SITA Società Italiana di Terapia Antinfettiva Antibatterica Antivirale Antifungina | 12° CONGRESSO NAZIONALE CATANIA | 17-18 novembre 2022

# FARMACI ANTIFUNGINI: ASPETTI DI FARMACOLOGIA CLINICA

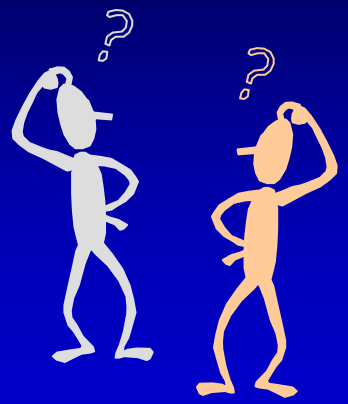

**FEDERICO PEA**

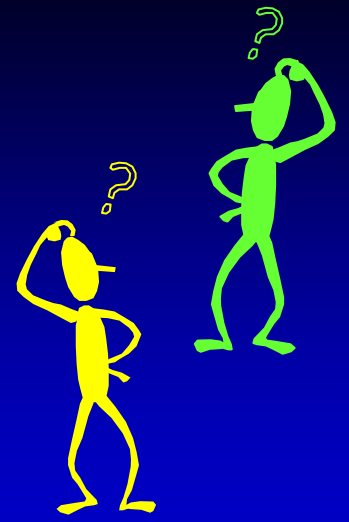
DIPARTIMENTO DI SCIENZE MEDICHE E CHIRURGICHE, ALMA MATER STUDIORUM, UNIVERSITA' DI BOLOGNA

FARMACOLOGIA CLINICA, IRCCS AZIENDA OSPEDALIERO UNIVERSITARIA DI BOLOGNA

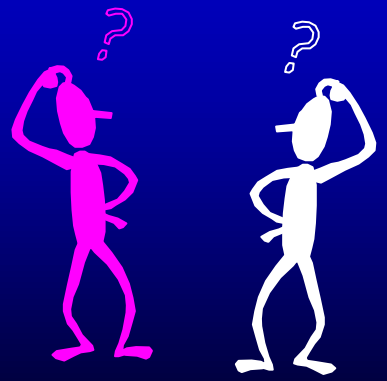
# DISCLOSURES OF INTEREST

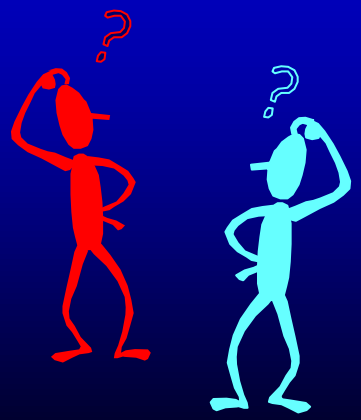
- Speaker's bureau: Angelini, BeiGene, Gilead, Menarini, MSD, Pfizer, Sanofi-Aventis, Shionogi
- Consultant: Angelini, BeiGene, Gilead, MSD, Pfizer, Shionogi





# CLINICAL PHARMACOLOGY OF ECHINOCANDINS





# PHARMACOKINETICS AND ANTIFUNGAL ACTIVITY OF ECHINOCANDINS IN ASCITES FLUID OF CRITICALLY ILL PATIENTS

Welte R et al. *Antimicrob Agents Chemother* 2021 Jun 17;65(7):e025652

ECHINOCANDIN PHARMACOKINETICS IN ASCITES FLUID OBTAINED FROM ASCITES DRAINS AND IN PLASMA WITH 24 H-SAMPLING PERIOD

| Patient | Sample | Drug | Day of therapy | Dose [mg/kg/d] | $C_{max}$ [µg/ml] | $C_{min}$ [µg/ml] | $T_{max}$ [h] | $AUC_{0-24}$ [µg × h/ml] | $t_{1/2}$ [h] | PR |
|---|---|---|---|---|---|---|---|---|---|---|
| **1** | **Ascites fluid** | **AFG** | **2** | **2.50** | **0.37** | **0.18** | **8** | **7.2** | | *0.20* |
| | Plasma | | | | 2.72 | 0.11 | 1.5 | 36.4 | 14.6 | |
| **2** | **Ascites fluid** | **AFG** | **9** | **1.35** | **1.01** | **0.51** | **8** | **21.3** | | *0.26* |
| | Plasma | | | | 5.32 | 2.40 | 1.5 | 80.9 | 23.8 | |
| **3** | **Ascites fluid** | **AFG** | **1** | **1.11** | **0.17** | **0.01** | **18** | **3.1** | | *0.05* |
| | Plasma | | | | 4.86 | 1.81 | 3 | 62.8 | 14.6 | |
| **4** | **Ascites fluid** | **AFG** | **4** | **2.56** | **0.57** | **0.33** | **4** | **10.7** | | *0.10* |
| | Plasma | | | | 6.50 | 3.02 | 1.5 | 103.8 | 27.2 | |
| **5** | **Ascites fluid** | **AFG** | **7** | **1.43** | **0.51** | **0.20** | **12** | **8.1** | | *0.12* |
| | Plasma | | | | 5.07 | 1.83 | 1.5 | 66.7 | 23.7 | |
| **11** | **Ascites fluid** | **AFG** | **1** | **1.18** | **0.63** | **0.09** | **8** | **10.8** | | *0.17* |
| | Plasma | | | | 6.72 | 1.70 | 1 | 61.6 | 24.9 | |
| **13** | **Ascites fluid** | **MFG** | **1** | **1.02** | **0.48** | **0.14** | **4** | **3.6** | | *0.15* |
| | Plasma | | | | 3.15 | 0.68 | 1 | 23.6 | 9.3 | |
| **14** | **Ascites fluid** | **MFG** | **3** | **1.96** | **0.26** | **0.02** | **24** | **4.2** | | *0.10* |
| | Plasma | | | | 5.22 | 0.64 | 1 | 42.4 | 8.5 | |
| **17** | **Ascites fluid** | **CAS** | **7** | **0.59** | **2.80** | **0.59** | **8** | **49.6** | | *0.58* |
| | Plasma | | | | 7.09 | 2.11 | 1 | 85.8 | 18.9 | |
| **18** | **Ascites fluid** | **CAS** | **3** | **0.67** | **0.53** | **0.04** | **18** | **8.9** | | *0.10* |
| | Plasma | | | | 6.74 | 1.84 | 1 | 85.7 | 39.2 | |
| **21** | **Ascites fluid** | **CAS** | **9** | **0.71** | **0.48** | **0.16** | **24** | **8.4** | | *0.08* |
| | Plasma | | | | 6.03 | 1.59 | 8 | 106.0 | 14.6 | |
| **22** | **Ascites fluid** | **CAS** | **3** | **0.77** | **0.52** | **0.23** | **18** | **11.0** | | *0.04* |
| | Plasma | | | | 27.40 | 6.21 | 1 | 271.3 | 19.8 | |
| **23** | **Ascites fluid** | **CAS** | **3** | **0.67** | **1.13** | **0.56** | **24** | **22.8** | | *0.26* |
| | Plasma | | | | 6.92 | 1.86 | 1 | 88.5 | 18.9 | |

# PK/PD OF CASPOFUNGIN IN PLASMA AND PERITONEAL FLUID OF LIVER TRANSPLANT RECIPIENTS

**Pressiat C et al. *Antimicrob Agents Chemother.* 2022; 66(1): e0118721**

**DEMOGRAPHIC, CLINICAL, AND LABORATORY CHARACTERISTICS OF LT RECIPIENTS (N = 20)**

| Variable[a] | Finding |
|---|---|
| Age (median [IQR]) (yr) | 45 [40.7–50] |
| Gender (no. male/female [% male]) | 9/11 [45] |
| Body weight (median [IQR]) (kg) | 72 [62–81] |
| BMI (median [IQR]) (kg/m$^2$) | 25.6 [24–29.6] |
| Indication for LT (no. [%]) | |
| Acute liver failure | 2 [10] |
| Hepatocellular carcinoma | 3 [15] |
| End-stage liver disease | 15 [75] |
| Etiology of cirrhosis (no. [%]) | |
| Alcohol | 7 [35] |
| Viral | 3 [15] |
| Autoimmune | 3 [15] |
| Cholestatic liver disorder | 2 [10] |
| Other | 3 [15] |
| Prognostic scores | |
| SOFA score (median [IQR]) | 13 [10.5–17.25] |
| MELD score (median [IQR]) | 29 [19.5–36] |
| MELD score of >30 (no. [%]) | 9 [45] |
| ACLF grade (no.) | |
| Grade 0 | 5 |
| Grade 1 | 4 |
| Grade 2 | 6 |
| Grade 3 | 5 |
| Charlson score (median [IQR]) | 5 [4–5.25] |

| Variable[a] | Finding |
|---|---|
| Comorbidities (no. [%]) | |
| Hepatorenal syndrome | 9 [45] |
| Hepatic encephalopathy | 11 [55] |
| Preoperative laboratory data | |
| PT (median [IQR]) (%) | 34 [30–50] |
| Total bilirubin level (median [IQR]) ($\mu$mol/L) | 90 [29–150] |
| Urea level (median [IQR]) (mmol/L) | 11.1 [8.8–17.4] |
| Serum creatinine level (median [IQR]) ($\mu$mol/L) | 128 [87–227] |
| ALT level (median [IQR]) (IU/L) | 43 [31–95] |
| AST level (median [IQR]) (IU/L) | 93 [60–144] |
| Leukocyte count (median [IQR]) (10$^9$ cells/L) | 8.1 [5.3–12.3] |
| C-reactive protein level (median [IQR]) (mg/L) | 45 [23–71] |
| Albuminemia (median [IQR]) (g/L) | 28 [24–33] |
| Perioperative resuscitation fluids | |
| Fluid infused (median [IQR]) (mL) | 3,750 [3,500–4,175] |
| Received transfusion (no. [%]) | 19 [95] |
| Red blood cells received (median [IQR]) (units) | 6 [5.5–10] |
| Blood loss (median [IQR]) (mL) | 1,600 [900–5,100] |

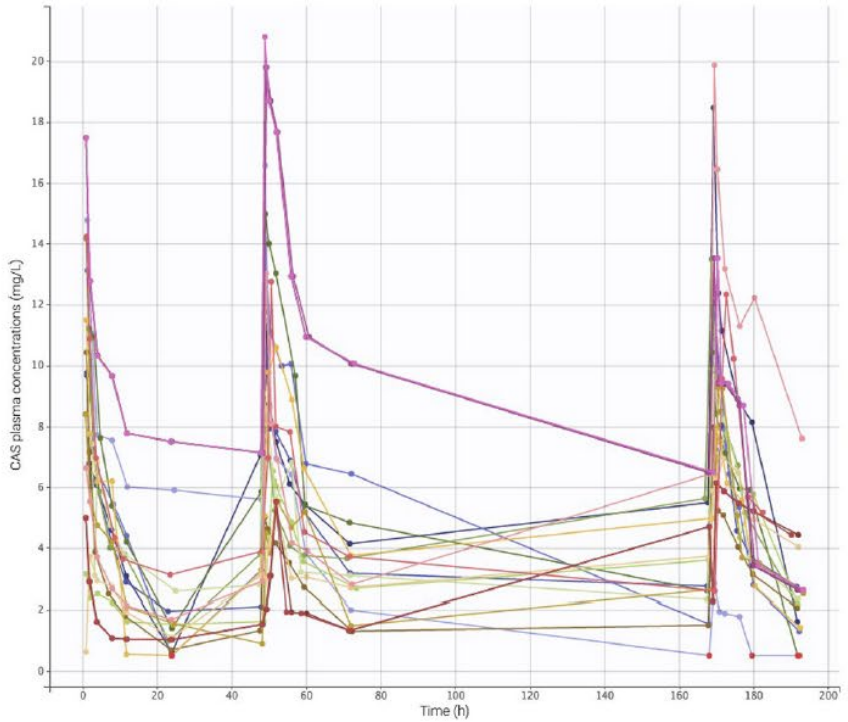
# PK/PD OF CASPOFUNGIN IN PLASMA AND PERITONEAL FLUID OF LIVER TRANSPLANT RECIPIENTS

Pressiat C et al. *Antimicrob Agents Chemother.* 2022; 66(1): e0118721

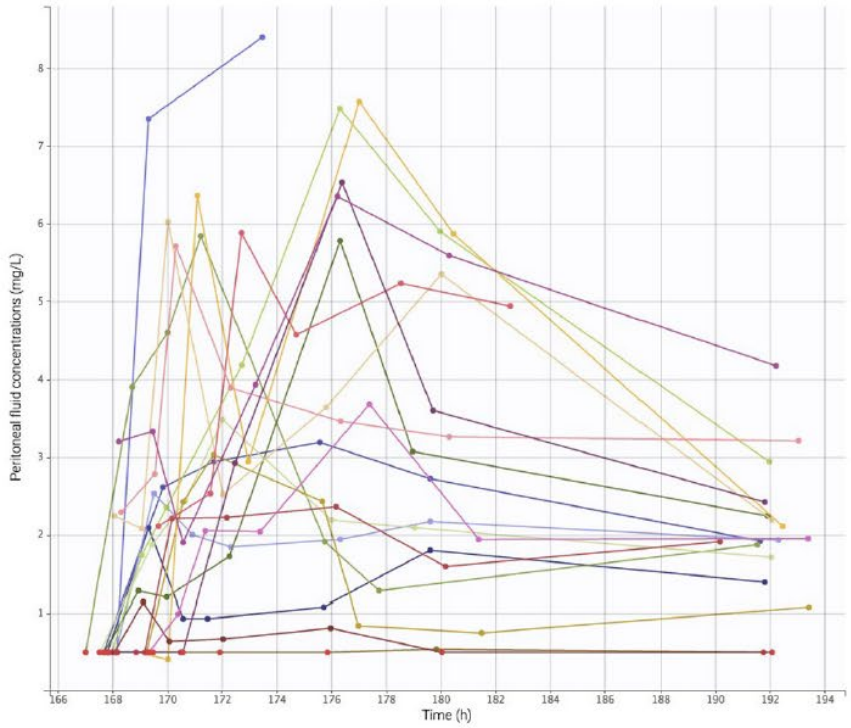
CONCENTRATION-TIME CURVES FOR CASPOFUNGIN IN PLASMA

CONCENTRATION-TIME CURVES FOR CASPOFUNGIN IN PERITONEAL FLUID

A.




B.



# PK/PD OF CASPOFUNGIN IN PLASMA AND PERITONEAL FLUID OF LIVER TRANSPLANT RECIPIENTS

Pressiat C et al. *Antimicrob Agents Chemother.* 2022; 66(1): e0118721

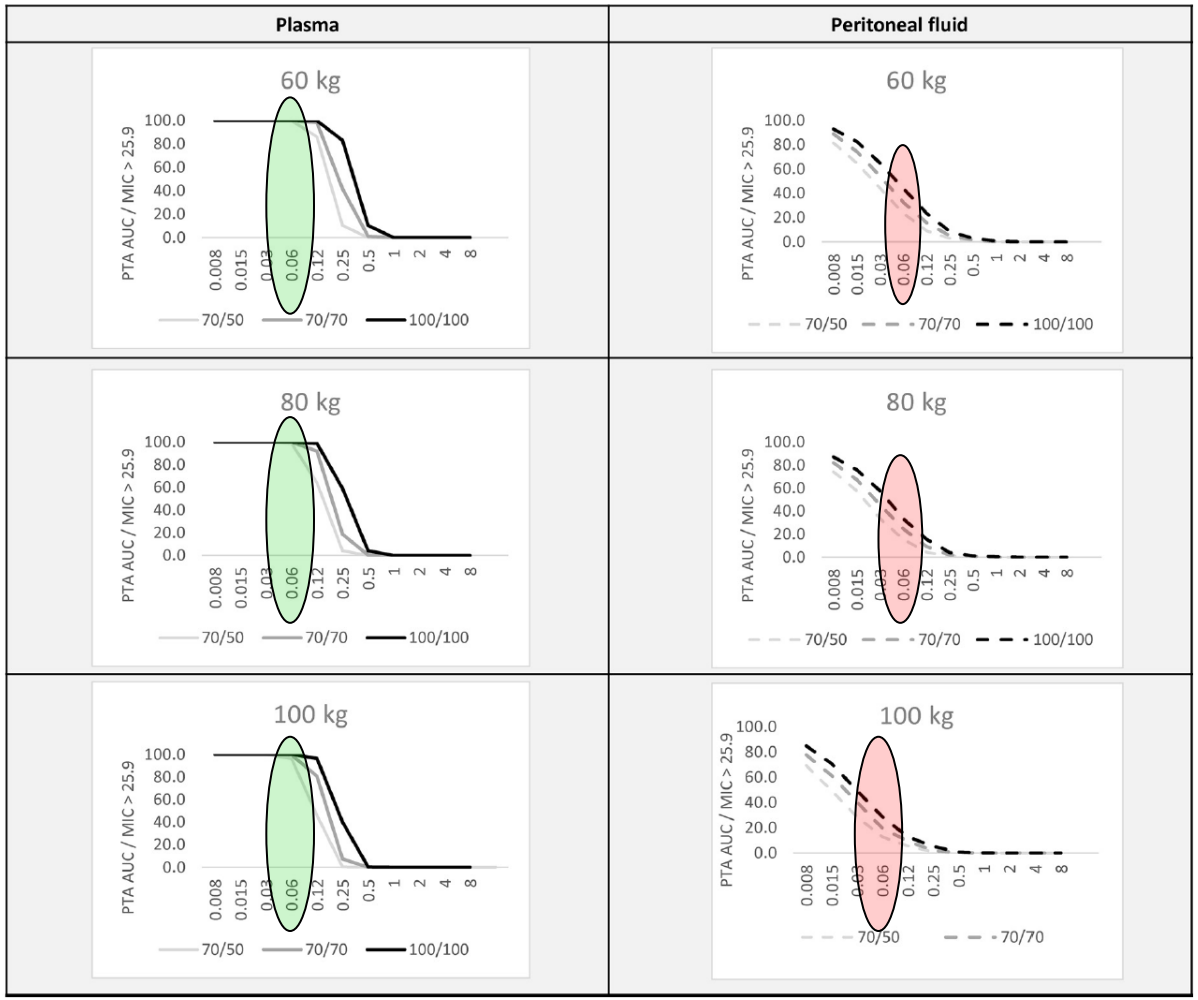
E-TEST MICs FOR CASPOFUNGIN MEASURED IN PATIENTS

| Patient | Day of administration | *Candida* species | MIC (mg/L) |
|---|---|---|---|
| P1 | D8 | *C. nivariensis* | 0.19 |
| | D10 | *C. parapsilosis* (candidemia) | 0.75 |
| P2 | D4 | *C. albicans* | 0.064 |
| P3 | D2 | *C. glabrata* | 0.19 |
| | D9 | *C. glabrata* | 0.19 |
| P5 | D2 | *C. glabrata* | 0.25 |
| | D9 | *C. glabrata* | 0.19 |
| P6 | D0 | *C. glabrata* | 0.125 |
| | D6 | *C. glabrata* | 0.19 |
| P7 | D10 | *C. glabrata* | 0.125 |
| P8 | D6 | *C. glabrata* | 0.125 |
| | | *C. albicans* | 0.047 |
| P10 | D7 | *C. albicans* | 0.125 |
| P13 | D1 | *C. albicans* | 0.094 |
| | | *C. glabrata* | 0.125 |
| P18 | D4 | *C. albicans* | 0.032 |
| | | *C. glabrata* | 0.094 |
| P19 | D4 | *C. albicans* | 0.032 |
| | | *C. tropicalis* | Not available |

# PK/PD OF CASPOFUNGIN IN PLASMA AND PERITONEAL FLUID OF LIVER TRANSPLANT RECIPIENTS

Pressiat C et al. *Antimicrob Agents Chemother*. 2022; 66(1): e0118721

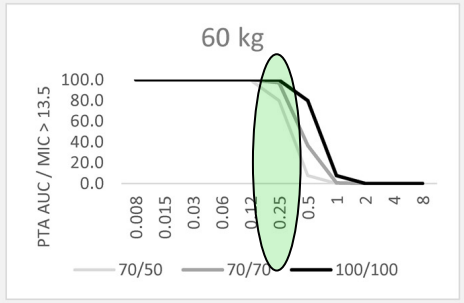
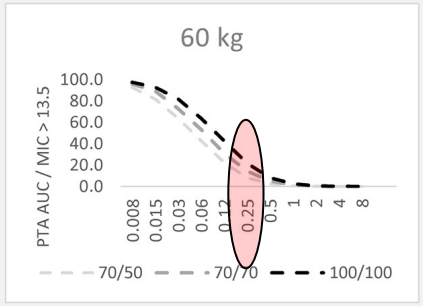
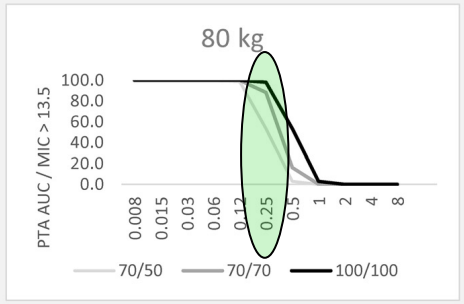
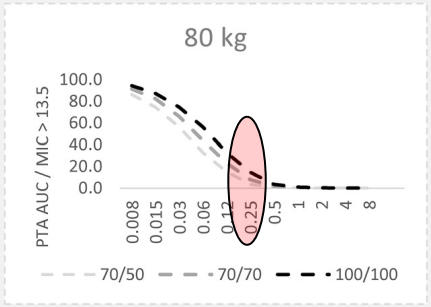
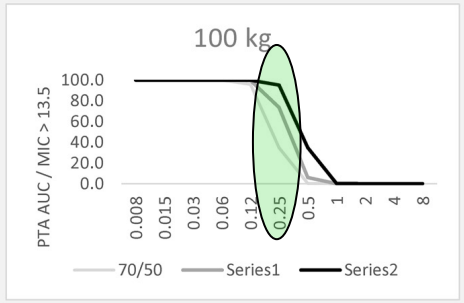
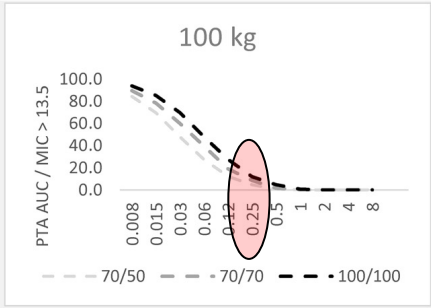
PTAs DEPENDING ON THE DOSAGE USED. FOR *Candida albicans* (AUC/MIC of > 25.9)



# PK/PD OF CASPOFUNGIN IN PLASMA AND PERITONEAL FLUID OF LIVER TRANSPLANT RECIPIENTS

Pressiat C et al. *Antimicrob Agents Chemother.* 2022; 66(1): e0118721

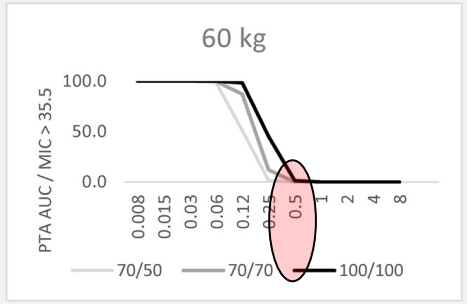
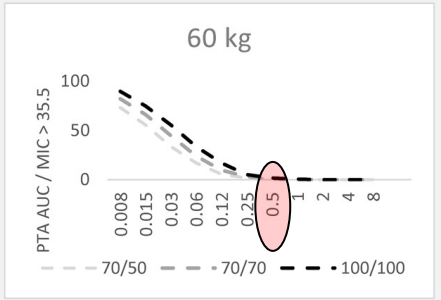
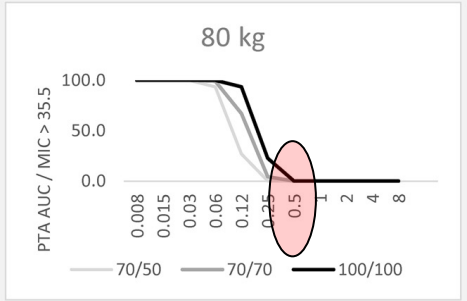
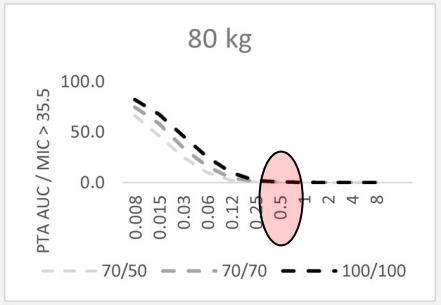
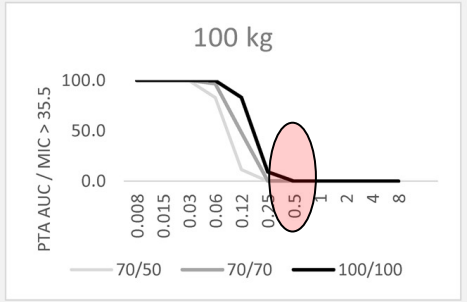
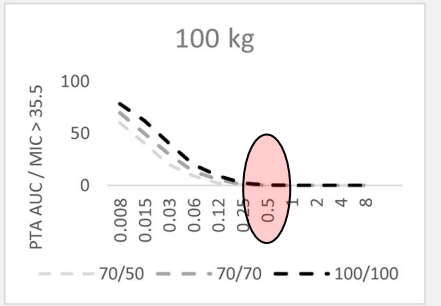
PTAs DEPENDING ON THE DOSAGE USEDFOR *Candida glabrata* (AUC/MIC of > 13.5)

| Plasma | Peritoneal fluid |
|---|---|
|  |  |
|  |  |
|  |  |

# PK/PF OF CASPOFUNGIN IN PLASMA AND PERITONEAL FLUID OF LIVER TRANSPLANT RECIPIENTS

Pressiat C et al. Antimicrob Agents Chemother. 2022 Jan 18;66(1):e0118721

PTAs DEPENDING ON THE DOSAGE USED FOR *Candida parapsilosis* (AUC/MIC of > 35.5)

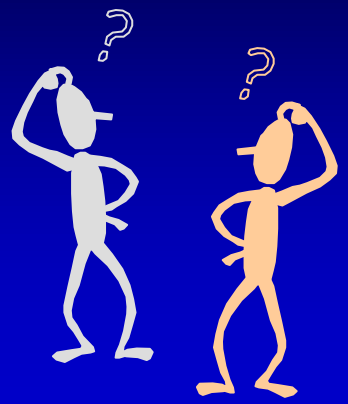
| Plasma | Peritoneal fluid |
|---|---|
|  |  |
|  |  |
|  |  |

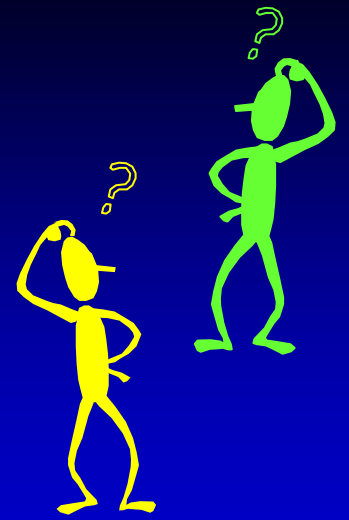
# PK/PF OF CASPOFUNGIN IN PLASMA AND PERITONEAL FLUID OF LIVER TRANSPLANT RECIPIENTS

Pressiat C et al. Antimicrob Agents Chemother. 2022 Jan 18;66(1):e0118721

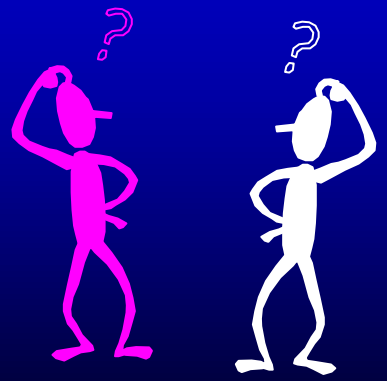
CONCLUSIONS

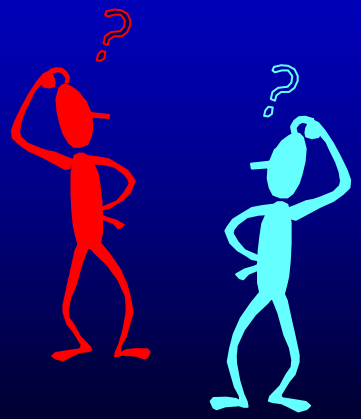
- We conclude that LT patients do not require higher doses, compared with other reference groups, regarding plasma PK parameters
- We also strongly recommend further debate regarding the peritoneal diffusion of caspofungin and the risks of the development of secondary resistance to this antifungal drug





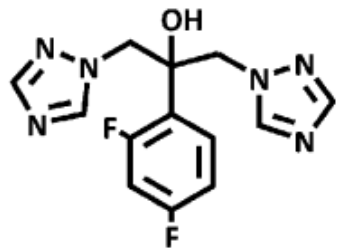
# CLINICAL PHARMACOLOGY OF TRIAZOLES



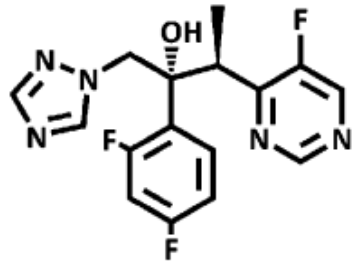


## CURRENTLY AVAILABLE TRIAZOLES

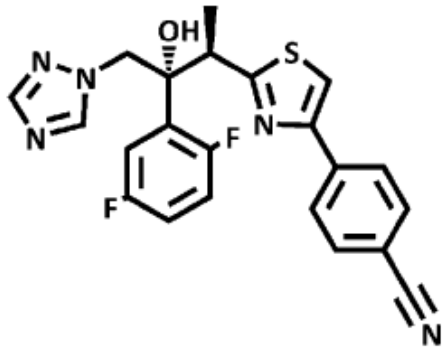
Fluconazole



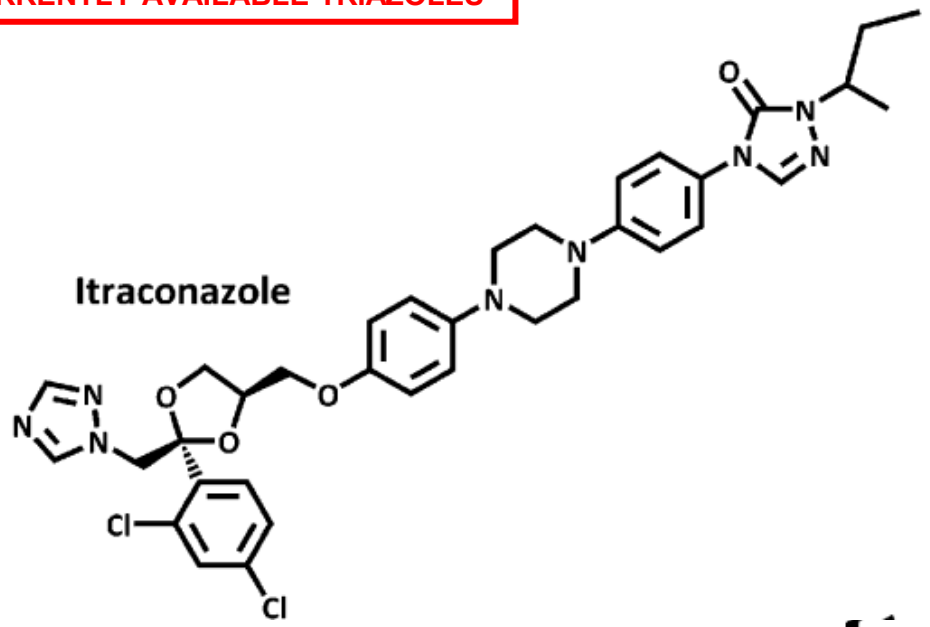
Voriconazole



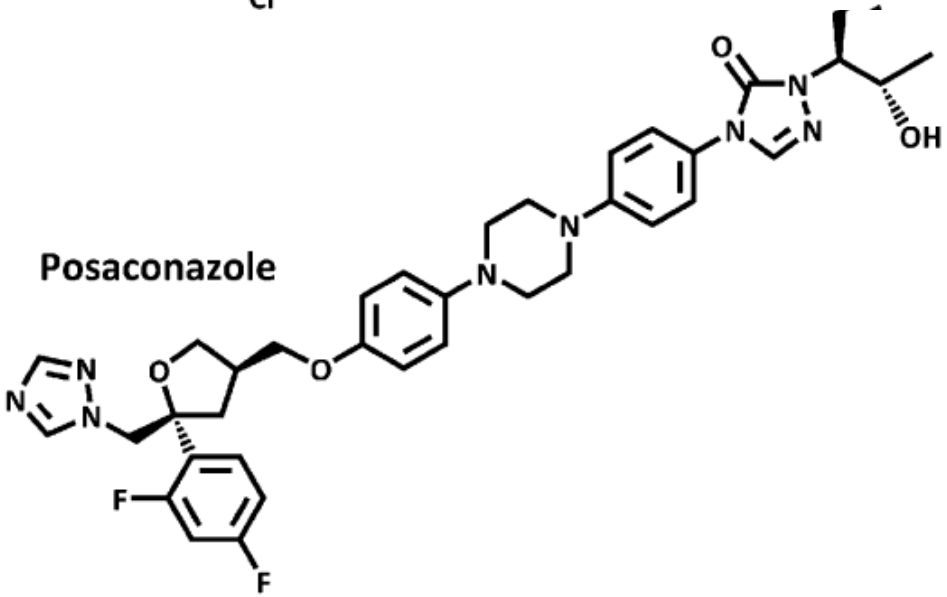
Isavuconazole



Itraconazole

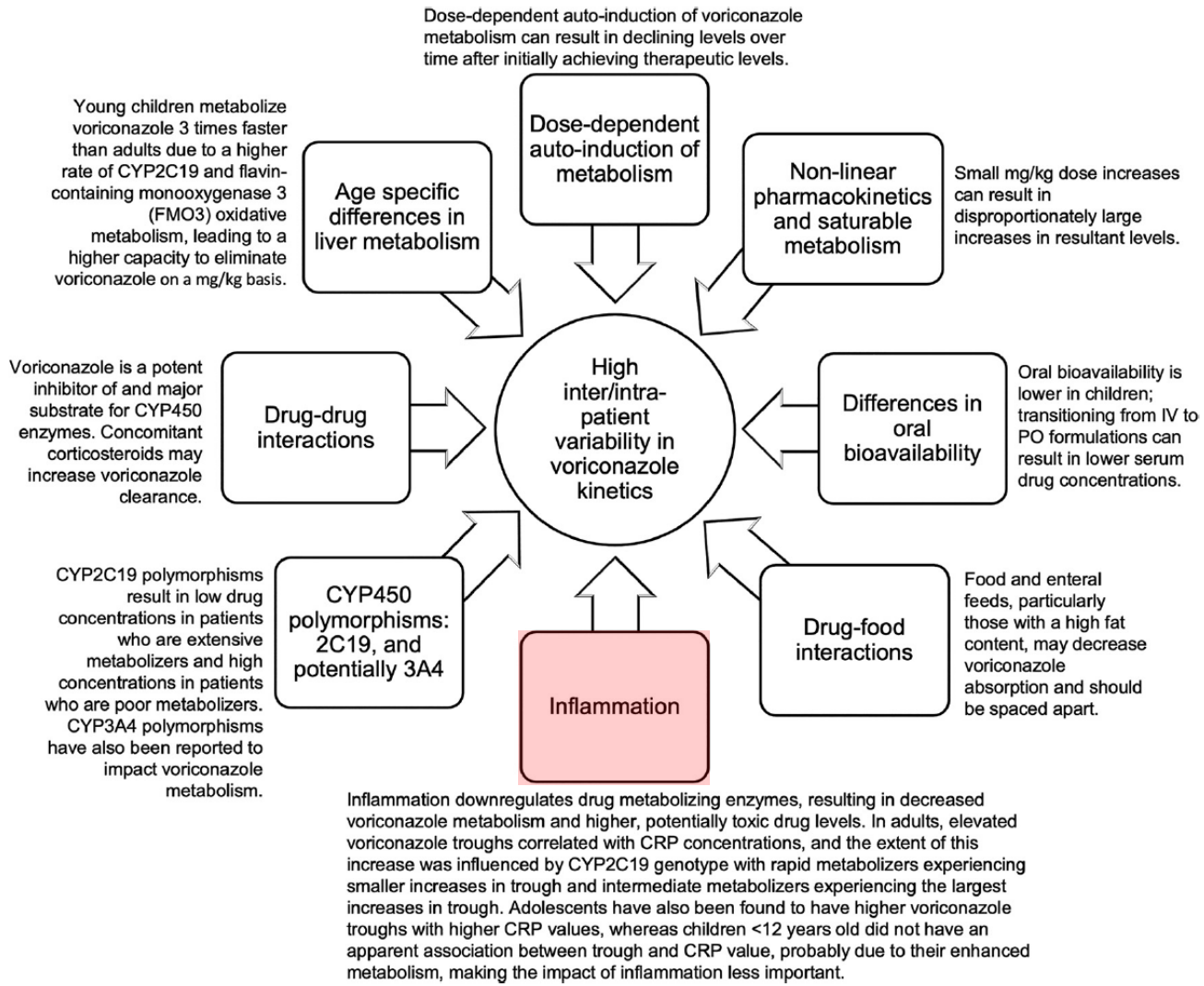


Posaconazole



Rybak JM et al. *Pharmacotherapy* 2015; 35(11): 1037–1051

# CAUSES OF INTER- AND INTRAPATIENT VARIABILITY IN VORICONAZOLE PHARMACOKINETICS.




Hsu AJ et al. Antimicrob Agents Chemother. 2022 Jul 19; 66(7): e0215621

Review > Br J Clin Pharmacol. 2022 Aug 16. doi: 10.1111/bcp.15495. Online ahead of print.

# Effects of inflammation on voriconazole levels: A systematic review

Xuejuan Li [1 2], Fangyuan Lai [2], Zhaohui Jiang [3], Meng Li [2], Zebin Chen [2], Junjie Cheng [2], Hao Cui [2], Feiqiu Wen [1]

Affiliations + expand

PMID: 35973037 DOI: 10.1111/bcp.15495

## Abstract

**Aims:** This study aimed to review the studies evaluating the effect of the inflammatory state on voriconazole (VRZ) levels.

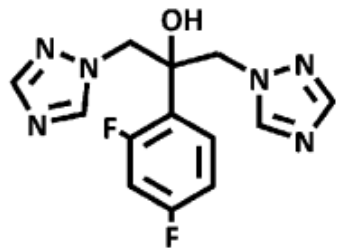
**Methods:** The study included randomized clinical trials, cohort studies, and case-control studies that focused on the influence of the inflammatory state on VRZ levels. Following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines, relevant articles published until 2021 were searched in several databases, including PubMed, Embase, Web of Science and the Cochrane Library.

**Results:** Twenty studies were included in this review, of which 15 described adult populations, three described paediatric populations, and two included both adult and paediatric populations. Seventeen studies used C-reactive protein (CRP) as an indicator of inflammation, six described a dose-response relationship for the effect of inflammation represented by CRP on VRZ concentrations, and four examined the effect of CRP on the metabolic rate of VRZ.

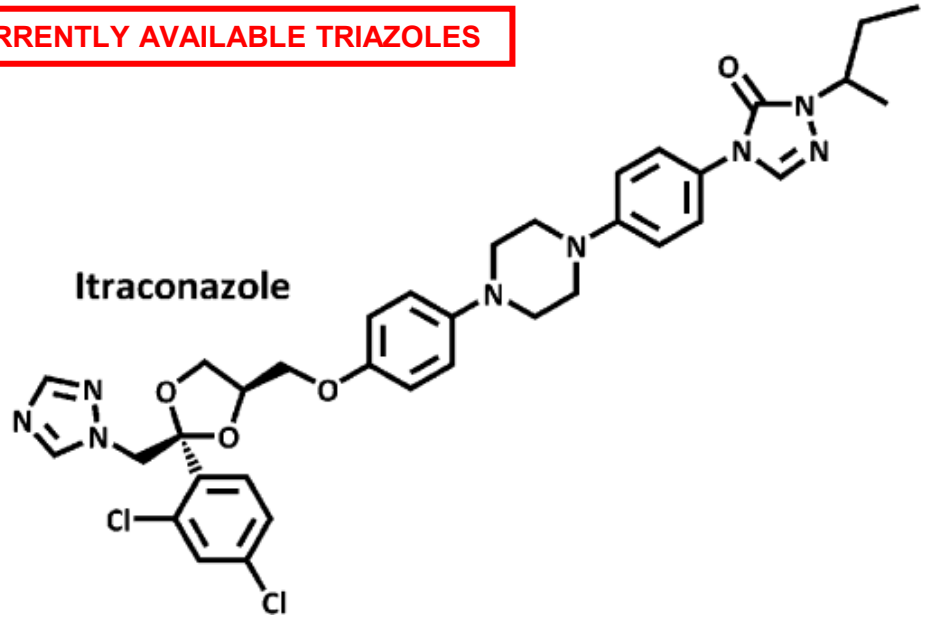
**Conclusions:** Our findings showed that the level of inflammation can significantly affect VRZ levels. However, the effect of inflammation on VRZ concentrations in children is controversial and must be analysed along with age. Clinicians dosing VRZ should take into account the patient's inflammatory state. The impact of inflammation on genotype-based dosing decisions requires further study to explain the high pharmacokinetic variability of VRZ.

## CURRENTLY AVAILABLE TRIAZOLES

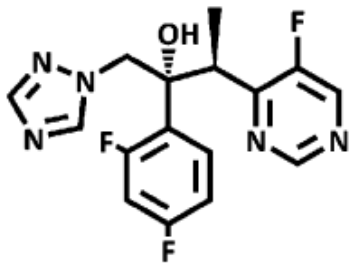
Fluconazole



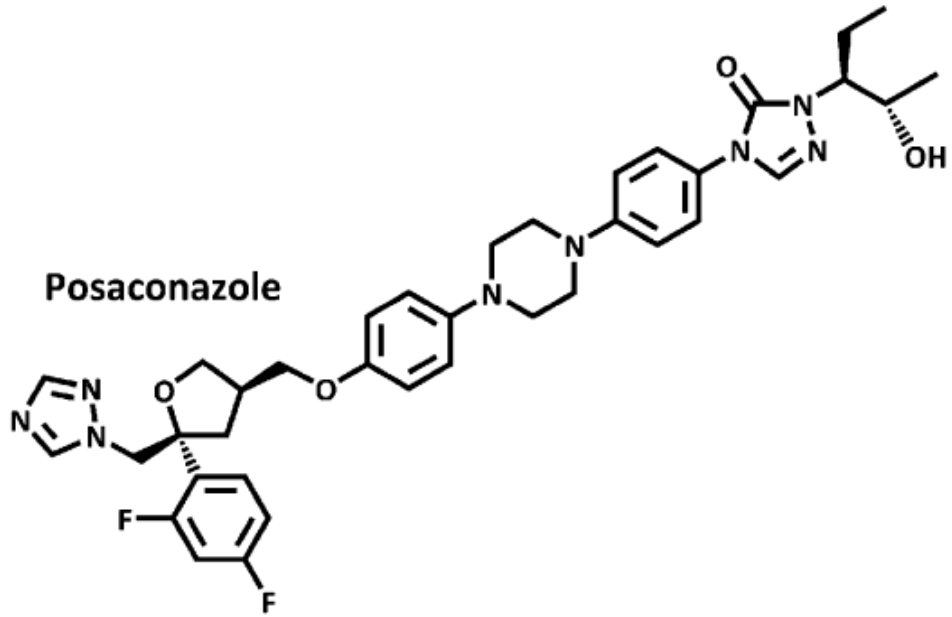
Itraconazole



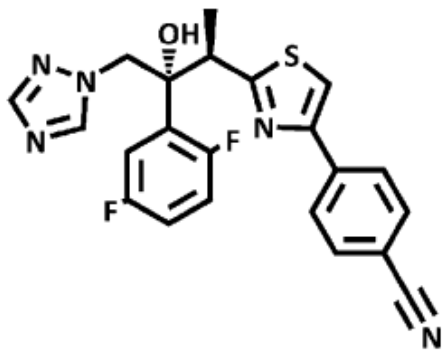
Voriconazole



Posaconazole



Isavuconazole



Rybak JM et al. *Pharmacotherapy* 2015; 35(11): 1037–1051

# POSACONAZOLE SERUM DRUG LEVELS ASSOCIATED WITH PSEUDOHYPERALDOSTERONISM

## Nguyen MVH et al. *Clin Infect Dis* 2020; 70(12): 2593–8

**DIFFERENCES AMONG PATIENTS WITH AND WITHOUT POSACONAZOLE-INDUCED PSEUDOHYPERALDOSTERONISM**

| Variable | PIPH(–) (n = 53) | PIPH(+) (n = 16) | *P* Value |
|---|---|---|---|
| Male, n (%) | 25 (47.2) | 8 (50.0) | .84 |
| Age, median (IQR), y | 44.7 (34.9–57.0) | 61.1 (47.3–69.6) | .007 |
| Ethnicity, n (%) | | | .77 |
| White | 31 (58.5) | 10 (62.5) | … |
| Hispanic | 13 (24.5) | 3 (18.8) | … |
| Asian | 6 (11.3) | 3 (18.8) | … |
| African American | 3 (5.7) | 0 (0.0) | … |
| Body mass index, median (IQR), kg/m$^2$ | 24.0 (21.3–28.1) | 26.2 (22.3–31.9) | .32 |
| Calcineurin inhibitor, n (%) | 24 (45) | 2 (13) | 0.02 |
| Systemic corticosteroid, n (%) | 5 (9) | 0 (%) | 0.58 |
| Diabetes mellitus, n (%) | 6 (11.3) | 2 (12.5) | >.99 |
| Hypertension,[a] n (%) | 17 (32.1) | 11 (68.8) | .009 |
| Creatinine clearance, median (IQR), mL/min | 102.7 (78.0–126.6) | 91.1 (66.6–113.6) | .41 |
| Indicated for antifungal treatment, n (%)[b] | 13 (24.5) | 10 (62.5) | .005 |
| Posaconazole daily dose, median (IQR), mg/kg | 4.7 (3.9–5.4) | 4.1 (3.1–4.9) | .11 |
| Serum bicarbonate change, median (IQR), mmol/L | –1 (–3-0) | 0 (–1.5–3) | .06 |
| Random serum posaconazole concentration, median (IQR), μg/mL | 1.2 (0.8–1.8) | 3.0 (2.1–4.1) | <.0001 |

Abbreviations: IQR, interquartile range; PIPH, posaconazole-induced pseudohyperaldosteronism.

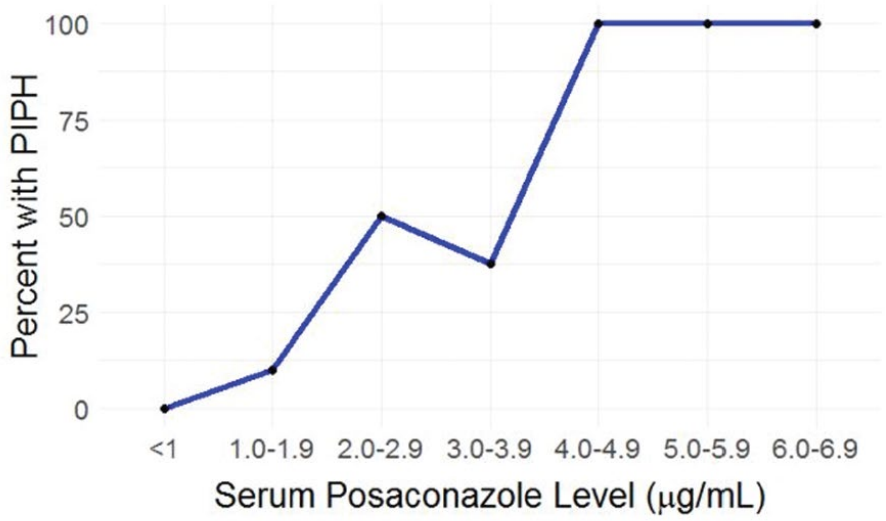
[a]Hypertension was present prior to starting posaconazole.

[b]This variable indicates that posaconazole was prescribed for antifungal treatment as opposed to prophylaxis of an active infection.

# POSACONAZOLE SERUM DRUG LEVELS ASSOCIATED WITH PSEUDOHYPERALDOSTERONISM

Nguyen MVH et al. *Clin Infect Dis* 2020; 70(12): 2593–8

SERUM POSACONAZOLE LEVELS AND ASSOCIATION WITH THE DEVELOPMENT OF POSACONAZOLE-INDUCED PSEUDOHYPERALDOSTERONISM (PIPH)

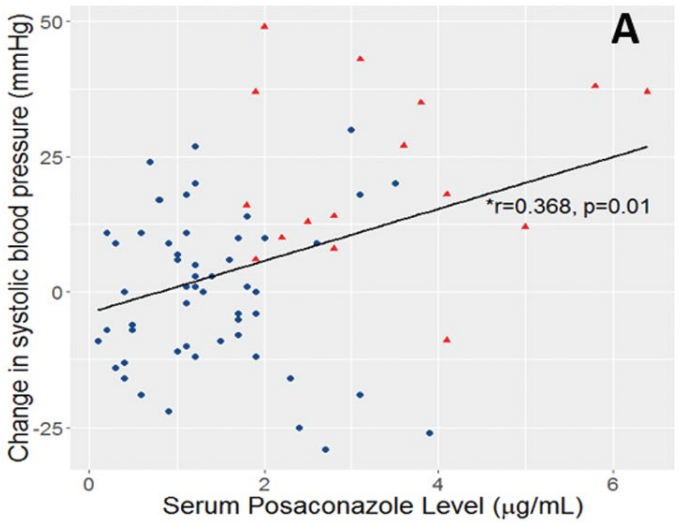


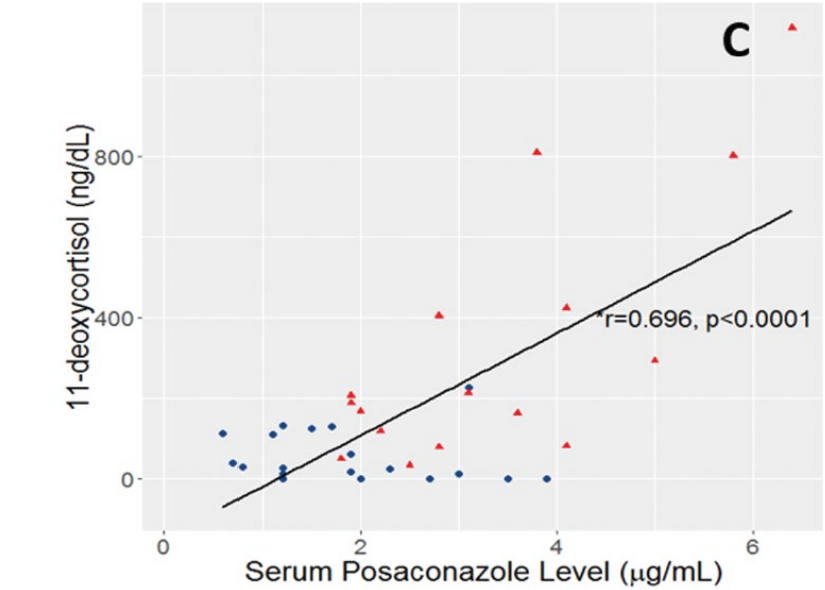

| Serum posaconazole level | #Pts without PIPH | #Pts with PIPH | Percent of patients with PIPH | Confidence interval | Fisher's Exact Test P value |
|---|---|---|---|---|---|
| <1 | 16 | 0 | 0% | 0.0-20.6% | NA |
| 1.0-1.9 | 27 | 3 | 10% | 2.1-26.5% | 0.54 |
| 2.0-2.9 | 5 | 5 | 50% | 18.7-81.3% | 0.004 |
| 3.0-3.9 | 5 | 3 | 37.50% | 8.5-75.5% | 0.03 |
| 4.0-4.9 | 0 | 2 | 100% | 15.8-100% | 0.007 |
| 5.0-5.9 | 0 | 2 | 100% | 15.8-100% | 0.007 |
| 6.0-6.9 | 0 | 1 | 100% | 2.5-100% | 0.06 |

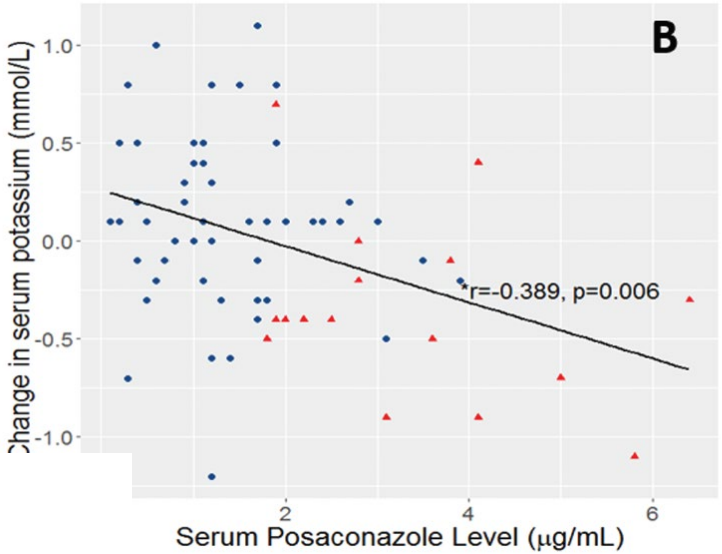
# POSACONAZOLE SERUM DRUG LEVELS ASSOCIATED WITH PSEUDOHYPERALDOSTERONISM

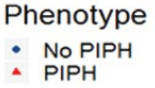
Nguyen MVH et al. *Clin Infect Dis* 2020; 70(12): 2593–8

**CORRELATION OF POSACONAZOLE WITH CLINICAL AND LABORATORY VARIABLES**



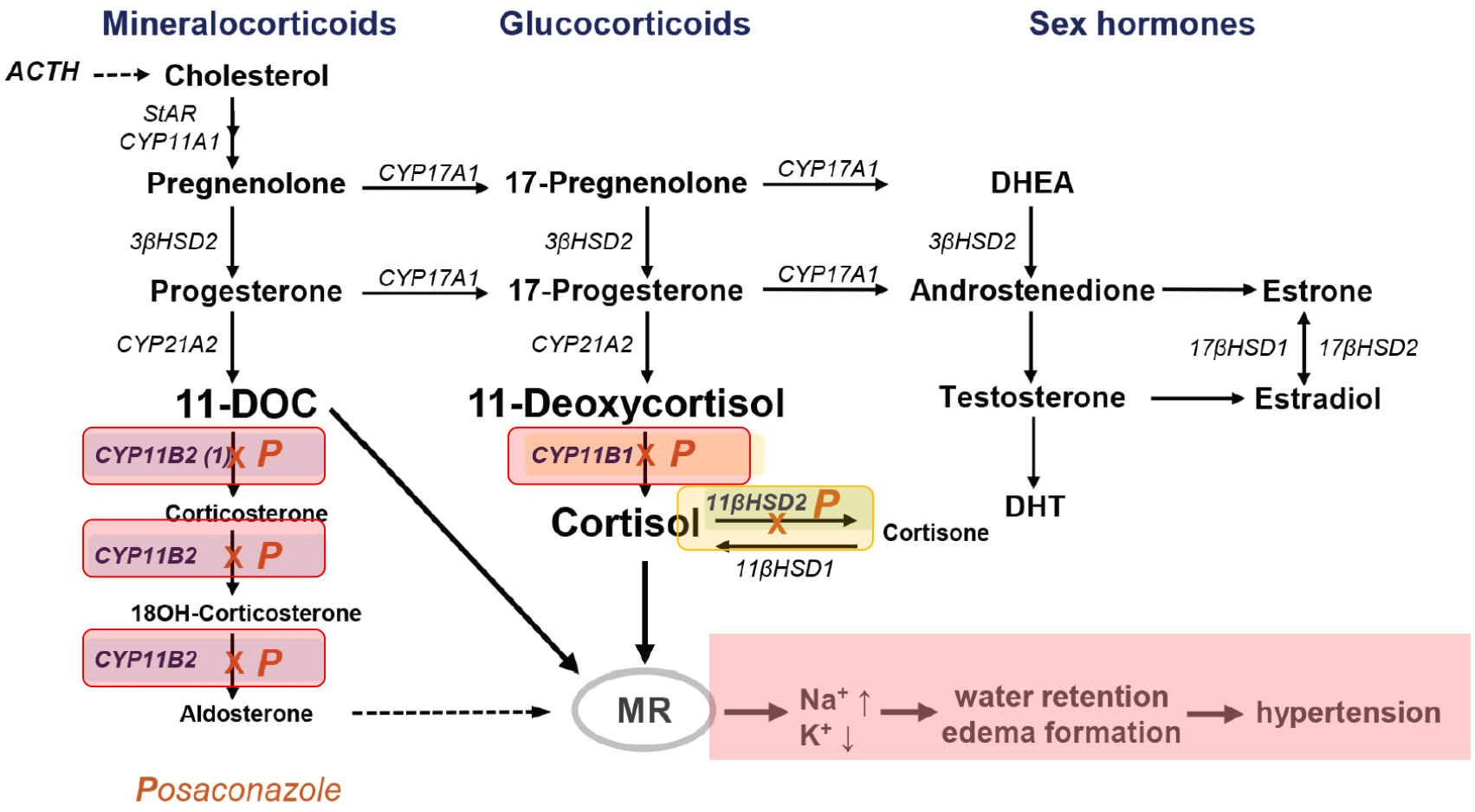





# POSACONAZOLE SERUM DRUG LEVELS ASSOCIATED WITH PSEUDOHYPERALDOSTERONISM

Nguyen MVH et al. *Clin Infect Dis* 2020; 70(12): 2593–8

PRIMARY PATHWAY OF STEROIDOGENESIS AND ENZYME INHIBITION BY POSACONAZOLE (P). INHIBITION OF CYP11B AND 11BHSD2 LEADS TO EXCESS 11-DEOXYCORTICOSTERONE AND CORTISOL, RESPECTIVELY. ACTIVATION OF THE MR BY THESE HORMONES RESULTS IN HYPERTENSION AND HYPOKALEMIA



The Journal of Steroid Biochemistry and Molecular Biology
Volume 199, May 2020, 105605

# Molecular mechanisms of posaconazole- and itraconazole-induced pseudohyperaldosteronism and assessment of other systemically used azole antifungals

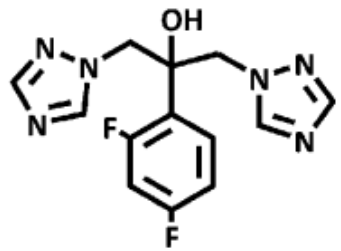
Katharina R. Beck [a] ✉, Lucija Telisman [a] ✉, Chris J. van Koppen [b] ✉, George R. Thompson III [c] ✉, Alex Odermatt [a] ✉

## Highlights

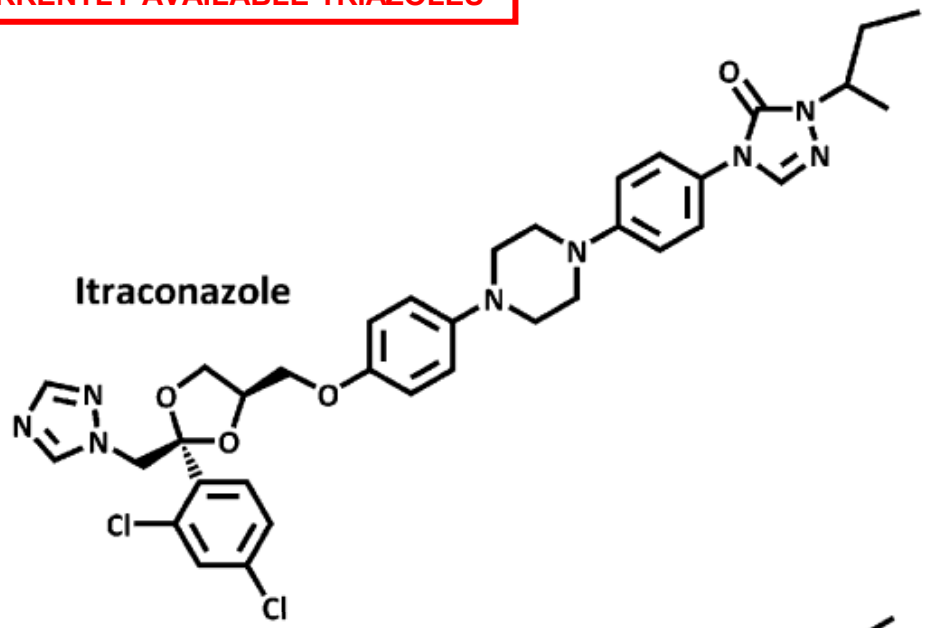
- Posaconazole and itraconazole can cause hypertension and hypokalemia.
- Posaconazole preferably inhibits CYP11B1 and itraconazole preferably 11β-HSD2.
- Voriconazole, fluconazole and isavuconazole neither inhibit CYP11B1 nor 11β-HSD2.

## CURRENTLY AVAILABLE TRIAZOLES

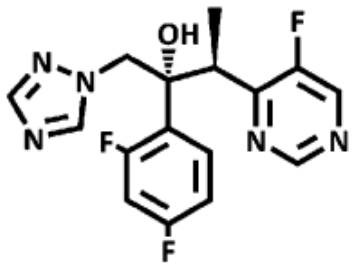
Fluconazole



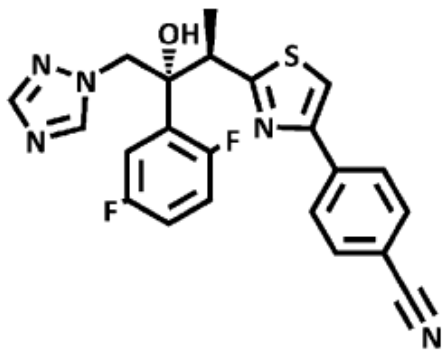
Itraconazole



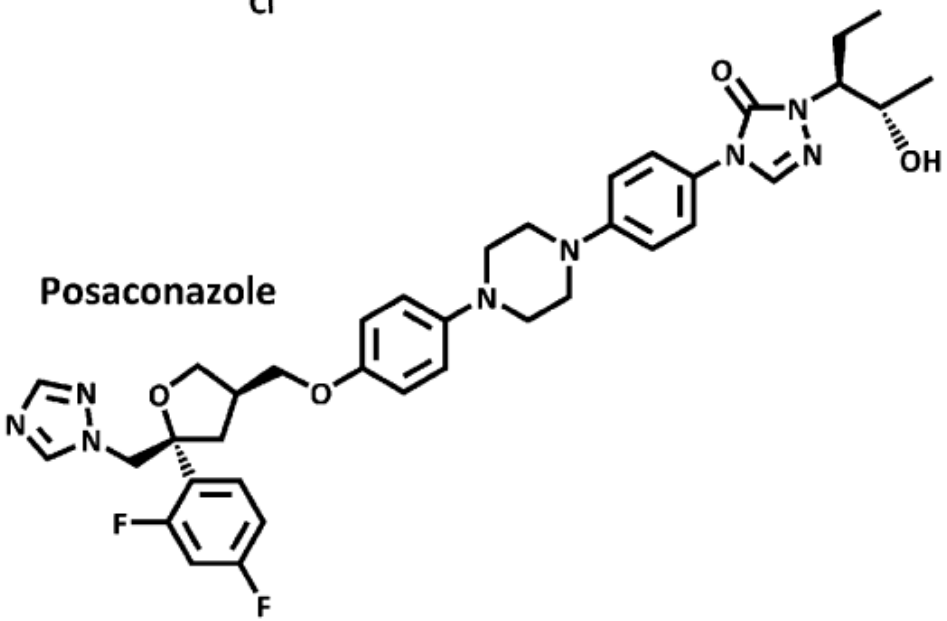
Voriconazole



Isavuconazole



Posaconazole



Rybak JM et al. *Pharmacotherapy* 2015; 35(11): 1037–1051

# PopPK AND PD TARGET ATTAINMENT OF ISAVUCONAZOLE vs. *A. fumigatus* AND *A. flavus* IN ADULT PATIENTS WITH IFDs: SHOULD TDM FOR ISAVUCONAZOLE BE CONSIDERED AS MANDATORY AS FOR THE OTHER MOLD-ACTIVE AZOLES?

Cojutti PG et al. Pharmaceutics 2021, 13, 2099. https://doi.org/10.3390/pharmaceutics13122099

## CHARACTERISTICS OF THE STUDY POPULATION (N = 50)

| Variable | Median or Count | Range or % |
|---|---|---|
| Age (years) | 61.5 | 51.3–72.0 |
| Gender (male/female) | 31/19 | 62/38 |
| Body weight (kg) | 65.0 | 55.5–71.5 |
| Albumin (g/L) | 35.0 | 28.4–40.0 |
| Total bilirubin (mg/dL) | 0.28 | 0.2–0.4 |
| Gamma-glutamyltransferase (IU/L) | 70.0 | 42.0–173.0 |
| Alanine-aminotransferase (IU/L) | 21.0 | 15.0–38.0 |
| Aspartate-aminotransferase (IU/L) | 20.0 | 15.0–31.0 |
| Type of infections | | |
| Invasive pulmonary aspergillosis | 40 | 80.0 |
| Invasive fusariosis | 2 | 4.0 |
| Cerebral mucormycosis | 1 | 2.0 |
| Scedosporium osteomyelitis | 1 | 2.0 |
| Aspergillus brain abscess | 1 | 2.0 |
| Invasive fungal disease, not specified | 5 | 10.0 |
| Underlying disease | | |
| Oncohematological malignancy | 25 | 50.0 |
| Nosocomial pneumonia | 11 | 22.0 |
| Immunosuppression° | 9 | 18.0 |
| Other | 5 | 10.0 |

| Variable | Median or Count | Range or % |
|---|---|---|
| Isavuconazole treatment | | |
| First-line or switch from other azoles | 45/5 | 90/10 |
| Dose (mg) | 200 | 200–200 |
| Total number of $C_{trough}$ | 175 | |
| $C_{trough}$ (mg/L) | 3.68 | 2.07–5.38 |
| Total number of $C_{peak}$ | 24 | |
| $C_{peak}$ (mg/L) | 4.67 | 3.78–5.96 |
| Number of TDM instances | 2.0 | 1.0–4.0 |
| Treatment duration (days) * | 48.0 | 19.0–91.0 |
| Clinical outcome at end of treatment * | | |
| Successful treatment | 32 | 68.1 |
| Treatment failure | 12 | 25.5 |
| Dead for other reasons | 3 | 6.4 |

$C_{trough}$, isavuconazole trough (minimum) concentration; $C_{peak}$, isavuconazole peak (maximum) concentration. * available only for patients who completed treatment course ($n$ = 47). Immunosuppression included: solid organ transplant, solid malignant neoplasms and rheumatological diseases.

# PopPK AND PD TARGET ATTAINMENT OF ISAVUCONAZOLE vs. *A. fumigatus* AND *A. flavus* IN ADULT PATIENTS WITH IFDs: SHOULD TDM FOR ISAVUCONAZOLE BE CONSIDERED AS MANDATORY AS FOR THE OTHER MOLD-ACTIVE AZOLES?

Cojutti PG et al. Pharmaceutics 2021, 13, 2099. https://doi.org/10.3390/pharmaceutics13122099

UNIVARIATE AND MULTIVARIATE MIXED-EFFECT LINEAR REGRESSION ANALYSIS OF CLINICAL VARIABLES ASSOCIATED WITH ISAVUCONAZOLE $C_{TROUGH}$

| | Univariate Analysis | | Multivariate Analysis | |
|---|---|---|---|---|
| Variables | Unstandardized β-Coefficient (95% CI) | *p*-Value | Unstandardized β-coefficient (95% CI) | *p*-Value |
| Age (years) | 0.037 (0.066–0.007) | 0.022 | 0.037 (0.061–0.013) | <0.001 |
| Weight (kg) | −0.029 (0.006–0.064) | 0.106 | | |
| Gender (male vs. female) | 0.099 (6.986–6.788) | 0.977 | | |
| Dose/kg daily (mg/kg) | 0.815 (1.164–0.466) | 0.010 | 0.402 (0.819–0.016) | 0.067 |
| Days from starting therapy (days) | 0.001 (0.007–0.005) | 0.747 | | |
| Albumin (g/L) | 0.034 (0.087–0.019) | 0.214 | | |
| Total bilirubin (mg/dL) | −0.346 (0.034–0.726) | 0.078 | | |
| ALT (IU/L) | −0.001 (0.007–0.009) | 0.730 | | |
| AST (IU/L) | −0.008 (-0.002–0.004) | 0.230 | | |
| γ-GT (IU/L) | 0.003 (0.005–0.001) | 0.022 | −0.0004 (0.002–0.002) | 0.751 |
| Cotreatment with CYP3A4 inhibitors | 2.39 (3.337–1.443) | 0.039 | 2.154 (3.248–1.060) | 0.018 |

# PopPK AND PD TARGET ATTAINMENT OF ISAVUCONAZOLE vs. *A. fumigatus* AND *A. flavus* IN ADULT PATIENTS WITH IFDs: SHOULD TDM FOR ISAVUCONAZOLE BE CONSIDERED AS MANDATORY AS FOR THE OTHER MOLD-ACTIVE AZOLES?

Cojutti PG et al. Pharmaceutics 2021, 13, 2099. https://doi.org/10.3390/pharmaceutics13122099

PROBABILITY OF ACHIEVEMENT OF ISAVUCONAZOLE TROUGH CONCENTRATIONS ($C_{TROUGH}$) < 1.0, 1.0–5.13, >5.13 MG/L

| | LD | MD of 100 mg Daily | | | | | MD of 200 mg Daily | | | | | MD of 300 mg Daily | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Isavuconazole $C_{trough}$ (mg/L) | Day 2 | Day 7 | Day 14 | Day 21 | Day 28 | Day 60 | Day 7 | Day 14 | Day 21 | Day 28 | Day 60 | Day 7 | Day 14 | Day 21 | Day 28 | Day 60 |
| <1.0 | 1.7 | 21.7 | 16.4 | 12.9 | 12.0 | 11.7 | 4.1 | 1.8 | 1.3 | 1.0 | 1.1 | 0.8 | 0.2 | 0.2 | 0.1 | 0.1 |
| 1.0–5.13 | 85.2 | 76.4 | 81.5 | 84.6 | 83.8 | 81.1 | 84.3 | 80.4 | 73.6 | 71.3 | 59.7 | 76.9 | 60.6 | 48.6 | 46.9 | 26.6 |
| >5.13 | 13.1 | 1.9 | 2.1 | 2.5 | 4.2 | 7.2 | 11.6 | 17.8 | 25.1 | 27.7 | 39.2 | 22.3 | 39.2 | 51.2 | 53.0 | 73.2 |

LD, loading dose (200 mg q8 h for 48 h); MD, maintenance dose.

# PopPK AND PD TARGET ATTAINMENT OF ISAVUCONAZOLE vs. *A. fumigatus* AND *A. flavus* IN ADULT PATIENTS WITH IFDs: SHOULD TDM FOR ISAVUCONAZOLE BE CONSIDERED AS MANDATORY AS FOR THE OTHER MOLD-ACTIVE AZOLES?

Cojutti PG et al. Pharmaceutics 2021, 13, 2099. https://doi.org/10.3390/pharmaceutics13122099

CUMULATIVE FRACTION OF RESPONSE (CFR) OF THREE ISAVUCONAZOLE DOSING REGIMENS AGAINST EUCAST MIC DISTRIBUTION OF *A. fumigatus* (n = 426) and *A. flavus* (n = 434)

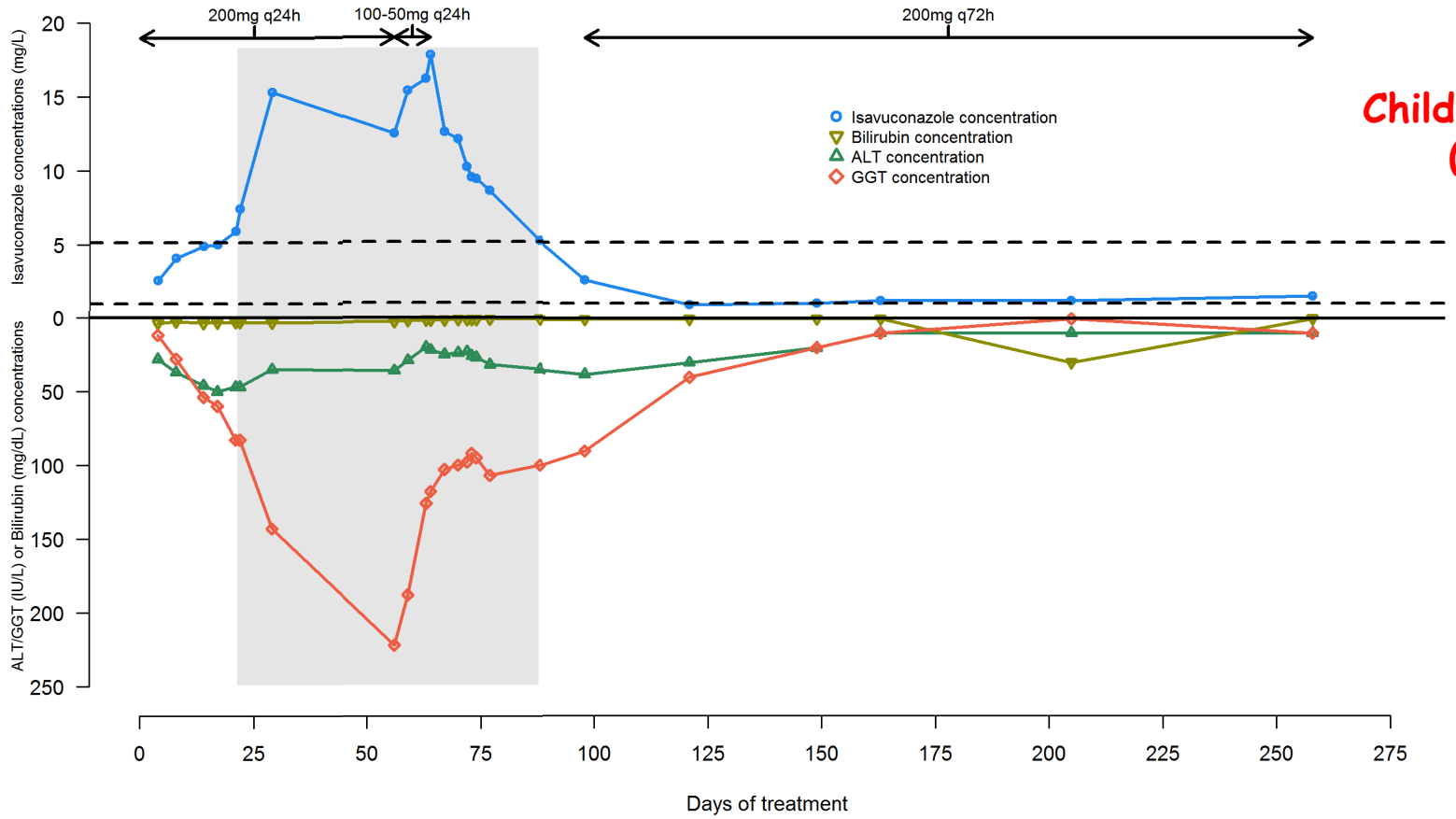
| | *Aspergillus fumigatus* | | | | | | *Aspergillus flavus* | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Isavuconazole Dosing Regimens** | **Day 2** | **Day 7** | **Day 14** | **Day 21** | **Day 28** | **Day 60** | **Day 2** | **Day 7** | **Day 14** | **Day 21** | **Day 28** | **Day 60** |
| LD + MD of 100 mg daily | 94.7 | 82.7 | 84.5 | 88.8 | 89.9 | 89.5 | 90.0 | 65.6 | 67.9 | 75.4 | 76.2 | 78.3 |
| LD + MD of 200 mg daily | 94.7 | 94.5 | 95.4 | 95.8 | 96.2 | 96.6 | 90.0 | 90.2 | 92.4 | 94.4 | 96.6 | 96.8 |
| LD + MD of 300 mg daily | 94.7 | 95.8 | 96.7 | 97.2 | 97.3 | 97.9 | 90.0 | 94.5 | 98.1 | 98.9 | 98.9 | 99.1 |

LD, loading dose (200 mg q8 h for 48 h); MD, maintenance dose.

# SUCCESSFUL AND SAFE REAL-TIME TDM-GUIDED TREATMENT OF INVASIVE PULMONARY AND CEREBRAL ASPERGILLOSIS USING LOW-DOSE ISAVUCONAZOLE IN A PATIENT WITH PRIMARY BILIARY CIRRHOSIS. GRAND ROUND/A CASE STUDY

Cojutti PG, Rinaldi M, Giannella M, Viale P, Pea F. *Ther Drug Monitor* 2022 in press

TEMPORAL TREND OF ISAVUCONAZOLE CONCENTRATIONS (UPPER PANEL) AND OF ALANINE-AMINOTRANSFERASE (ALT), GAMMA-GLUTAMYLTRANSFERASE (GGT) AND BILIRUBIN CONCENTRATIONS (LOWER PANEL).

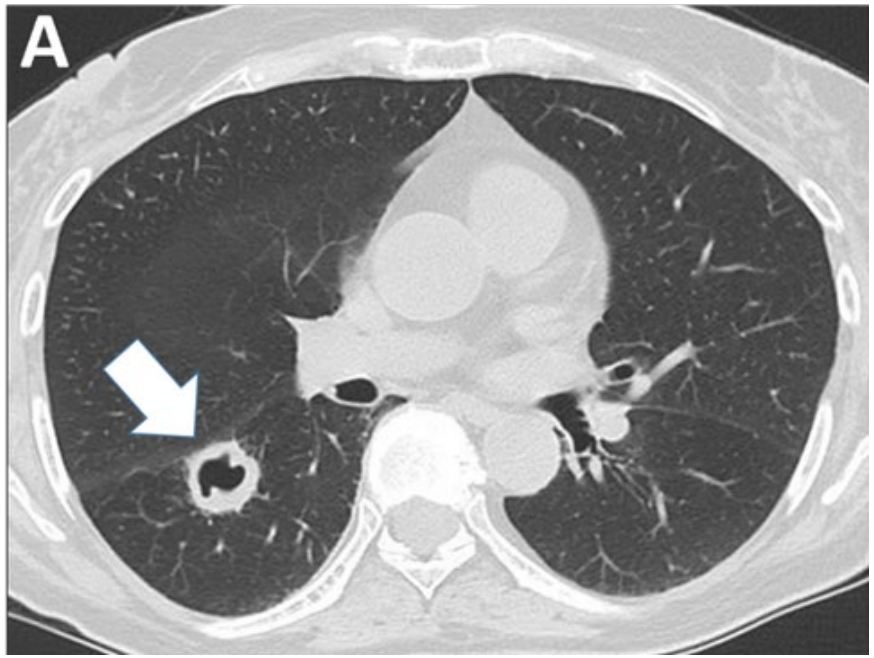



**Child-Pugh (CP) class B-8 (MELD score 18)**

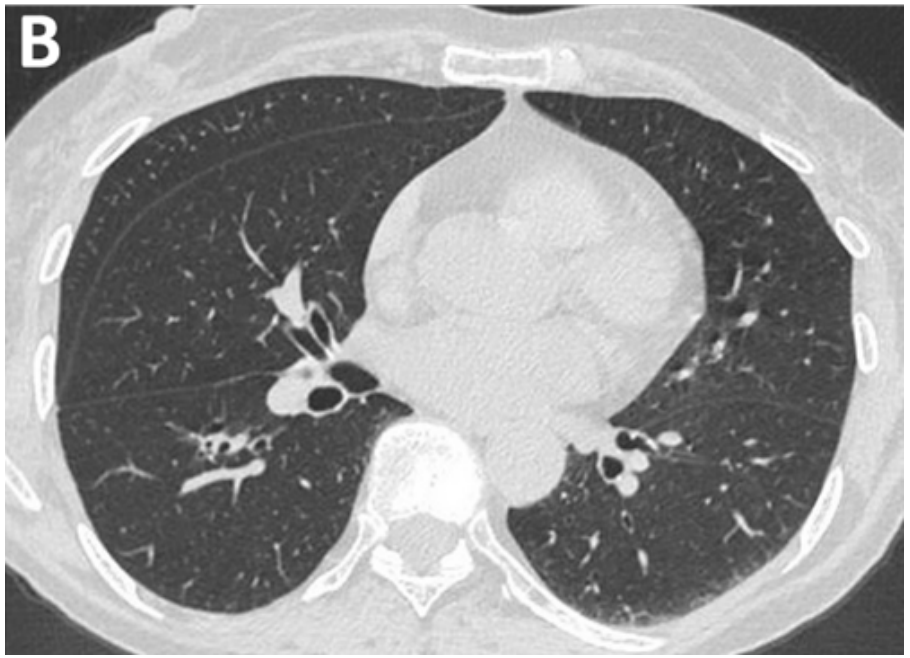
# SUCCESSFUL AND SAFE REAL-TIME TDM-GUIDED TREATMENT OF INVASIVE PULMONARY AND CEREBRAL ASPERGILLOSIS USING LOW-DOSE ISAVUCONAZOLE IN A PATIENT WITH PRIMARY BILIARY CIRRHOSIS. GRAND ROUND/A CASE STUDY

Cojutti PG, Rinaldi M, Giannella M, Viale P, Pea F. *Ther Drug Monitor* 2022 in press

CHEST CT SCAN AT BASELINE




CHEST CT SCAN AT THE END OF ISAVUCONAZOLE TREATMENT (DAY 258)



# ISAVUCONAZOLE PLASMA CONCENTRATIONS IN CRITICALLY ILL PATIENTS DURING EXTRACORPOREAL MEMBRANE OXYGENATION

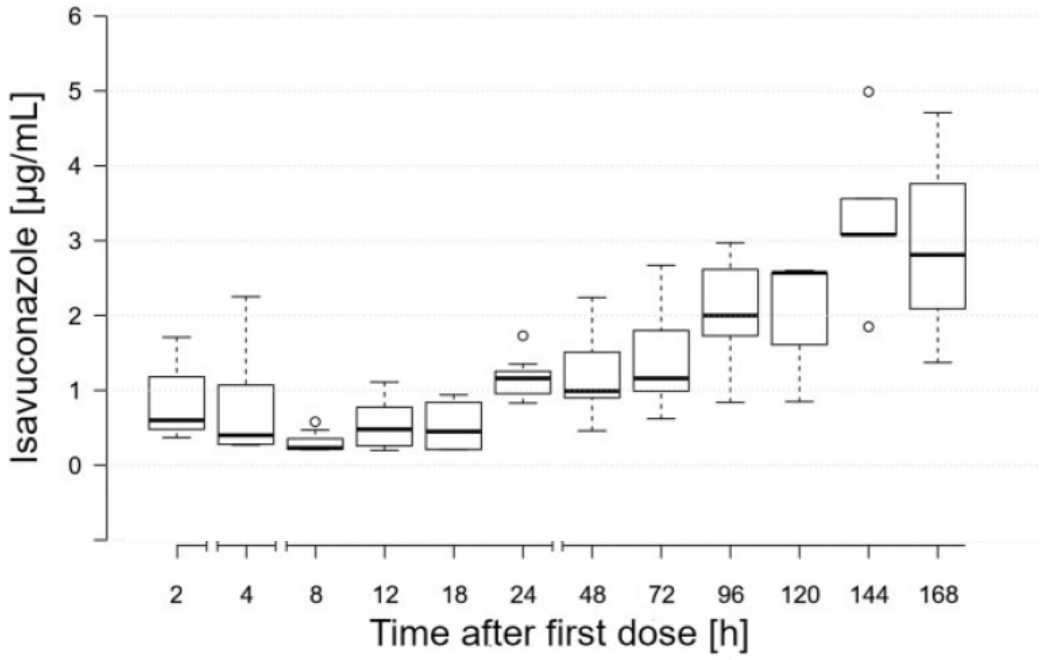
Kriegl L et al. J Antimicrob Chemother; 2022 Sept, 77: 2500–2505

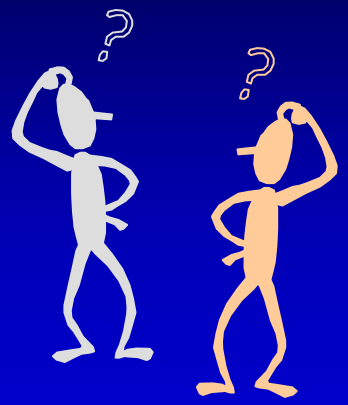
**CLINICAL AND LABORATORY CHARACTERISTICS OF THE STUDY POPULATION OF SEVEN PATIENTS RECEIVING ISAVUCONAZOLE AND ECMO**

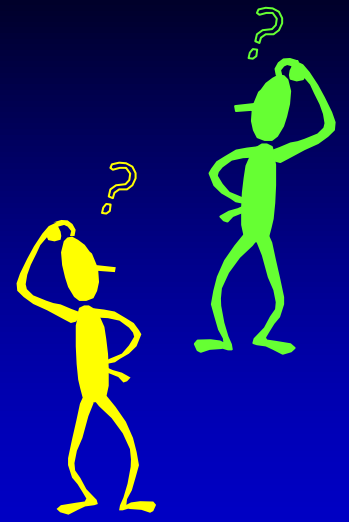
| Variable | Patients ($n=7$) |
|---|---|
| Demographic variables | |
| Age (years) [IQR] | 58 [50–62] |
| Female gender, *n* (%) | 3 (43%) |
| BMI (kg/m$^2$) [IQR] | 29.8 [26.9–35.2] |
| Comorbidities, *n* (%) | |
| No co-existing conditions | 3 (43%) |
| Thromboembolic disease | 1 (14%) |
| Collagenosis | 1 (14%) |
| Asthma | 1 (14%) |
| Aortic valve stenosis | 1 (14%) |
| Laboratory parameters | |
| Creatinine (mg/dL) [IQR] | 0.84 [0.72–1.02] |
| Bilirubin (mg/dL) [IQR] | 0.53 [0.42–0.66] |
| AST (U/L) [IQR] | 43 [27–81] |
| ALT (U/L) [IQR] | 49 [24–84] |
| Reason for ECMO, *n* (%) | |
| ARDS (COVID-19) | 6 (86%) |
| Cardiac arrest | 1 (14%) |
| Extracorporeal circuits, *n* (%) | |
| Veno-venous ECMO | 6 (86%) |
| Veno-arterial ECMO | 1 (14%) |
| Outcomes | |
| Deceased at data cut off | 4 |
| ECMO duration (days) [IQR] | 15 [5–21] |

Abbreviations: AST, aspartate transaminase; ALT, alanine transaminase; ECMO, extracorporeal membrane oxygenation; ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019.

**ISAVUCONAZOLE PLASMA CONCENTRATIONS IN ECMO PATIENTS AT GIVEN TIMEPOINTS**

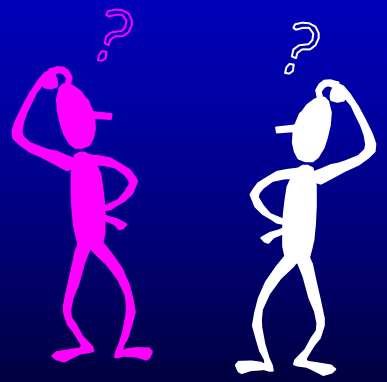


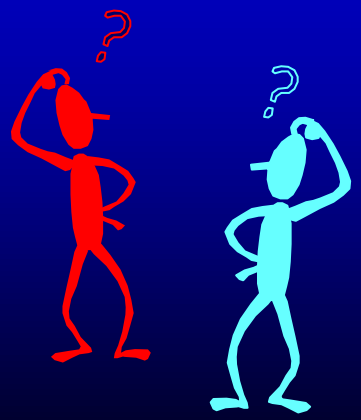




# CLINICAL PHARMACOLOGY

# OF LIPID FORMULATIONS OF AMPHOTERICIN B





› Med Mycol. 2022 Oct 12;60(10):myac074. doi: 10.1093/mmy/myac074.

# Liposomal amphotericin B exposure in critically ill patients: a prospective pharmacokinetic study

Ruth Van Daele [1], Joost Wauters [2], Omar Elkayal [3], Erwin Dreesen [3], Yves Debaveye [4], Katrien Lagrou [5], Yvo de Beer [6], Johan Maertens [7], Roger J Brüggemann [8], Isabel Spriet [1]

Affiliations + expand

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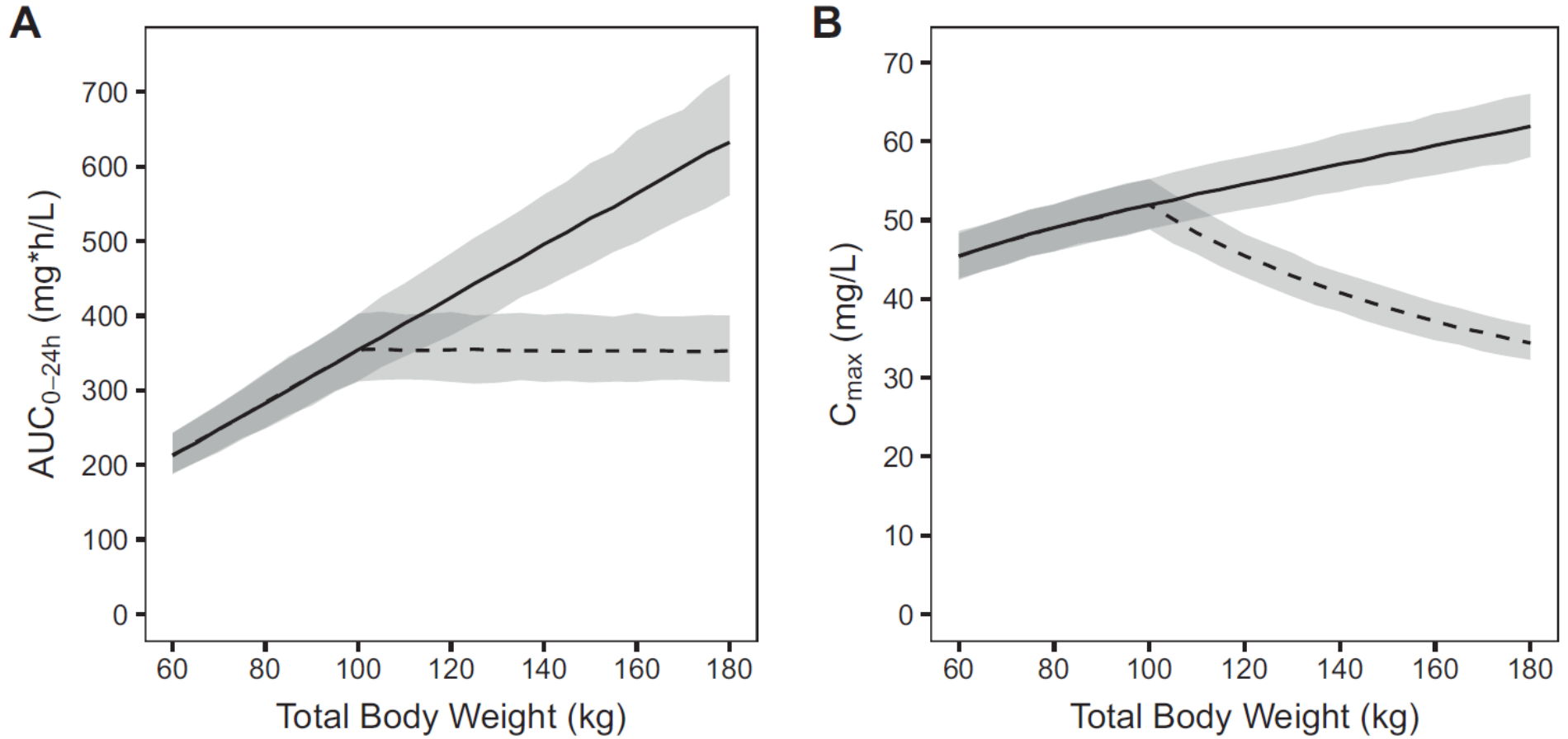
## Abstract

Liposomal amphotericin B (L-AmB) is a broad-spectrum antifungal drug. Little is known about its pharmacokinetics (PK) in critically ill patients. The aim of this study was to document the PK of L-AmB in this population. It was also explored if covariates may be identified that influence its exposure. All adult, critically ill patients (at the intensive care unit or hematology ward) treated with L-AmB between October 2016 and January 2020 were eligible for this study. The administered dose was left at the discretion of the treating clinician. Plasma samples were collected at predose and 1, 2, 4, 8, 12, 16, 20 and 24 h postdose at an early (day 2-3) and/or later (≥ day 6) treatment day. Additionally, daily trough concentrations were collected until day 14. Of 33 included patients, 31 were evaluable; their median [IQR] age and body weight was 59 [54-64] years and 68 [59-77] kg, respectively. L-AmB was administered at doses between 2.7 mg/kg and 12.3 mg/kg, with a median [IQR] trough concentration of 3.1 [2.0-4.7] mg/l. The overall median area under the 24 h concentration-time curve (AUC0-24) and peak plasma concentration (Cmax) were 169.0 [117.0-253.0] mg h/l and 23.2 [16.9-33.7] mg/l, respectively. A considerable intra- and interpatient PK variability for Cmax and AUC0-24 was observed but no explaining variables, except the administered dose, could be identified. The PK of L-AmB in critically ill patients was documented. A considerable variability in exposure was observed between and within patients; however, it was not associated with a multitude of patient-related characteristics.

# FIXED DOSING OF LIPOSOMAL AMPHOTERICIN B IN MORBIDLY OBESE INDIVIDUALS

Wasmann RE et al. *Clin Infect Dis* 2020 May 6;70(10):2213-2215

MONTE-CARLO SIMULATIONS BASED ON THE FINAL MODEL OF THE STEADY-STATE AUC0-24H AND CMAX AFTER A DAILY 3-MG/KG (SOLID LINE) L-AMB DOSE INFUSED IN 1 HOUR. THE DASHED LINE REPRESENTS THE SITUATION WERE THE DOSE IS CAPPED ON A 100-KG INDIVIDUAL (300 MG AMBISOME).



# FIXED DOSING OF LIPOSOMAL AMPHOTERICIN B IN MORBIDLY OBESE INDIVIDUALS

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CONCLUSIONS

- Body weight–derived dosing might lead to an increased risk of toxicity in obese patients as clearance and therefore exposure to AmB is not affected by body weight
- In obese patients specifically, we recommend using the licensed 3 or 5 mg/kg dose and cap the dose at a maximum weight of 100 kg, resulting in a 300- or 500-mg fixed dose, respectively

# SINGLE-DOSE LIPOSOMAL AMPHOTERICIN B TREATMENT FOR CRYPTOCOCCAL MENINGITIS

Jarvis JN et al. *N Engl J Med* 2022; 386(12): 1109-1120

STUDY DESIGN

- In this phase 3 randomized, controlled, non-inferiority trial conducted in five African countries, we assigned HIV-positive adults with cryptococcal meningitis in a 1:1 ratio to:
- either a single high dose of liposomal amphotericin B (10 mg/kg) on day 1 plus 14 days of flucytosine (100 mg/kg/day) and fluconazole (1200 mg/day)
- or the current WHO-recommended treatment, which includes amphotericin B deoxycholate (1 mg/kg/day) plus flucytosine (100 mg/kg/day) for 7 days, followed by fluconazole (1200 mg/day) for 7 days (control).
- The primary end point was death from any cause at 10 weeks; the trial was powered to show non-inferiority at a 10-percentage-point margin.

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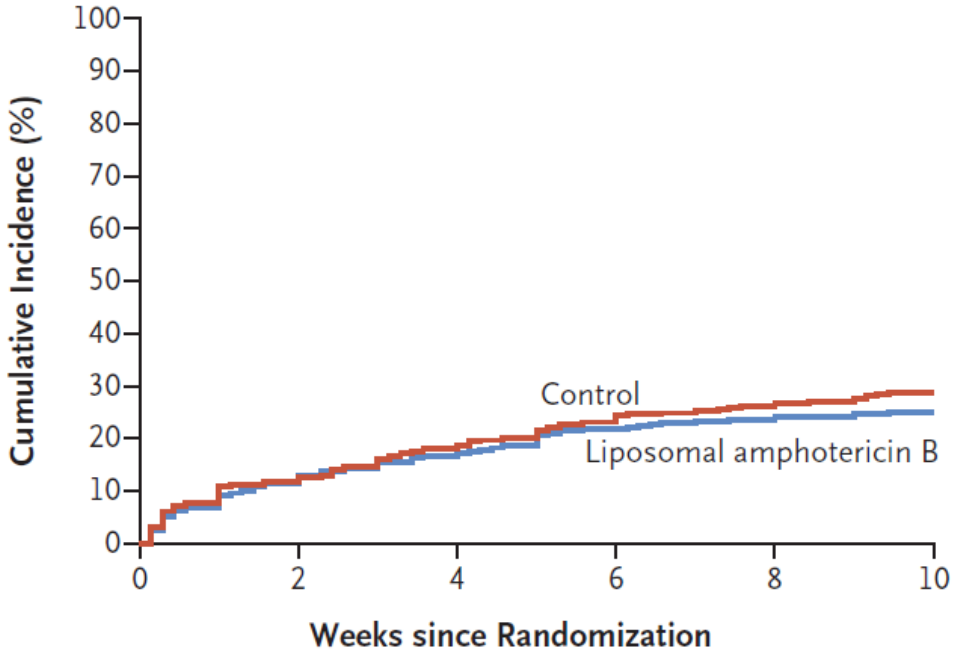
RESULTS

**A** All-Cause Mortality at Wk 10




| No. at Risk | | | | | | |
|---|---|---|---|---|---|---|
| Control | 407 | 359 | 332 | 311 | 299 | 288 |
| Liposomal amphotericin B | 407 | 360 | 337 | 317 | 310 | 304 |

**B** Noninferiority for Differences in All-Cause Mortality at Wk 10