

Anidulafungin exposure and population pharmacokinetics in critically ill patients with invasive candidiasis

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Background

- Anidulafungin is an echinocandin, recommended as a first line treatment of candida infections, especially in critically ill patients.
- Recent evidence suggests that PK variability in **critically ill patients** may lead to **lower anidulafungin exposure**.¹
- There is growing evidence that patients with **higher bodyweight (BW)** are at increased risk for **lower anidulafungin exposure** due to PK alterations.²
- The anidulafungin PKPD target is an AUC₀₋₂₄/MIC of **2782**.³
- With the 0.03 mg/L EUCAST epidemiological cut-off value for *C. albicans* as a MIC, the AUC_{24h} exposure target is **83.5 mg × h/L**.

Objectives

- To assess anidulafungin **exposure** and **PKPD target attainment** under standard dosing in critically ill patients.
- To develop a **popPK model** for anidulafungin in critically ill patients.
- To identify **covariates** with a **clinically relevant** impact on anidulafungin exposure.

Methods

- Adult patients admitted to the ICU receiving standard anidulafungin dosing (200 mg IV on day 1, followed by 100 mg IV q24h from day 2) were included in the study (NCT04045366). Rich blood sampling was performed on an early (day 2 ± 1) and/or a late (day 5 ± 1) treatment day.
- Using total anidulafungin plasma concentrations, a popPK model was developed using NONMEM version 7.5. Stepwise covariate modelling was used to identify covariate effects.
- Monte Carlo simulations were performed to evaluate PKPD target attainment and the clinical relevance of covariates under standard dosing.

Data

Table 1. Summary of patient characteristics (n=20)

Parameter	Value
Demographics at ICU admission	
Sex (female), n (%)	13 [65]
Bodyweight (kg) at baseline, median [range]	66 [50–134]
APACHE II score at baseline, median [range]	22 [11–34]
SOFA score, median [range]	10 [1–23]
Candidemia, n (%)	11 (55)
Laboratory parameters at baseline	
Serum albumin (g/L), median [range]	29.3 [20.2–39.1]
Plasma creatinine (mg/dL), median [range]	1.32 [0.39–3.27]
eGFR _{CKD-EPI} (mL/min/1.73 m ²), median [range]	52 [13–114]
C-reactive protein (mg/L), median [range]	67.1 [6.6–267.0]
Fungal pathogens	
<i>Candida albicans</i> , n (%)	8 (40)
<i>Candida glabrata</i> , n (%)	1 (5)
<i>Candida tropicalis</i> , n (%)	1 (5)
<i>Candida albicans</i> & <i>Candida glabrata</i> , n (%)	7 (35)
<i>Candida albicans</i> , <i>Candida glabrata</i> & <i>Candida tropicalis</i> , n (%)	1 (5)
<i>Saccharomyces cerevisiae</i> , n (%)	1 (5)
No culture results, n (%)	1 (5)
Anidulafungin sampling	
Number of plasma samples, n	188
Number of plasma samples per patient, median [range]	8 [3–17]
Number of rich sampling occasions, n	26
Survival	
Mortality 28 days after hospital admission, n (%)	2 (10)
Mortality 6 months after hospital admission, n (%)	10 (50)

APACHE: Acute physiology and chronic health evaluation; eGFR_{CKD-EPI}: Estimated glomerular filtration rate calculated using the Chronic Kidney Disease Epidemiology Collaboration equation; SOFA: Sequential Organ Failure Assessment score.

Anidulafungin exposure

Table 2. Anidulafungin exposure metrics

Exposure metric	Early sampling day	Late sampling day	Overall
C _{min} , median [range], mg/L	2.4 [1.3–6.1]	3.4 [1.4–7.8]	2.9 [1.3–7.9]
C _{max} , median [range], mg/L	6.1 [2.3–14.3]	5.8 [4.1–14.0]	6.0 [2.3–14.3]
AUC ₀₋₂₄ , median [range], mg×h/L	81.3 [29.9–189.4]	93.1 [26.9–222.0]	91.4 [26.9–220.0]
PKPD target attainment, %	45	65	55

AUC₀₋₂₄: 24-hour AUC estimated from the developed popPK model. On day 2 ± 1 of anidulafungin treatment, the AUC₀₋₂₄ was estimated on day 3. On day 5 ± 1 of anidulafungin treatment, the AUC₀₋₂₄ was estimated on day 6.

PopPK model

Table 3. Parameter estimates

Parameter	Base model estimates (%RSE) [%shrinkage]	Final model estimates (%RSE) [%shrinkage]	Bootstrap median (95% CI)
<i>Typical values</i>			
CL (L/h)	0.99 (9.2)	0.98 (5.2)	0.97 (0.80–1.12)
V _c (L)	8.62 (9.4)	5.81 (23.1)	6.72 (3.02–19.29)
Q (L/h)	19.41 (18.5)	20.90 (19.9)	19.76 (7.87–29.88)
V _p (L)	27.60 (22.9)	27.60 (12.5)	26.67 (14.93–34.51)
<i>Covariate effects</i>			
Bodyweight on CL		1.34 (26.6)	1.33 (0.06–1.95)
Serum albumin on V _c		-5.32 (21.8)	-5.09 (-7.78–1.50)
<i>Interindividual variability</i>			
on CL (%CV)	39.6 (24.5) [9]	35.4 (11.6) [7]	32.9 (14.98–40.93)
on V _c (%CV)	227.4 (25.7) [18]	220.7 (32.2) [22]	186.4 (75.61–432.20)
on V _p (%CV)	74.9 (51.2) [11]	53.4 (23.5) [16]	55.7 (27.41–125.56)
<i>Residual variability</i>			
Proportional error (%CV)	20.4 (7.8) [11]	19.8 (10.7) [11]	18.9 (16.04–21.80)

1809 out of 2,000 bootstrap runs (90.5%) were successful.

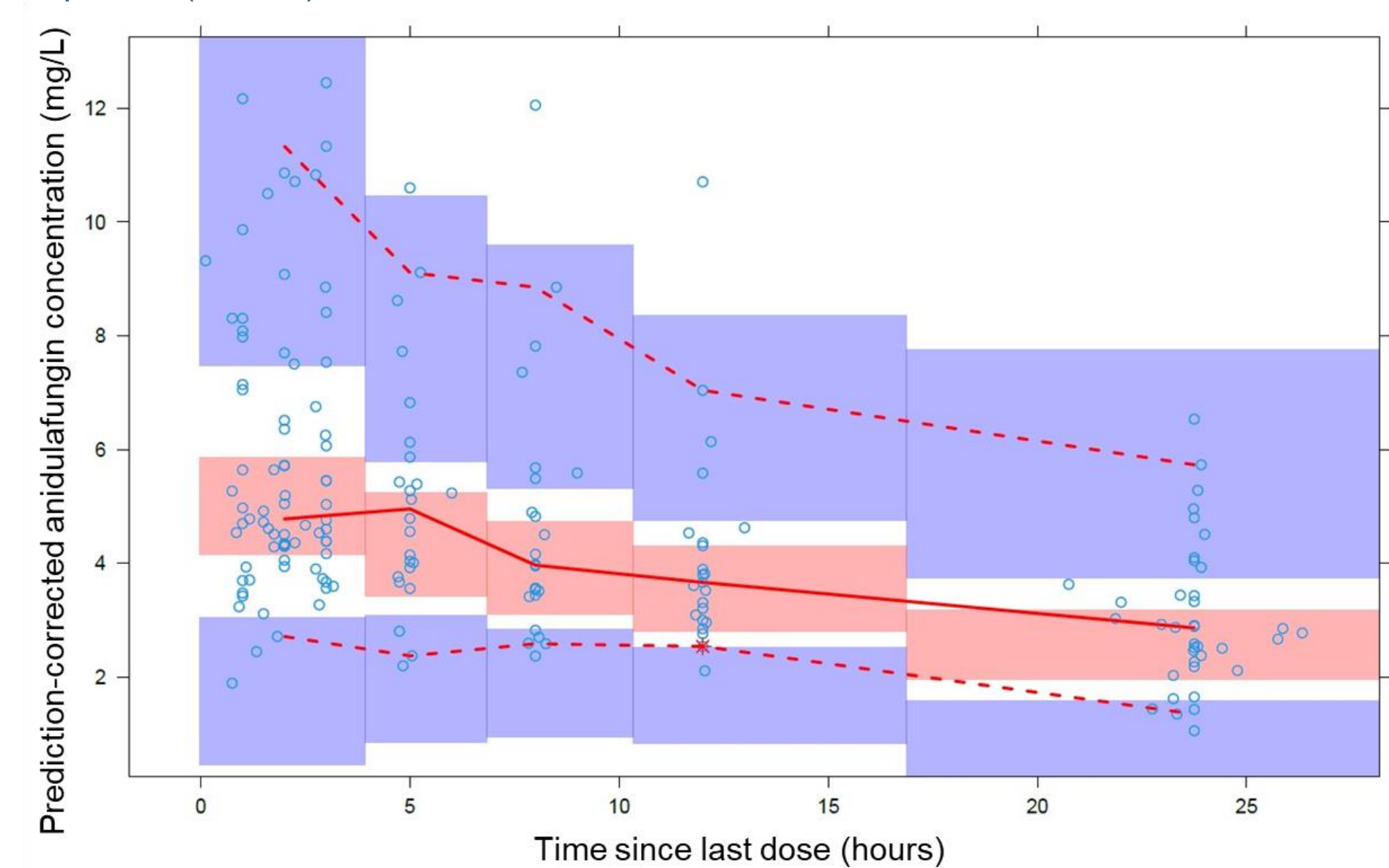


Figure 1. Prediction-corrected visual predictive check

Monte Carlo simulations

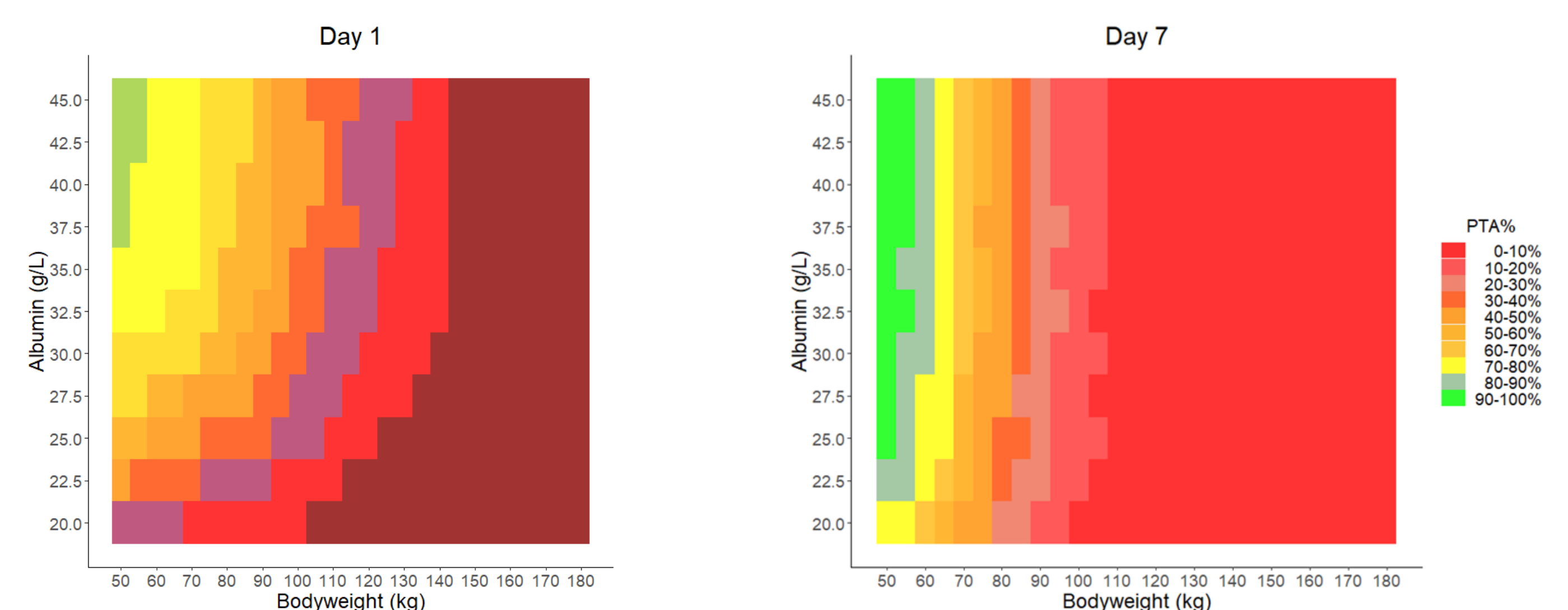


Figure 2. Heat map of anidulafungin PKPD PTA on day 1 and day 7 under standard dosing.

Conclusion

Standard anidulafungin dosing is insufficient for achieving adequate exposure in critically ill patients. BW and serum albumin should be considered when dosing anidulafungin in the ICU.

References

- [1] Liu X *et al.* 2020 J Clin Pharm Therapy [PMID: 32672361]
- [2] Alsowaida YS *et al.* 2023 AM J Health Syst Pharm [PMID: 36680786]
- [3] Andes *et al.* 2010 Antimicrob Agents Chemother [PMID: 20385855]

