 18.5 kg/m^2 in this study is comparable with the AUC in acute myeloid leukemia patients [60]. This finding suggests that patients with a BMI < 18.5 kg/m^2 may be at risk for supratherapeutic isavuconazole concentrations as opposed to higher BMIs being at risk for subtherapeutic isavuconazole [59].

Azole Summary

The data on dosing triazole antifungal agents in obese patients is very limited. Despite this, some dosing guidance can be derived. The evidence for dosing fluconazole in obese patients suggests using TBW. Different than this, the dosing for voriconazole seems to best correlate with an AdjBW for both intravenous and oral dosage forms; however, due to high interpatient variability and the influence of pharmacogenomics, TDM is recommended for voriconazole. For posaconazole OS,

the VD was significantly increased in patients ≥ 77 kg, while in DR tablets, patients weighing > 90 kg or those with a BMI > 30 kg/m^2 may be at risk for treatment failures due to subtherapeutic concentrations, both of which may warrant TDM. Lastly, weight and/or BMI have correlated to increases in isavuconazole VD; however, these factors did not alter isavuconazole exposure, and therefore, no dosage adjustments or TDM is recommended for isavuconazole in obese patients.

Echinocandins

Overview

In recent years, the proportion of echinocandin usage has increased for the treatment of candidiasis [4]. One recent conference abstract even reported that the proportion of echinocandin usage was greater in obese patients compared to non-obese patients, while outcomes were less favorable in obese patients [61]. There are currently three FDA-licensed echinocandins: caspofungin, micafungin, and anidulafungin. In our previous review, we had very little research to consider on echinocandins [3]. Since that time, several research publications have focused on weight-based assessment or obesity dosing with the three licensed agents.

Class Review

The available data with echinocandins does suggest more similarities than differences within the class of agents. The echinocandins are highly protein-bound agents with similar chemical structures. They appear to be well characterized pharmacokinetically by two-compartment models, although a recent study employed a three-compartment model with anidulafungin [62••]. The echinocandins have an excellent safety profile with minimal drug interactions. Various pharmacokinetic and pharmacodynamics modeling studies have tried assisting in answering these questions. The next sections will go through the available data for each echinocandin.

Caspofungin

Caspofungin was the first licensed agent in the class. Early studies suggested the potential for lower drug exposure in obese patients with patients weighing > 75 kg having significantly lower caspofungin C_{min} than those ≤ 75 kg [63, 64]. Since the time of our last writing on this topic, Hall and colleagues carried out a prospective single-dose (70 mg) pharmacokinetic analysis of caspofungin in 18 adult volunteer subjects (Table 1) [65•]. Subjects were equally grouped as normal weight (BMI < 25 kg/m^2), overweight/obese (BMI 25 to 40 kg/m^2), or morbidly obese (BMI > 40 kg/m^2). Earlier work with echinocandins led these investigators to use a higher-order complexity fractal geometry model in their assessment [66]. BMI differences were not associated with any significant pharmacokinetic parameters. However, these investigators did find a positive correlation between subject weight and VD and systemic CL, as well as a negative correlation with AUC and peak concentration. Using fractal geometry principles, their data suggested that increased weight may result in higher, non-linear declines in drug concentrations, which is concerning (Table 1). As a result, the investigators suggest that increasing doses in heavier patients may be needed to reach pharmacodynamic targets. An assessment of a multiple-dose regimen with similar methods may provide additional value [65•]. Caspofungin was assessed in a population pharmacokinetic study where it was given alone or with liposomal amphotericin B in stem cell transplant patients [67]. BW in these patients ranged from 53.6 to 99.2 kg, with 15 of the 36 patients weighing over 80 kg. These investigators were not able to show that weight was a significant covariate in their model. The pharmacokinetics of caspofungin 100 mg daily in an obese ICU patient has been described. The day 4 pharmacokinetics are provided in Table 2 [68]. The 100-mg dose of caspofungin exceeded the AUC/MIC target of 860 (actual AUC/MIC 1123; MIC = 0.125 mg/L) and the patient responded to therapy (Table 1) [68].

Micafungin

Micafungin was the second marketed echinocandin. In general candidiasis treatment, the micafungin pharmacodynamic target of $AUC_{0–24}$/MIC > 3000 is the best regarded in the current literature [69]. Much of the available data with overweight or obese patients suggests that it will be difficult to achieve such drug exposure, especially with higher MIC organisms. To cloud the picture even more, the standard dose of 100 mg may be inadequate for many indications in normal weight individuals [70]. Data from our prior review suggested that patients weighing > 66.3 kg may require doses of 150 mg to achieve similar pharmacokinetics as those < 66.3 kg [71]. Since our previous review, Hall and colleagues performed another single-dose pharmacometric study with 36 adult volunteers receiving either 100 mg or 300 mg of micafungin (Table 1) [66]. The volunteers had a median weight of 96.2 kg, with a range of 43.0–154.8 kg. Subjects were equally grouped as normal weight (BMI < 25 kg/m^2), overweight/obese (BMI 25 to 40 kg/m^2), or morbidly obese (BMI > 40 kg/m^2). BMI differences did not correlate well with pharmacokinetic parameters including CL. However, BW did display a strong linear relationship with CL for patients weighing more than 66 kg. In a follow-up study, Pasipandoya et al. developed a Monte Carlo simulation model to simulate 100,000 candidemia subjects interfacing with the MIC variability of 5346 clinical *Candida* isolates [72••]. One of the goals of the study was to develop and test a weight-based

bedside dosing equation for micafungin that could maximize the achievement *a* > 3000 $AUC_{0–24}$/MIC target. After consideration of several rule iterations, they arrived at the following bedside dosing formula for micafungin in overweight or obese patients: dose (mg) = patient weight (kg) + 42. The formula was tested in a 5000 patient Monte Carlo simulation with weights ranging up to 200 kg. The formula achieved $AUC_{0–24}$/MIC target attainment 73% of the time versus 31% of the time with the standard dose of 100 mg in simulated patients. A separate investigator group completed another Monte Carlo simulation where they not only considered attainment of the > 3000 $AUC_{0–24}$/MIC target, but they also considered the species-level $AUC_{0–24}$/MIC targets of > 285 and > 5000 for *Candida parapsilosis* and non-parapsilosis *Candida* species, respectively (Table 1) [73••]. The dosing simulations were based on a range of 45 to 185 kg of BW across MICs from 0.008 to 1 mcg/mL. Daily dosages considered in the model were 100 mg, 150 mg, and 200 mg. The 100-mg dose was found to be inadequate at achieving the $AUC_{0–24}$/MIC of 5000 target at all MICs and was only adequate against organisms with an MIC of 0.008 mcg/mL using the 3000 $AUC_{0–24}$/MIC target, regardless of weight simulated. Their conclusion was that a dosage of 150 mg would achieve adequate target attainment in patients ≤ 115 kg and a dose of 200 mg would achieve target attainment in patients ≤ 185 kg for *Candida albicans* infections. They also found that a daily dose of 200 mg had adequate target attainment for *Candida glabrata* in patients ≤ 115 kg. An additional case for consideration is the published letter of a 230-kg (BMI 102 kg/m^2) woman who was treated with 100 mg micafungin daily and had serum concentrations significantly lower than previously published concentrations and unfortunately no formal pharmacokinetic analysis [74]. Interestingly, this patient had a positive outcome, despite these lower drug concentrations.

Anidulafungin

Anidulafungin was the third licensed echinocandin and the least frequently used. One practical limitation to anidulafungin is maximal infusion rate requirement of < 1.1 mg/min [75]. Infusions of higher anidulafungin doses (≥ 200 mg) would require infusions ≥ 2 h, and this may not be desired compared to other echinocandins. BW was recognized early on as a determinant of central VD [76]. Since the time of our previous review, the manufacturer and a group of Dutch researchers have completed several studies that add to our knowledge of anidulafungin dosing in obese patients, and these studies are described below.

Anidulafungin's manufacturer performed a retrospective population pharmacokinetic-pharmacodynamic analysis from data gathered in four phase II and III studies [77]. Patients received either a regimen of 50 mg daily after a loading dose of 100 mg, or 100 mg daily following a loading dose of 200 mg. Patient weights ranged from 31 to 154 kg (median = 61 kg). Decreased drug exposure (AUC) was noted with heavier patients. These differences did not translate into worse clinical outcomes in heavier patients, nor were there higher rates of adverse effects seen with smaller patients. Despite the lack of clinical differences, the author recommended caution when using standard doses in patients > 150 kg. In another manufacturer-sponsored pharmacokinetic study, anidulafungin was studied in critically ill patients. Included in that study was the assessment of one morbidly obese woman (240 kg, BMI 83 kg/m^2) [78]. She was given a higher dose (150 mg daily) because of concerns of reduced drug exposure. Her blood concentrations of anidulafungin were similar to normal-weight patients who received 100-mg daily doses. She also experienced a clinical cure. Based on these findings, the authors suggest that a dosage increase of 50% may be prudent in patients weighing ≥ 200 kg or BMI ≥ 80 kg/m^2. A population pharmacokinetic analysis was conducted on anidulafungin when used in combination with voriconazole for invasive aspergillosis in 305 patients [79]. The patient weights for the 140 patients who received anidulafungin ranged from 36.9 to 116.8 kg (median = 68.3 kg). The investigators found weight to be the most influential covariate, with a correlation between increasing weight and decreasing AUC. None of these pharmacokinetic differences were associated with changes in clinical outcomes. This study also lacked the presence of morbidly obese patients. A recent Dutch study was designed to evaluate reduced-frequency dosing of anidulafungin for antifungal prophylaxis in immunocompromised patients [80]. The study had two groups, composed of 10 patients receiving 200 mg every 48 h, and 10 patients receiving 300 mg every 72 h. The median weight of patients was 77 kg (52–113 kg). The pharmacokinetic modeling data from these patients was integrated into a Monte Carlo simulation that was set for 18,000 virtual patients. The model used data from 1706 AML/MDS and stem cell transplant patients with weights ranging from 39 to 145 kg (mean 76.4 kg). Weight was determined to be a significant covariate on central VD. Specifically, the higher the LBW, the larger the VD. No clinical outcome differences were observed the across weight spectrum.

Lempers and colleagues conducted a single-dose (100 mg) study to observe the pharmacokinetics of anidulafungin in morbidly obese (BMI > 40 kg/m^2) subjects (Table 1) [81••]. The ADOPT Trial enrolled eight subjects who were to have bariatric surgery. The patients' mean lean body mass was 144.7 kg (124.1–166.5 kg). The mean AUC in these obese patients was reported to be 32.5% lower than the AUC reported in historic controls of a more "general population." Using linear kinetics as a guide, these investigators suggest that increasing the anidulafungin loading dose and maintenance dose by 50% would make drug concentrations more normalized in morbidly obese patients. This same group of

investigators then compared the data from the eight morbidly obese patients from the ADOPT Trial with data from 12 normal-weight subjects from two phase I studies (Table 1) [62••]. The goal was to develop a population pharmacokinetic model across a wide BW range. A three-compartment, zero-order pharmacokinetic model provided the best fit. Similar to other echinocandin studies, TBW displayed a relationship with both CL and central VD (Table 1). The recommendation from this study was to increase loading and maintenance dose by 25% in patients weighing more than 140 kg.

Echinocandin Summary

Each of the echinocandins demonstrates altered pharmacokinetics with increasing weights, but the starting point for these alterations is 66–75 kg, which is far from patients who are obese. In the case of micafungin, standard doses of 100 mg may not be adequate in normal-weight individuals and subsequently obese patients given the above data. Thus, it seems reasonable and necessary to increase the doses of echinocandins in obese patients; however, clinical studies have not demonstrated reduced efficacy in obese patients. This finding may be limited by the sheer number of obese patients included in these datasets. Therefore, in cases of serious infections, empiric use of higher doses of echinocandins appears to be reasonable. Unfortunately, precision drug dosing is not well developed across the spectrum of higher weights, and the dose recommendation may differ slightly with each agent. Clinicians must consider extent of illness, hepatic function, weight, location of infection, and organism susceptibility when determining whether to use higher doses of echinocandins. Despite this, larger doses of these agents that are generally well tolerated will not likely create too many additional adverse effects. However, cost containment will likely be a bigger issue (*pun intended*).

Conclusions

Data regarding dosing antifungals in obese patients is still limited, and voriconazole is the only agent that has a multipatient pharmacokinetic study. The majority of evidence with azoles, including voriconazole, comes from TDM studies and/or population pharmacokinetic analyses. Similarly, the data regarding echinocandins is indirect and comes from population pharmacokinetic studies. The applicability of population-modeling studies is questionable as obese patients are underrepresented in these data sets. Despite the limited data, these are our summary findings.

Fluconazole and voriconazole dosing should be based on TBW and AdjBW, respectively. Posaconazole may have reduced exposures in obese patients; however, the new oral dosage form is more reliable, which may mitigate the need for dosage adjustments. Isavuconazole appears to be unaffected by weight. Echinocandin doses likely need to be increased in obese patients; however, the exact weight and dosages remain uncertain. Our summary recommendations for dosing can be found in Fig. 1.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of obesity among adults and youth: United States, 2015-2016. NCHS Data Brief. 2017;288:1–8.
2. Genoni G, Prodam F, Marolda A, Giglione E, Demarchi I, Bellone S, et al. Obesity and infection: two sides of one coin. Eur J Pediatr. 2014;173:25–32.
3. Amsden JR, Slain D. Antifungal dosing in obesity: a review of the literature. Curr Fungal Infect Rep. 2011;5:83–91.
4. Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2015;62:e1–50.
5. Patterson TF, Thompson GR, Denning DW, Fishman JA, Hadley S, Herbrecht R, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;63:433–42.
6. Gubbins PO. Triazole antifungal agents drug-drug interactions involving hepatic cytochrome P450. Expert Opin Drug Metab Toxicol. 2011;7:1411–29.
7. Barone JA, Moskovitz BL, Guarnieri J, Hassell AE, Colaizzi JL, Bierman RH, et al. Enhanced bioavailability of itraconazole in hydroxypropyl-ß-cyclodextrin solution versus capsules in healthy volunteers. Antimicrob Agents Chemother. 1998;42:1862–5.
8. Poirier JM, Cheymol G. Optimisation of itraconazole therapy using target drug concentrations. Clin Pharmacokinet. 1998;35:461–73.
9. Theuretzbacher U, Ihle F, Derendorf H. Pharmacokinetic/pharmacodynamic profile of voriconazole. Clin Pharmacokinet. 2006;45:649–63.
10. Guarascio AJ, Slain D. Review of the new delayed-release oral tablet and intravenous dosage forms of posaconazole. Pharmacotherapy. 2015;35:208–19.
11. Rybak JM, Marx KR, Nishimoto AT, David Rogers P, Rogers PD. Isavuconazole: pharmacology, pharmacodynamics, and current clinical experience with a new triazole antifungal agent. Pharmacotherapy. 2015;35:1037–51.

12. Slain D, Cleary JD. Isavuconazonium sulfate: a novel antifungal agent. Curr Fungal Infect Rep. 2015;9:302–13.
13. Amsden JR, Gubbins PO. Pharmacogenomics of triazole antifungal agents: implications for safety, tolerability and efficacy. Expert Opin Drug Metab Toxicol. 2017;13:1135–46.
14. Lepak AJ, Andes DR. Antifungal pharmacokinetics and pharmacodynamics. Cold Spring Harb Perspect Med. 2014;5:a019653.
15. Dolton MJ, Ray JE, Chen SC, Ng K, Pont L, McLachlan AJ. Multicenter study of posaconazole therapeutic drug monitoring: exposure-response relationship and factors affecting concentration. Antimicrob Agents Chemother. 2012;56:5503–10.
16. Dolton MJ, McLachlan AJ. Voriconazole pharmacokinetics and exposure-response relationships: assessing the links between exposure, efficacy and toxicity. Int J Antimicrob Agents. 2014;44:183–93.
17. Desai AV, Kovanda LL, Hope WW, Andes D, Mouton JW, Kowalski DL, et al. Exposure-response relationships for isavuconazole in patients with invasive aspergillosis and other filamentous fungi. Antimicrob Agents Chemother. 2017;61:1–9.
18. Kovanda LL, Marty FM, Maertens J, Desai AV, Lademacher C, Engelhardt M, et al. Impact of mucositis on absorption and systemic drug exposure of isavuconazole. Antimicrob Agents Chemother. 2017;61:e00101–17.
19. Dolton MJ, McLachlan AJ. Optimizing azole antifungal therapy in the prophylaxis and treatment of fungal infections. Curr Opin Infect Dis. 2014;27:493–500.
20. Ashbee HR, Barnes RA, Johnson EM, Richardson MD, Gorton R, Hope WW. Therapeutic drug monitoring (TDM) of antifungal agents: guidelines from the British Society for Medical Mycology. J Antimicrob Chemother. 2014;69:1162–76.
21. Lopez ND, Phillips KM. Fluconazole pharmacokinetics in a morbidly obese, critically ill patient receiving continuous venovenous hemofiltration. Pharmacotherapy. 2014;34:e162–8.
22.•• Alobaid AS, Wallis SC, Jarrett P, Starr T, Stuart J, Lassig-Smith M, et al. Effect of obesity on the population pharmacokinetics of fluconazole in critically ill patients. Antimicrob Agents Chemother. 2016;60:6550–7. **With regard to population modeling, this is one of the few studies that included serum concentrations from obese patients in their model. Additionally, this is one of the few studies to model fluconazole pharmacokinetics. When put together, this study provides fluconazole population pharmacokinetic data that sheds light on the variables that effect fluconazole disposition. This study further utilizes Monte Carlo simulations to predict fAUC/MIC target attainment across a variety of fluconazole doses, BMI strata, and creatinine clearances. In the end, the authors provide dosing recommendations that are strikingly similar to published case reports.**
23. Janmahasatian S, Duffull SB, Ash S, Ward LC, Byrne NMGB. Quantification of lean body weight. Clin Pharmacokinet. 2005;44:1051–65.
24. Charlier C, Hart E, Lefort A, Ribaud P, Dromer F, Denning DW, et al. Fluconazole for the management of invasive candidiasis: where do we stand after 15 years? J Antimicrob Chemother. 2006;57:384–410.
25. Dickmeyer NJ, Kiel PJ. Dosing voriconazole in an obese patient. Clin Infect Dis. 2011;53:745.
26. Moriyama B, Jarosinski PF, Figg WD, Henning SA, Danner RL, Penzak SR, et al. Pharmacokinetics of intravenous voriconazole in obese patients: implications of CYP2C19 homozygous poor metabolizer genotype. Pharmacotherapy. 2013;33:e19–22.
27.• Pai MP, Lodise TP. Steady-state plasma pharmacokinetics of oral voriconazole in obese adults. Antimicrob Agents Chemother. 2011;55:2601–5. **This study is not recent, but it is still the only study to perform a multipatient pharmacokinetic analysis on an antifungal agent (voriconazole) in obese patients. This study attempts to determine the best weight descriptor with which to dose voriconazole in obese patients. The results of this study demonstrate that no weight descriptor accurately characterizes voriconazole pharmacokinetics and that total body weight should not be used to dose voriconazole.**
28. Koselke E, Kraft S, Smith J, Nagel J. Evaluation of the effect of obesity on voriconazole serum concentrations. J Antimicrob Chemother. 2012;67:2957–62.
29. Mitsani D, Nguyen MH, Shields RK, Toyoda Y, Kwak EJ, Silveira FP, et al. Prospective, observational study of voriconazole therapeutic drug monitoring among lung transplant recipients receiving prophylaxis: factors impacting levels of and associations between serum troughs, efficacy, and toxicity. Antimicrob Agents Chemother. 2012;56:2371–7.
30. Pascual A, Csajka C, Buclin T, Bolay S, Bille J, Calandra T, et al. Challenging recommended oral and intravenous voriconazole doses for improved efficacy and safety: population pharmacokinetics–based analysis of adult patients with invasive fungal infections. Clin Infect Dis. 2012;55:381–90.
31. Davies-Vorbrodt S, Ito JI, Tegtmeier BR, Dadwal SS, Kriengkauykiat J. Voriconazole serum concentrations in obese and overweight immunocompromised patients: a retrospective review. Pharmacotherapy. 2013;33:22–30.
32. Sebaaly JC, MacVane SH, Hassig TB. Voriconazole concentration monitoring at an academic medical center. Am J Heal Pharm. 2016;73:S14–21.
33.•• Richards PG, Dang KM, Kauffman CA, Stalker KL, Sudekum D, Kerr L, et al. Therapeutic drug monitoring and use of an adjusted body weight strategy for high-dose voriconazole therapy. J Antimicrob Chemother. 2017;72:1178–83. **This study compares the percentage of patients who reached voriconazole therapeutic drug concentrations among obese and non-obese patients. The interesting part of this study is that obese patients have their voriconazole dose based upon AdjBW while non-obese patients had their dose based upon total body weight. The findings suggest that dosing voriconazole based upon an AdjBW results in a higher percentage of patients reaching their target concentrations compared to non-obese patients. There were also less supratherapeutic and subtherapeutic concentration in the obese group. Furthermore, the maintenance dose (which was strictly defined in the study) was 0.1 mg/kg/day different between groups despite using different weight for initial dosing.**
34. Owusu Obeng A, Egelund EF, Alsultan A, Peloquin CA, Johnson JA. CYP2C19 polymorphisms and therapeutic drug monitoring of voriconazole: are we ready for clinical implementation of pharmacogenomics? Pharmacotherapy. 2014;34:703–18.
35. Shields RK, Clancy CJ, Vadnerkar A, Kwak EJ, Silveira FP, Massih RCA, et al. Posaconazole serum concentrations among cardiothoracic transplant recipients: factors impacting trough levels and correlation with clinical response to therapy. Antimicrob Agents Chemother. 2011;55:1308–11.
36. Cornely OA, Duarte RF, Haider S, Chandrasekar P, Helfgott D, Jiménez JL, et al. Phase 3 pharmacokinetics and safety study of a posaconazole tablet formulation in patients at risk for invasive fungal disease. J Antimicrob Chemother. 2016;71:718–26.
37. Pham AN, Bubalo JS, Lewis JS. Comparison of posaconazole serum concentrations from haematological cancer patients on posaconazole tablet and oral suspension for treatment and prevention of invasive fungal infections. Mycoses. 2016;59:226–33.
38. Chin A, Pergam SA, Fredricks DN, Hoofnagle AN, Baker KK, Jain R. Evaluation of posaconazole serum concentrations from delayed-release tablets in patients at high risk for fungal infections. Antimicrob Agents Chemother. 2017;61:e00569–17.
39. Belling M, Kanate AS, Shillingburg A, Lu X, Wen S, Shah N, et al. Evaluation of serum posaconazole concentrations in patients with hematological malignancies receiving posaconazole suspension

compared to the delayed-release tablet formulation. Leuk Res Treatment. 2017;3460892:1–6.
40. Petitcollin A, Boglione-Kerrien C, Tron C, Nimubona S, Lalanne S, Lemaitre F, et al. Population pharmacokinetics of posaconazole tablets and Monte Carlo simulations to determine whether all patients should receive the same dose. Antimicrob Agents Chemother. 2017;61:e01166–17.
41. Tverdek FP, Heo ST, Aitken SL, Granwehr B, Kontoyiannis DP. Real-life assessment of the safety and effectiveness of the new tablet and intravenous formulations of posaconazole in the prophylaxis of invasive fungal infections via analysis of 343 courses. Antimicrob Agents Chemother. 2017;61:e00188–17.
42. van Iersel MLPS, Rossenu S, de Greef R, Waskin H. A population pharmacokinetic model for a solid oral tablet formulation of posaconazole. Antimicrob Agents Chemother. 2018;62:e02465–17.
43. Sime FB, Stuart J, Butler J, Starr T, Wallis SC, Pandey S, et al. Pharmacokinetics of intravenous posaconazole in critically ill patients. Antimicrob Agents Chemother. 2018;62:e00242–18.
44. Stelzer D, Weber A, Ihle F, Matthes S, Ceelen F, Zimmermann G, et al. Posaconazole liquid vs tablet formulation in lung transplant recipients. Mycoses. 2018;61:186–94.
45. Cojutti PG, Candoni A, Lazzarotto D, Rabassi N, Fanin R, Hope W, et al. Co-administration of proton pump inhibitors and/or of steroids may be a risk factor for low trough concentrations of posaconazole delayed-released tablets in adult patients with haematological malignancies. Br J Clin Pharmacol. 2018;84:2544–50.
46.• Vehreschild JJ, Müller C, Farowski F, MJGT V, Cornely OA, Fuhr U, et al. Factors influencing the pharmacokinetics of prophylactic posaconazole oral suspension in patients with acute myeloid leukemia or myelodysplastic syndrome. Eur J Clin Pharmacol. 2012;68:987–95. **This study is often quoted as one of the reasons that TDM should be employed with posaconazole, particularly the oral suspension. This study demonstrated that posaconazole oral suspension volume of distribution is increased in patients greater than 77 kg; however, no information is provided on posaconazole pharmacokinetics or exposure and this result has not been reproduced in other studies using oral solution or other dosage formulations.**
47. Boglione-Kerrien C, Picard S, Tron C, Nimubona S, Gangneux J-P, Lalanne S, et al. Safety study and therapeutic drug monitoring of the oral tablet formulation of posaconazole in patients with haematological malignancies. J Cancer Res Clin Oncol. 2018;144:127–34.
48. Allegra S, Fatiguso G, De Francia S, Favata F, Pirro E, Carcieri C, et al. Evaluation of posaconazole pharmacokinetics in adult patients with invasive fungal infection. Biomedicine. 2017;5:66.
49. Hoenigl M, Raggam RB, Salzer HJF, Valentin T, Valentin A, Zollner-Schwetz I, et al. Posaconazole plasma concentrations and invasive mould infections in patients with haematological malignancies. Int J Antimicrob Agents. 2012;39:510–3.
50. Eiden C, Meniane JC, Peyriere H, Eymard-Duvernay S, Le Falher G, Ceballos P, et al. Therapeutic drug monitoring of posaconazole in hematology adults under posaconazole prophylaxis: influence of food intake. Eur J Clin Microbiol Infect Dis. 2012;31:161–7.
51. Gross BN, Ihorst G, Jung M, Wäsch R, Engelhardt M. Posaconazole therapeutic drug monitoring in the real-life setting: a single-center experience and review of the literature. Pharmacotherapy. 2013;33:1117–25.
52. Dolton MJ, Brüggemann RJM, Burger DM, McLachlan AJ. Understanding variability in posaconazole exposure using an integrated population pharmacokinetic analysis. Antimicrob Agents Chemother. 2014;58:6879–85.
53.• Miceli MH, Perissinotti AJ, Kauffman CA, Couriel DR. Serum posaconazole levels among haematological cancer patients taking extended release tablets is affected by body weight and diarrhoea: single centre retrospective analysis. Mycoses. 2015;58:432–6. **This was a retrospective posaconazole DR tablet TDM study in hematology oncology patients. The results of this study demonstrated lower mean posaconazole troughs in patients > 90 kg as well as in those with a BMI ≥ 30 kg/m^2. This study is limited by its sample size, the presence of diarrhea (which also resulted in lower posaconazole concentrations), and the fact that > 70% of patient reached their posaconazole target concentrations. Nevertheless, this study questions the reliability of posaconazole DR tablets in obese patients.**
54. Mattiuzzi G, Yilmaz M, Kantarjian H, Borthakur G, Konopleva M, Jabbour E, et al. Pharmacokinetics of posaconazole prophylaxis of patients with acute myeloid leukemia. J Infect Chemother. 2015;21:663–7.
55. Gesquiere I, Hens B, Van der Schueren B, Mols R, de Hoon J, Lannoo M, et al. Drug disposition before and after gastric bypass: fenofibrate and posaconazole. Br J Clin Pharmacol. 2016;82:1325–32.
56. Krishna G, Moton A, Ma L, Medlock MM, McLeod J. Pharmacokinetics and absorption of posaconazole oral suspension under various gastric conditions in healthy volunteers. Antimicrob Agents Chemother. 2009;53:958–66.
57. Desai A, Schmitt-Hoffmann A-H, Mujais S, Townsend R. Population pharmacokinetics of isavuconazole in subjects with mild or moderate hepatic impairment. Antimicrob Agents Chemother. 2016;60:3025–31.
58.• Kovanda LL, Desai AV, Lu Q, Townsend RW, Akhtar S, Bonate P, et al. Isavuconazole population pharmacokinetic analysis using nonparametric estimation in patients with invasive fungal disease (results from the VITAL study). Antimicrob Agents Chemother. 2016;60:4568–76. **This study developed a population pharmacokinetic model from data included in the isavuconazole Phase III Vital study. The model only included a small number of obese patients; however, it demonstrated that both BMI and weight effected isavuconazole clearance while only weight effected VD. The inclusion of weight failed to improve the model; however, this finding warrants future study.**
59. Wu X, Clancy CJ, Rivosecchi RM, Zhao W, Shields RK, Marini RV, et al. Pharmacokinetics of intravenous isavuconazole in solid-organ transplant recipients. Antimicrob Agents Chemother. 2018;62(12):e01643–18 01643-18.
60. Cornely OA, Böhme A, Schmitt-Hoffmann A, Ullmann AJ. Safety and pharmacokinetics of isavuconazole as antifungal prophylaxis in acute myeloid leukemia patients with neutropenia: results of a phase 2, dose escalation study. Antimicrob Agents Chemother. 2015;59:2078–85.
61. Barber KE, Wagner JL, Miller J, Lewis E, Stover KR. Impact of obesity in patients with candida bloodstream infections [Abst 366]. Progam Abstr 2018 ID Week Conf. San Francisco, CA: Infectious Diseases Society of America; 2018. p. Abstract 366.
62.•• Wasmann RE, Ter Heine R, van Dongen EP, Burger DM, Lempers VJ, Knibbe CA, et al. Pharmacokinetics of anidulafungin in obese and normal-weight adults. Antimicrob Agents Chemother. 2018;62:1–10. **This study is a single-dose anidulafungin population pharmacokinetic study that included 20 patients (8 morbidly obese). The results of the study demonstrated that weight affects anidulafungin clearance and volume of distribution and ultimately reduces anidulafungin exposure. The authors quantified this exposure reduction and using Monte Carlo simulations demonstrated that patients > 140 kg need increased doses of anidulafungin.**
63. Stone JA, Winchell GA, Bi S, et al. Population pharmacokinetics of caspofungin in candidiasis patients [abstract A-1571]. Progr Abstr 43rd Annu Meet Intersci Conf Antimicrob Agents Chemother. Chicago, IL; 2009. p. abstract A-1571.
64. Nguyen TH, Hoppe-Tichy T, Geiss HK, Rastall AC, Swoboda S, Schmidt J, et al. Factors influencing caspofungin plasma

concentrations in patients of a surgical intensive care unit. J Antimicrob Chemother. 2007;60:100–6.

65.• Hall RG, Swancutt MA, Meek C, Leff R, Gumbo T. Weight drives caspofungin pharmacokinetic variability in overweight and obese people: fractal power signatures beyond two-thirds or three-fourths. Antimicrob Agents Chemother. 2013;57:2259–64. **The authors of this paper using fractal geometry demonstrated that weight, but not BMI, correlates with caspofungin volume of distribution and systemic clearance across obese and non-obese patients. This finding is important because echinocandins are concentration-dependent and if weight reduces the peak concentration through increases in the central compartment and/or through increases in systemic clearance which will reduce the area under the curve both of which may hinder the funcicidal activity of capsofungin. Therefore, weight may be the most important varible that guides caspofungin dosing and not the label of obesity.**

66. Hall RG, Swancutt MA, Gumbo T. Fractal geometry and the pharmacometrics of micafungin in overweight, obese, and extremely obese people. Antimicrob Agents Chemother. 2011;55:5107–12.

67. Wurthwein G, Young C, Lanvers-Kaminsky C, Hempel G, Trame MN, Schwerdtfeger R, et al. Population pharmacokinetics of liposomal amphotericin B and caspofungin in allogeneic hematopoietic stem cell recipients. Antimicrob Agents Chemother. 2012;56:536–43.

68. Ferriols-Lisart R, Aguilar G, Pérez-Pitarch A, Puig J, Ezquer-Garín C, Alós M. Plasma concentrations of caspofungin in a critically ill patient with morbid obesity. Crit Care Critical Care. 2017;21:200–1.

69. Andes D, Ambrose PG, Hammel JP. Use of pharmacokinetic-pharmacodynamic analyses to optimize therapy with the systemic antifungal micafungin for invasive candidiasis or candidemia. Antimicrob Agents Chemother. 2011;55:2113–21.

70. Agrifoglio A, Cachafeiro L, Herrero E, Sanchez M, Garcia de Lorenzo A. Are we near to the end of the standard dose of micafungin? Crit Care. 2018;22:149.

71. Gumbo T, Hiemenz J, Ma L, Keirns JJ, Buell DN, Drusano GL. Population pharmacokinetics of micafungin in adult patients. Diagn Microbiol Infect Dis. 2008;60:329–31.

72.•• Pasipanodya JP, Hall RG, Gumbo T. In silico-derived bedside formula for individualized micafungin dosing for obese patients in the age of deterministic chaos. Clin Pharmacol Ther. 2015;97:292–7. **This study is a follow-up study based upon previous work from this group. The authors performed simulations in 100,000 patients in an effort to provide clinicians with an easy to calculate dosing formula for micafungin. After several iterations, the authors developed a simple formula for micafungin dosing that achieved AUC/MIC ≥ 3000 in patients up to 200 kg.**

73.•• Maseda E, Grau S, Luque S, Castillo-Mafla M-P, Suárez-de-la-Rica A, Montero-Feijoo A, et al. Population pharmacokinetics/pharmacodynamics of micafungin against Candida species in obese, critically ill, and morbidly obese critically ill patients. Crit Care. 2018;22:94–103. **This micafungin population pharmacokinetic study included 31 patients with 21 obese and morbidly obese. The results of this study demonstrate the effect of weight on micafungin clearance. Upon their Monte Carlo analysis, the authors determined that doses needed to achieve > 90% target attainment (AUC/MIC ratios) against various *Candida* species. This analysis determined that doses > 150 mg daily are needed irrespective of weight. This study calls into question whether the standard dose of micafungin is adequate for normal-weight patients and identifies doses for obese patients to achieve optimal AUC/MIC ratios.**

74. Zomp A, Bookstaver PB, Ahmed Y, Turner JE, King C. Micafungin therapy in a critically ill, morbidly obese patient. J Antimicrob Chemother. 2011;66:2678–80.

75. ERAXIS (anidulafungin) for Injection. Pfizer, New York. 2018.

76. Dowell JA, Knebel W, Ludden T, Stogniew M, Krause D, Henkel T. Population pharmacokinetic analysis of anidulafungin, an echinocandin antifungal. J Clin Pharmacol. 2004;44:590–8.

77. Liu P. Population pharmacokinetic-pharmacodynamic analysis of anidulafungin in adult patients with fungal infections. Antimicrob Agents Chemother. 2013;57:466–74.

78. Liu P, Ruhnke M, Meersseman W, Paiva JA, Kantecki M, Damle B, et al. Pharmacokinetics of anidulafungin in critically ill patients with candidemia/invasive candidiasis. Antimicrob Agents Chemother. 2013;57:1672–6.

79. Liu P, Mould DR. Population pharmacokinetic analysis of voriconazole and anidulafungin in adult patients with invasive aspergillosis. Antimicrob Agents Chemother. 2014;58:4718–26.

80. Bruggemann RJM, Van Der Velden WJFM, Knibbe CAJ, Colbers A, Hol S, Burger DM, et al. A rationale for reduced-frequency dosing of anidulafungin for antifungal prophylaxis in immunocompromised patients. J Antimicrob Chemother. 2015;70:1166–74.

81.•• Lempers VJ, van Rongen A, van Dongen EP, van Ramshorst B, Burger DM, Aarnoutse RE, et al. Does weight impact anidulafungin pharmacokinetics? Clin Pharmacokinet. 2016;55:1289–94. **This study is an anidulafungin single-dose pharmacokinetic analysis in "healthy" bariatric patients prior to their procedure. The study provides a full pharmacokinetic analysis in morbidly obese patients. The findings demonstrate a lower exposure in obese patients and the authors provide dosing guidance based upon this data.**