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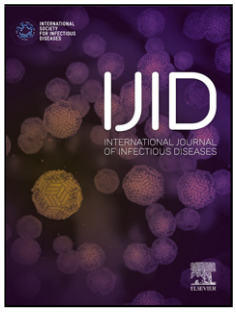

Pharmacokinetics of Echinocandins in Suspected Candida Peritonitis: a Potential Risk for Resistance

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Tittle

Pharmacokinetics of Echinocandins in Suspected Candida Peritonitis: a Potential Risk for Resistance

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Highlights

- Peritoneal and serum concentrations of echinocandins were analyzed in surgical patients with suspected candida peritonitis.
- The peritoneal concentrations obtained for the three candins in the present study ranged from 0.21 to 0.46 µg/mL for caspofungin, 0.68 to 0.88 µg/mL for micafungin and to 0.66 to 1.82 µg/mL for anidulafungin, and most concentrations were below 1 µg/mL.
- The levels of echinocandins that are achieved in the peritoneum are below the concentration of resistant mutant selection published by other authors.
- These data warn about mutant selection in patients on prolonged treatment with echinocandins and suboptimal control of the abdominal infection.

Abstract

Introduction: A possible increase of Candida resistance, specially in C. glabrata, has been speculated according to a poor diffusion of echinocandins to peritoneal fluid.

Materials/methods: Peritoneal and serum concentrations of Caspofungin, micafungin and anidulafungin were analyzed in surgical patients with suspected candida peritonitis. After four days of starting therapy serum and peritoneal samples (through peritoneal drainage) were obtained at baseline, 1 h, 6 h, 12h, and 24h of drug administration. Micafungin and anidulafungin concentrations were determined using high-performance liquid chromatography (HPLC/F), whereas caspofungin concentration were stablished by bioassay.

Results: A total of 23 critically ill patients with suspected abdominal fungal infection who were receiving an echinocandin were prospectively recruited. No specific criteria were applied to prescribe one specific echinocadin. No special clinical differences were observed among the 3 groups of patients. All were receiving antibiotic therapy, 80% required inotropic drugs and finally fungal peritonitis were confirmed in 74% of them. The AUC_{0_24h} (mg*h/L) obtained in serum and peritoneal fluid were: 126.84 and 34.38; 98.52 and 18.83; and 66.9 and 8.78 for anidulafungin, micafungin and caspofungin, respectively. The median concentration in peritoneal fluid ranged from 0.66 to 1.82 µg/ml for anidulafungin, 0.68 to 0.88 µg/mL for micafungin and 0.21 to 0.46 µg/ml for caspofungin.

Conclusion: The results show a moderate penetration of echinocandins into the peritoneal fluid in these patients. These levels are below the threshold of resistance mutant selection published by other authors. It could justify a potential risk of resistance in patients with prolonged treatments with echinocandins and suboptimal control of the abdominal infection.

Keywords:

Echinocandins; Pharmacokinetics, Candida, Peritonitis, Resistance

Introduction

The low sensitivity of echinocandins of *Candida parapsilosis* and the development of resistance, especially in *Candida glabrata*, in patients receiving prolonged treatment with echinocandins have recently been the focus of diffusion studies on these antifungals at the intra-abdominal level[1-5]. Different pharmacokinetic/pharmacodynamic (PK/PD) studies have recently been published for echinocandins[6-11], but very few studies have focused on candidiasic peritonitis or intra-abdominal fungal infection. None of these studies have jointly analyzed the behavior of the three echinocandins in the management of abdominal fungal infection.

Intra-abdominal candidiasis (IAC) is still poorly understood compared with candidemia. To date, data and studies on the efficacy of echinocandins in IAC are scarce, and although IAC has a high mortality rate, all current international guidelines mainly address candidaemia[12].

Recent studies indicate that echinocandin resistance rates among *C. glabrata* have increased worldwide[13-16]. Resistance has been reported to easily develop *in vitro*[17-20] and in patients after echinocandin exposure[13,21-23], which occurs because of the presence of point mutations in hot-spot regions of the FKS1 and FKS2 genes[13,21,22]. These mutations have been associated with higher minimal inhibitory concentrations (MICs) and therapeutic failure[21,23].

The aims of this study was to analyze PK/PD parameters of the three echinocandins (anidulafungin, micafungin, and caspofungin) in serum and peritoneal fluid (PF) in post-surgical critically ill patients with proven or suspected IAC; Other aspects related to this series, such as IAC diagnosis (including the role of multiplex quantitative real-time PCR and β-D-glucan in serum), etiological agents, therapeutic response and prognosis have been recently published and complement the information of this work[24]

The study was performed prospectively from 2016 to 2019 at a single center, and only patients who provided written consent were included.

Methods

This was a prospective PK study in critically ill adult patients who were admitted to the Anaesthesiology and Surgical Critical Care Department at

Ramon y Cajal Hospital, Madrid, Spain.

The inclusion criteria were age ≥18 years, a diagnosis of post-surgical nosocomial peritonitis that was refractory to >4 days of antibiotics, and undergoing PF drainage.

"IAC was defined following the 2013 European Consensus criteria[25]: Yeast detection by direct microscopy examination or growth in culture from purulent or necrotic intra-abdominal specimens obtained during surgery or by percutaneous aspiration; *Candida* growth from bile, intra-biliary ducts devices, and biopsy of intra-abdominal organs; *Candida* growth from blood cultures in the clinical setting of secondary and tertiary peritonitis in the absence of any other pathogen; *Candida* growth from drainage tubes only if placed less than 24 h. before the cultures".

The following variables were obtained for all patients: age, gender, central catheter, parenteral nutrition, ICU, septic shock, APACHE II, intestinal perforation or leak, pancreatitis, solid tumor, chemotherapy, diabetes, previus chemotherapy, dialysis, Pittet index, Candida score, source of intra-abdominal candidiasis, blood cultures, candida isolates, empirical antifungal started and 30-days mortality. Blood cultures were processed in the Microbiology Department at Ramon y Cajal Hospital using the BACTEC FX blood culture system (Becton Dickinson Diagnostic Instrument Systems, MD, USA). Fungi were identified using mass spectrometry (matrix-assisted laser desorption/ionization time-of-flight [MALDI-TOF]; Bruker, Germany).

Four days after starting anidulafungin (100 mg/d, first day 200 mg), caspofungin (50 mg/d, first day 70 mg), or micafungin (100 mg/d) therapy when the patients were at steady state, serum and peritoneal samples (through peritoneal drainage) were obtained at the following time points: baseline and at 1, 6, 12, and 24 h after antifungal administration. The samples were frozen at −80°C until analysis. Anidulafungin and micafungin concentrations were determined using a validated high-pressure liquid chromatography (HPLC/UV-F) method. Caspofungin concentrations were established using a bioassay.

Bioassay

The bioassay involved measuring the biological activity of caspofungin in serum samples in a diffusion assay. Preparation of the medium, assay

reagents, and the test organism (Candida kefyr ATCC 28838; caspofungin MIC, 0.06 µg/mL) were previously described[26].

High-pressure liquid chromatography assay

A new HPLC/UV-F assay was developed using a stepwise gradient elution profile. The proposed method enables the specific quantification of echinocandin in 150 µL of sample (CS and clinical samples) after a first step of protein precipitation and direct injection of resulting supernatant. A HPLC assay (Waters 2695 separation module) was developed using a stepwise gradient elution profile on a reverse-phase C18, 2.7-µm CortecT3 analytical column (100 × 4.6 mm) that was maintained at 25°C in conjunction with a Cortecs T3 guard column (VanGuard 3.9 × 5 mm). The mobile phase consisted of acetonitrile and ammonium acetate (pH 5.5) at a flow rate of 0.6 mL/min. The stepwise gradient elution profile was programmed as follows: Solvent A (acetonitrile) was initially 35% for 1 min and then increased to 70% for 7 min, and finally decreased to 35% again for the next 3 min. Detection was performed by the specific characterization of each compound by its UV profile. Additionally, in-series fluorescence detection was also performed (Waters 2475 multi λ Fluorescence Detector) because these candins have fluorescence properties. Dual detection allows a more specific and sensitive method of quantification.

The wavelengths of excitation and emission were set at 273 nm and 464 nm, respectively. The Empower Software (version 3.0, Waters Corporation, MA, USA) controlled the HPLC system control, and acquisition and processing of the data. For each candin characterization, a comparison of retention times and a UV-F profile with authentic standards was performed.

PK evaluation

Data were processed using Empower Software (version 3.0, Waters Chromatography, S.A., Spain). Echinocandin PK analysis was determined using a non-compartmental model. All calculations were performed using Microsoft Excel® (Microsoft, Redmond, WA, USA) spread sheets, using the PK solver add-in program, which has demonstrated equivalence calculating PK/PD parameters compared to others specific PK programs. Plots were created with GraphPad Prism 7, (La Jolla, CA, USA). The primary PK parameters that were

evaluated were the area under the concentration-time curves from 0 to 24 h ($AUC_{0–24}$), maximum concentration (C_{max} in mg/L), and minimum concentration (C_{min} in mg/L).

The Ramon y Cajal Hospital institutional review board approved the study protocol, and informed consent was obtained from the patients or their representatives.

Results

Twenty-three critically ill patients with suspected abdominal fungal infections were recruited.

At our center, no specific criteria are applied to prescribe a specific echinocandin. Anidulafungin, caspofungin, or micafungin were prescribed in 11, eight, and four patients, respectively, in this study. Table 1 shows the principal characteristics of the patients. All patients had recently undergone surgery and had a recently implanted abdominal drain. No differences were observed among these three groups: all the patients were in critical condition, were admitted into the surgical intensive care unit, and more than 80% required inotropic drugs. Before antifungal therapy was started, all patients were receiving antibiotic therapy for previously confirmed bacterial peritonitis, and fungal peritonitis was confirmed in three-quarters of them. Only one patient in each of the drug groups required hemodialysis, and no differences in weight or serum levels of creatinine, bilirubin, protein, or albumin were observed among the three drug groups. All patients were treated with echinocandins at conventional doses.

After 4 days of therapy (steady state), serum and PF (through peritoneal drainage) were collected at baseline, and at 1, 6, 12, and 24 h after echinocandin administration. The PK/PD analysis was performed using a non-compartmental approach and the principal results are shown in Table 2 and Figure 1.

The $AUC_{0\text{-}24h}$ (mg×h/L) that was obtained in serum and PF was highest for anidulafungin, followed by micafungin and caspofungin. The ratio of PF-to-serum (%) was also higher for anidulafungin and the lowest for caspofungin. In summary, the results show a moderate penetration of echinocandins into the PF in patients with intra-abdominal infections, with a median $AUC_{0\text{-}24h}$ for the PF-to-

plasma ratio of 0.13 to 0.27 at the assumed steady-state. The median concentration in PF ranged from 0.66 to 1.82 µg/mL for anidulafungin, 0.68 to 0.88 µg/mL for micafungin, and 0.21 to 0.46 µg/mL for caspofungin

Discussion

The peritoneal concentrations obtained for the three candins in the present study ranged from 0.21 to 0.46 µg/mL for caspofungin to 0.66 to 1.82 µg/mL for anidulafungin, and most concentrations were below 1 µg/mL. This is consistent with results published by other authors as a safeguard of efficacy for managing patients with IAC because these levels far exceed the MIC90 that EUCAST suggests for the usual strains of *Candida albicans* (0.03 µg/mL), and for *Candida krusei*, C. *glabrata*, and *Candida tropicalis* (0.06 µg/mL). However, they would be insufficient for the management of *Candida parapsilosis* (4 µg/mL)[27].

Recently, Grau et al. conducted a similar study in which they analyzed micafungin PK/PD in surgical patients, and on day 3, they found an $AUC_{0\text{-}24h}$ in plasma and PF of 56.5 (52–77.7) mg×h/L and 23.9 (18.8–31.7) mg×h/L, respectively, corresponding to a median PF-to-plasma ratio of 0.3[1]. The only covariates that were statistically significant and improved the fit of the model were total body weight normalized to 70 kg and serum albumin concentration normalized to 2.2 g/d, according to the high protein binding of echinocandins[1]. The effect of weight on PK results for echinocandins has also previously been demonstrated for caspofungin[8] and anidulafungin[6], and some studies showed that a 25% increase in the anidulafungin dose is recommended in morbidly obese patients[28]. However, in the present study, no morbidly obese patients were included, and all the patients in the three groups presented a homogeneous profile of weight and albuminemia, which were close to the average values mentioned in previous studies. Thus, we believe that the data obtained in our study adequately represent the PK of the three candins in this type of patient.

~~maxmin0-24~~[4]~~0-24h0-24h~~[27].

The levels obtained in PF in our patients were similar to those obtained by other authors, and they confirmed a moderate penetration of echinocandins into the PF in patients with IAC. Perez-Civantos et al. confirmed anidulafungin

levels between 0.7 and 0.9 µg/mL, with an average AUC_{0-24} of 57.9 mg×h/L,[2] which was similar to the levels obtained by Welte et al. (0.12–0.99 µg×h/mL)[3].

~~28~~0-24 Andes et al.[7] demonstrated that the AUC/MIC ratio, APACHE II score, and history of corticosteroid use were significant independent predictors of a favorable response for all *Candida* species. This study analyzed 493 patients who were included in two large clinical trials with mycafungin. The MIC90 of *C. albicans*, *C. tropicalis*, *C. glabata*, and *C. krusei* was 0.008 µg/mL, 0.016 µg/mL, 0.016 µg/mL, and 0.125 µg/mL, respectively, and 1.0 µg/mL for *C. parapsilosis*[7]. In plasma, fractional target AUC/MIC ratios of 3000 and 285 were associated with positive therapeutic outcome in a population PK/PD model of patients with invasive candidiasis or candidemia caused by other species different to *C. parapsilosis* and *C. parapsilosis*, respectively[7]. ~~11~~.

Our results confirmed an AUC/3000 ratio in serum of 0.042, 0.032, and 0.022 for anidulafungin, micafungin, and caspofungin, respectively, which would be achieved using the current EUCAST susceptibility cut-off for *C. albicans* (0.03 mg/L), but it would be sub-optimal for *C. glabrata*, *C. krusei*, and *C. tropicalis* (0.06 mg/L). The AUC/285 ratio in our study was 0.44, 0.34, and 0.23, respectively, which is below the threshold for *C. parapsilosis* (4 mg/L). Although these PK/PD parameters have not been optimized outside serum, low levels were obtained in the peritoneum in our study, and other similar studies suggest therapeutic this difficulty, especially for *C. parapsilosis* and *C. glabrata*.

Despite this unfavorable PK/PD data, echinocandins have shown high success rates in the treatment of candidemia and other forms of invasive candidiasis, including IAC, which are caused by different *Candida* species such as *C. parapsilosis*. Recently Sganga et al. performed a post hoc analysis to determine the efficacy and safety of anidulafungin treatment in patients with IAC from five prospective studies [5]. and anidulafungin showed a global response rate that was similar to the anidulafungin registrational trial of candidemia, with no differences in outcomes in patients with *C. albicans* compared to *C. glabrata* ~~5312930~~

Recent studies indicated that echinocandin resistance rates among *C. glabrata* clinical isolates have increased worldwide[13-16]. Rivero et al. exposed *in vitro* susceptible isolates from two patients to an increasing concentration range micafungin, and they obtained echinocandin-resistant and FKS mutant colonies

after exposure to the lowest micafungin concentration that was considered to confer resistance by EUCAST (0.06 mg/L) in less than 48 h of incubation. The mutant prevention concentration (MPC), which is defined as the lowest concentration that can completely inhibit fungal growth for each isolate after 5 days of incubation, was documented in this study[13], and no significant differences were found between the MPC geometric mean after anidulafungin or micafungin exposure after 5 days of incubation (2.44 mg/L versus 1.72 mg/L)[13]. [33]. This finding is significant because the mean peritoneal concentrations of the three echinocandins obtained in our study were always below these MPCs. Results obtained in the *in vitro* studies on how echinocandin-susceptible *C. glabrata* strains are able to develop resistance after exposure to low echinocandin concentrations supports the fact that *C. glabrata* is able to colonize and survive in certain reservoirs of the human body, such as the abdomen[29], peritoneum[1], gastrointestinal tract[30], or mucosal surfaces[31], because of long-term penetration of echinocandins at lower concentrations compared to those that prevent resistance acquisition.

This study has several limitations. The sample size was small, and the PK variability was high in this population, but the more significant factors that were associated with this variability such as weight and serum albumin were similar among our patients. PK/PD targets for echinocandins obtained in other studies have been developed using plasma data in patients with candidemia, and thus, the results could not be directly applied to PF data. We did not correlate PK/PD target attainment with clinical response because of the small number of patients, with only three-quarters of our patients having a microbiologically confirmed fungal infection. Finally, we did not confirm resistance to echinocandins in our study, but the study was not designed for this purpose, and long-term *Candida* sp. isolates at the peritoneal level or in colonization were not analyzed.

In conclusion, our study confirms, as in other similar studies, that there is poor diffusion of echinocandins into PF. Anidulafungin has a higher concentration and a higher PF-to-plasma ratio compared to micafungin and caspofungin, although this was not a differential aspect in clinical response in the few studies that focused on the use of echinocandins in IAC. The levels of echinocandins that are achieved in the peritoneum are below the concentration

of resistant mutant selection that were published by other authors; this was clear for *C. parapsilosis* and for high-risk *C. glabrata*. These data can explain the development of resistance in *C. glabrata* and warn about mutant selection in patients on prolonged treatment with echinocandins and suboptimal control of the abdominal infection.

Declarations section

Ethical Approval and Consent to participate

The Ramon y Cajal Hospital institutional review board approved the study protocol, and informed consent was obtained from the patients or their representatives

Consent for publication

Not applicable

Availability of supporting data and patients

PubMed, the Cochrane library, and Medline databases.
Patients: critically ill adult patients admitted to the Anaesthesiology and Surgical Critical Care Department at Ramon y Cajal Hospital, Madrid, Spain.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

FG, AGL, MEA, EGG, PMD and JF wrote the manuscript. MCE and SM made significant alterations. All authors read and approved the final manuscript.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

1. Grau S, Luque S, Campillo N, Samsó E, Rodríguez U, García-Bernedo CA, et al. Plasma and peritoneal fluid population pharmacokinetics of micafungin in post-surgical patients with severe peritonitis. J Antimicrob Chemother 2015;70(10):2854-61.

2. Pérez Civantos DV, Robles Marcos M, Azanza Perea JR, Pazos Pacheco C, García-Montoto Pérez F, Jerez Gómez-Coronado V. Pharmacokinetics of anidulafungin in critically ill patients with Candida peritonitis. Int J Infect Dis 2019;86:142-146.

3. Welte R, Eller P, Lorenz I, Joannidis M, Bellmann R. Anidulafungin pharmacokinetics in ascites fluid and pleural effusion of critically ill patients. Antimicrob Agents Chemother 2018;62.

4. Dupont H, Massias L, Jung B, Ammenouche N, Montravers P. Pharmacokinetic study of anidulafungin in ICU patients with intraabdominal candidiasis. J Antimicrob Chemother 2017; 72: 1429–1432

5. Sganga G, Wang M, Capparella R, Tawadrous M, Yan JL, Aram JA, Montravers P. Evaluation of anidulafungin in the treatment of intra-abdominal candidiasis: a pooled analysis of patient-level data from 5 prospective studies. European Journal of Clinical Microbiology & Infectious Diseases 2019;38:1849–1856

6. Luque S, Hope W, Campillo N, Muñoz-Bermúdez R, Sorli L, Barceló-Vidal J, et al. Population Pharmacokinetics of Anidulafungin in Critically Ill Patients. Antimicrob Agents Chemother 2019;63(7).

7. Andes D, Ambrose PG, Hammel JP, Van Wart SA, Iyer V, Reynolds DK, et al. Use of pharmacokinetic-pharmacodynamic analyses to optimize therapy with the systemic antifungal micafungin for invasive candidiasis or candidemia. Antimicrob Agents Chemother 2011;55(5):2113-21

8. Hall RG, Swancutt MA, Meek C et al.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.

9. Aguilar G, Azanza JR, Sádaba B, Badenes R, Ferrando C, Delgado C, et al. Anidulafungin dosing in critically ill patients with continuous venovenous haemodiafiltration. J Antimicrob Chemother 2014;69:1620–3.

10. Aguilar G, Azanza JR, Carbonell JA, Ferrando C, Badenes R, Parra MA, et al. Pharmacokinetics of anidulafungin during albumin dialysis. Crit Care 2014;1:422.

11. Andes D, Diekema DJ, Pfaller MA, Bohrmuller J, Marchillo K, Lepak A. In vivo comparison of the pharmacodynamic target among echinocandin drugs and Candida species. Antimicrob Agents Chemother 2010;54:2497–2506

12. Cornely OA, Bassetti M, Calandra T, Garbino J, Kullberg BJ, Lortholary O, et al. ESCMID guideline for the diagnosis and management of Candida diseases 2012: non-neutropenic adult patients. Clin Microbiol Infect 2012;18:19–37.

13. Rivero-Menendez O, Navarro-Rodriguez P, Bernal-Martinez L, Martin-Cano G, Lopez-Perez L, Sanchez-Romero I, et al. Clinical and Laboratory Development of Echinocandin Resistance in Candida glabrata: Molecular Characterization. Front Microbiol 2019;10:1585.

14. Guinea, J., Zaragoza, O., Escribano, P., Martin-Mazuelos, E., Peman, J., Sanchez-Reus, F., et al. Molecular identification and antifungal susceptibility of yeast isolates causing fungemia collected in a population-based study in Spain in 2010 and 2011. Antimicrob. Agents Chemother 2014;58,1529–1537.

15. Chapman, B., Slavin, M.,Marriott, D., Halliday, C., Kidd, S., Arthur, I., et al. Changing

epidemiology of candidaemia in Australia. J. Antimicrob. Chemother 2017; 72,1103–1108.

16. Hou, X., Xiao, M., Chen, S. C., Kong, F., Wang, H., Chu, Y. Z., et al. (2017). Molecular epidemiology and antifungal susceptibility of Candida glabrata in China (August 2009 to July 2014): a multi-center study. Front Microbiol 2017 May 23;8:880.

17. Bordallo-Cardona, M. A., Escribano, P., de la Pedrosa, E. G., Marcos-Zambrano, L. J., Canton, R., Bouza, E., et al. (2017). In vitro exposure to increasing micafungin concentrations easily promotes echinocandin resistance in Candida glabrata isolates. Antimicrob Agents Chemother 2017;61:e1542-16.

18. Bordallo-Cardona, M. A., Escribano, P., Marcos-Zambrano, L. J., Diaz-Garcia, J., de la Pedrosa, E. G., Canton, R., et al. (2018a). Low and constant micafungin concentrations may be sufficient to lead to resistance mutations in FKS2 gene of Candida glabrata. Med. Mycol 2018; 56,903–906.

19. Bordallo-Cardona, M. A., Marcos-Zambrano, L. J., Sanchez-Carrillo, C., de la Pedrosa, E. G. G., Canton, R., Bouza, E., et al. (2018c). Mutant prevention concentration and mutant selection window of micafungin and anidulafungin in clinical Candida glabrata isolates. Antimicrob Agents Chemother 2018; 62:e1982-17.

20. Shields, R. K., Kline, E. G., Healey, K. R., Kordalewska, M., Perlin, D. S., Nguyen, M. H., et al. (2019). Spontaneous mutational frequency and FKS mutation rates vary by echinocandin agent against Candida glabrata. Antimicrob Agents Chemother 2019;63:e1692-18.

21. Shields, R. K., Nguyen, M. H., Press, E. G., Kwa, A. L., Cheng, S., Du, C., et al. (2012). The presence of an FKS mutation rather than MIC is an independent risk factor for failure of echinocandin therapy among patients with invasive candidiasis due to Candida glabrata. Antimicrob Agents Chemother 2012;56,4862–4869.

22. Bizerra, F. C., Jimenez-Ortigosa, C., Souza, A. C., Breda, G. L., Queiroz-Telles, F., Perlin, D. S., et al. (2014). Breakthrough candidemia due to multidrugresistant Candida glabrata during prophylaxis with a low dose of micafungin. Antimicrob Agents Chemother 2014; 58, 2438–2440.

23. Sasso, M., Roger, C., and Lachaud, L. (2017). Rapid emergence of FKS mutations in Candida glabrata isolates in a peritoneal candidiasis. Med Mycol 2017; Case Rep.16, 28–30.

24. Fortún J, Buitrago MJ, Gioia F, Gómez-Gª de la Pedrosa E, Alvarez ME, Martín-Dávila P, et al. Roles of the multiplex real-time PCR assay and β-D-glucan in a high-risk population for intra-abdominal candidiasis (IAC). Med Mycol 2020 Aug 1;58(6):789-796.

25. Bassetti M, Marchetti M, Chakrabarti A, Colizza S, Garnacho-Montero J, Kett DH, et al. A research agenda on the management of intraabdominal candidiasis: results from a consensus of multinational experts. Intensive Care Med 2013;39:2092–2106

26. Cendejas-Bueno E, Cuenca-Estrella M, Gomez-Lopez A.Determination of voriconazole serum concentration by bioassay, a valid method for therapeutic drug monitoring for clinical laboratories. Antimicrob Agents Chemother. 2013 Jul;57(7):3437-40. doi: 10.1128/AAC.00323-13. Epub 2013 May 6)

27. “The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs for antifungal agents, version 10.0, 2020. http://www.eucast.org/astoffungi/clinicalbreakpointsforantifungals/.

28. Wasmann RE, ter Heine R, van Dongen EP, Burger DM, Lempers VJ, Knibbe CA,

Brüggemann RJ. 2018. Pharmacokinetics of anidulafungin in obese and normalweight adults. Antimicrob Agents Chemother 2018;62:e00063-18.

29. Shields, R. K., Nguyen, M. H., Press, E. G., and Clancy, C. J. (2014). Abdominal candidiasis is a hidden reservoir of echinocandin resistance. Antimicrob Agents Chemother 2014;58:7601–7605.

30. Healey, K. R., Nagasaki, Y., Zimmerman, M., Kordalewska, M., Park, S., Zhao, Y., et al. The gastrointestinal tract is a major source of echinocandin drug resistance in a murine model of Candida glabrata colonization and systemic dissemination. Antimicrob. Agents Chemother 2007;61: e1412–e1417.

31. Jensen, R. H., Johansen, H. K., Soes, L. M., Lemming, L. E., Rosenvinge, F. S., Nielsen, L., et al. Posttreatment antifungal resistance among colonizing candida isolates in candidemia patients: results from a systematic multicenter study. Antimicrob. Agents Chemother 2015; 60: 1500–1508.

Figure 1. Observed echinocandin concentrations in serum and in peritoneal fluid. Median concentrations and standar desviation at baseline, 1h, 6h, 12h and 24h on day +4 of therapy (anidulafungin: 200 mg on day 1, followed by 100 mg/d thereafter; caspofungin: 70 mg on day 1, followed by 50 mg/d thereafter; micafungin: 100 mg/d (no charge doses)

Figure 1a: anidulafungin

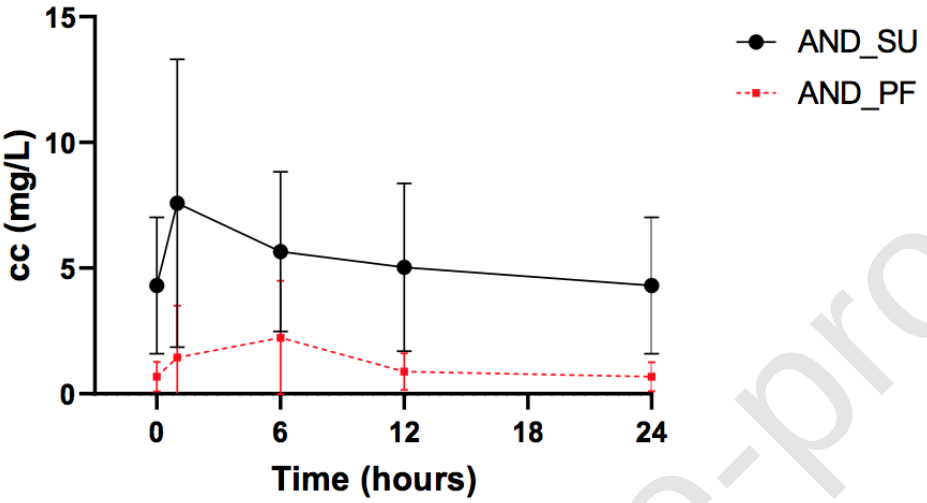

Figure 1b: micafungin

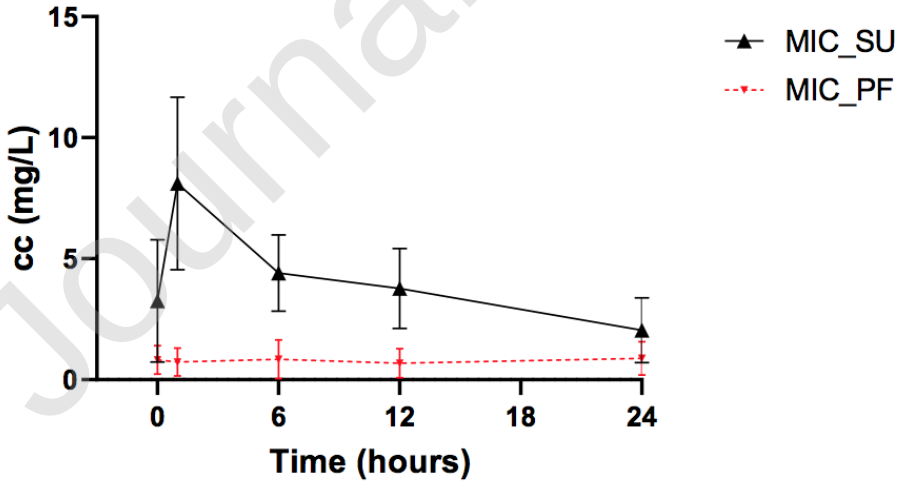

Figure 1c: caspofungin

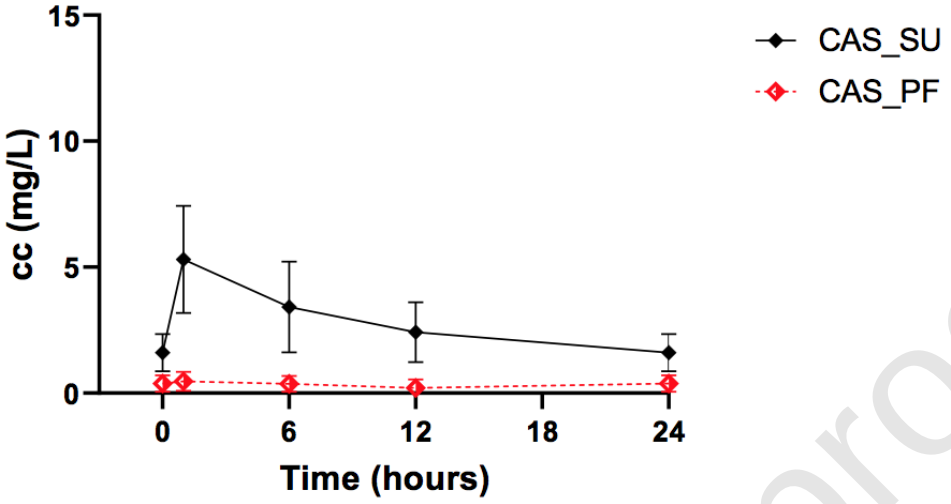

Table 1. Characteristics of patients included in the study

	Anidulafungin (n: 11)	Caspofungin (n: 8)	Micafungin (n: 4)
Male, Kg, %	7/11, 63.6%	7/8, 87.5%	3/4, 75%
APACHE>14, %	9/11, 81.8%	5/8, 62.5%	4/4, 100%
Inotropic requirements, %	9/11, 81.8%	7/8, 87.5%	4/4, 100%
Multi-organic failure, %	6/11, 54.5%	3/8, 37.5%	3/4, 75%
Confirmed bacterial peritonitis, %	11/11, 100%	8/8, 100%	4/4, 100%
Confirmed fungal peritonitis, %	8/11, 72.7%	6/8, 75%	3/4, 75%
Candidemia, %	1/11, 9.1%	0	0
Hemodialysis, %	1/11. 9.1%	1/8, 12.5%	1/4, 25%
Weight, mean (range)	77.8 (53-98)	78.8 (67-100)	68.2 (45-80)
Serum bilirubin, mean (mg/dl, range)	1.17 (0.30-4.61)	1.28 (0.31-3.72)	1.12 (0.40-2.31)
Serum creatinine, mean (mg/dl, range)	1.07 (0.40-1.91)	0.82 (0.51-1.92)	1.20 (0.59-1.94)
Serum albumin, mean (g/dl, range)	2.24 (1.31-3.74)	2.23 (1.62-.3.71)	2.23 (1.30-3.70)
Serum protein, mean (g/dl, range)	4.69 (3.62-6.31)	5.05 (3.57-6.34)	4.50 (4.20-5.21)

Table 2. Echinocandin pharmacoinetic parameters (mean ± standard deviation values)(*S*: serum; PF: peritoneal fluid)

Antifungal (n)		S	PF	Ratio PF/serum (%)
AND (11)	Cmax (mg/L)	7.96±5.40	2.57±2.19	32.3
	Cmin (mg/L)	3.99±2.73	0.64±0.35	16.1
	AUC_{0_24h} (mg*h/L)	**126.84±78.66**	**34.38±20.17**	27.1
MCF (4)	Cmax (mg/L)	8.45±3.24	0.88±0.69	**10.4**
	Cmin (mg/L)	2.04±1.34	0.66±0.47	**32.5**
	AUC_{0_24} (mg*h/L)	**98.52±34.55**	**18.83±14.05**	**19.1**
CAS (8)	Cmax (mg/L)	5.30±2.66	0.49±0.39	**9.2**
	Cmin (mg/L)	1.43±0.73	0.24±0.27	**16.9**
	AUC_{0_24} (mg*h/L)	**66.90±32.71**	**8.78±7.83**	**13.1**

AND: anidulafungin; MCF: micafungin; CAS: caspofungin