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CLINICAL THERAPEUTICS

# Pharmacokinetics and Antifungal Activity of Echinocandins in Ascites Fluid of Critically Ill Patients

**René Welte,[a] Herbert Oberacher,[b] Tiziana Gasperetti,[a] Hartwig Pfisterer,[c] Andrea Griesmacher,[c] Tobias Santner,[c] Cornelia Lass-Flörl,[d] Caroline Hörtnagl,[d] Sandra Leitner-Rupprich,[d] Maria Aigner,[d]* Ingo Lorenz,[e] Stefan Schmid,[f] Michael Edlinger,[g] Philipp Eller,[h] Daniel Dankl,[i] Michael Joannidis,[j] Romuald Bellmann[a,j]**

[a]Clinical Pharmacokinetics Unit, Division of Medical Intensive Care and Emergency Medicine, Department of Internal Medicine I, Medical University of Innsbruck, Innsbruck, Austria
[b]Institute of Legal Medicine and Core Facility Metabolomics, Medical University of Innsbruck, Innsbruck, Austria
[c]Central Institute for Medical and Chemical Laboratory Diagnostics, Innsbruck General Hospital, Innsbruck, Austria
[d]Department of Hygiene and Medical Microbiology, Medical University of Innsbruck, Innsbruck, Austria
[e]General and Surgical ICU, Department of General and Surgical Intensive Care Medicine, Center of Operative Medicine, Medical University of Innsbruck, Innsbruck, Austria
[f]Traumatological ICU, Department of General and Surgical Intensive Care Medicine, Center of Operative Medicine, Innsbruck General Hospital and Medical University of Innsbruck, Innsbruck, Austria
[g]Division of Medical Statistics and Informatics, Department of Medical Statistics, Informatics, and Health Economics, Medical University of Innsbruck, Innsbruck, Austria
[h]Department of Internal Medicine, Medical University of Graz, Graz, Austria
[i]Salzburg General Hospital and Paracelsus Private Medical University, Salzburg, Salzburg, Austria
[j]Division of Medical Intensive Care and Emergency Medicine, Department of Internal Medicine I, Medical University of Innsbruck, Innsbruck, Austria

**ABSTRACT** The pharmacokinetics and antifungal activity of the echinocandins anidulafungin (AFG), micafungin (MFG), and caspofungin (CAS) were assessed in ascites fluid and plasma of critically ill adults treated for suspected or proven invasive candidiasis. Ascites fluid was obtained from ascites drains or during paracentesis. The antifungal activity of the echinocandins in ascites fluid was assessed by incubation of *Candida albicans* and *Candida glabrata* at concentrations of 0.03 to 16.00 $\mu$g/ml. In addition, ascites fluid samples obtained from our study patients were inoculated with the same isolates and evaluated for fungal growth. These patient samples had to be spiked with echinocandins to restore the original concentrations because echinocandins had been lost during sterile filtration. In ascites fluid specimens of 29 patients, echinocandin concentrations were below the simultaneous plasma levels. Serial sampling in 20 patients revealed a slower rise and decline of echinocandin concentrations in ascites fluid than in plasma. Proliferation of *C. albicans* in ascites fluid was slower than in culture medium and growth of *C. glabrata* was lacking, even in the absence of antifungals. In CAS-spiked ascites fluid samples, fungal CFU counts moderately declined, whereas spiking with AFG or MFG had no relevant effect. In ascites fluid of our study patients, echinocandin concentrations achieved by therapeutic doses did not result in a consistent eradication of *C. albicans* or *C. glabrata*. Thus, therapeutic doses of AFG, MFG, or CAS may result in ascites fluid concentrations preventing relevant proliferation of *C. albicans* and *C. glabrata*, but do not warrant reliable eradication.

**KEYWORDS** antifungals, invasive candidiasis, fungal peritonitis, target-site pharmacokinetics, antifungal pharmacodynamics

*Candida* peritonitis is associated with a high morbidity and a mortality of 20% to 30% (1, 2). It may occur after gastrointestinal perforation, as a complication of intra-abdominal surgery, in patients on chronic peritoneal dialysis, or in patients with

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Address correspondence to Romuald Bellmann, romuald.bellmann@i-med.ac.at.

* Present address: Maria Aigner, INNPATH GmbH, Tirol Kliniken, Innsbruck, Austria.

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liver cirrhosis presenting with ascites, particularly in those with acute on chronic liver failure (2–14). Controlled clinical studies on the treatment of *Candida* peritonitis are lacking. Current guidelines recommend antifungal treatment with an echinocandin along with drainage and surgical source control (15). The three commercially available echinocandins anidulafungin (AFG), micafungin (MFG), and caspofungin (CAS) are amphophilic cyclic hexapeptides displaying a plasma protein binding of more than 90% (16). As information on the penetration of echinocandins into ascites fluid are sparse, we assessed the pharmacokinetics and antifungal activity of AFG, MFG, and CAS in ascites fluid of critically ill adult patients treated for suspected or proven invasive candidiasis.

## RESULTS

**Study population, echinocandin concentrations, and pharmacokinetics.** Twenty-nine patients were enrolled. Eleven patients (3 females, 8 males; median age [range], 63 [34 to 82] years) were treated with AFG, 6 patients (1 female, 5 males; age, 53 [20 to 73] years), received MFG, and 13 (6 females, 7 males; age, 68 [32 to 83] years) were on CAS treatment. One patient (patient 11) was initially treated with AFG and switched to MFG after 6 days by the treating physician. Ascites drains had been inserted in 20 patients allowing for the assessment of echinocandin pharmacokinetics in ascites fluid (Table 1). Serial ascites fluid sampling over the entire dosage interval of 24 h was possible in 13 patients (Table 2). From another seven patients, serial samples were obtained over 8, 12, or 18 h (Table 3). In ascites fluid, concentrations of AFG, MFG, and CAS displayed a slower rise, a slower decline, and lower fluctuations than in plasma. Pharmacokinetics of AFG, MFG, and CAS in ascites fluid were highly variable (Tables 2 and 3). From 10 additional patients, 12 single-sample pairs (ascites fluid and plasma) were drawn during paracentesis at different times from echinocandin infusion. Echinocandin concentrations and penetration ratios (PRs) are listed in Table 4. In ascites fluid, echinocandin concentrations were significantly lower than the simultaneous plasma levels ($P < 0.05$). However, there was no significant difference between the PRs of the three echinocandins.

**Echinocandin pharmacodynamics in ascites fluid.** Proliferation of *C. albicans* and *C. glabrata* in ascites fluid was slower than that in RPMI culture medium (see Fig. 1 and 2). Incubation of *C. albicans* or *C. glabrata* in ascites fluid spiked with AFG or MFG at concentrations of 0.03 to 16.00 $\mu$g/ml did not result in a consistent decline in CFU. In CAS-spiked ascites fluid, a slight decrease of CFU of *C. albicans* was observed at concentrations of $\geq$2.00 $\mu$g/ml, whereas the CFU counts of *C. glabrata* decreased at concentrations of $\geq$0.25 $\mu$g/ml (Fig. 1). In culture medium, AFG concentrations of $\geq$0.125 $\mu$g/ml, MFG levels of $\geq$0.03 $\mu$g/ml, and CAS concentrations of $\geq$1.00 $\mu$g/ml resulted in a decrease of CFU of both *Candida* species (Fig. 1). In ascites fluid of selected study patients, the clinically achieved AFG concentrations had no effect on the growth of *C. albicans* or *C. glabrata*. An MFG concentration of 1.23 $\mu$g/ml was associated with a slight reduction of CFU of both *Candida* species in ascites fluid of patient 15, whereas no effect of MFG was observed in ascites fluid of patient 11 ($C_{max}$ = 0.11 $\mu$g/ml) and patient 12 ($C_{max}$ = 1.94 $\mu$g/ml). At CAS concentrations of 1.46 to 3.46 $\mu$g/ml (patient 25), however, CFU counts of *C. glabrata* declined, but CFU counts of *C. albicans* remained unchanged. CAS exposure was associated with a decrease of CFU counts of *C. glabrata* in ascites fluid of two of four patients (patients 21 and 25). In ascites fluid of patients 19 and 22, CAS peak concentrations of 0.97 and 0.52 $\mu$g/ml, respectively, were ineffective against *C. glabrata*. In all the tested patient ascites fluid samples, *C. albicans* displayed largely unchanged CFU counts (Fig. 2). No relevant proliferation of *C. albicans* or *C. glabrata* in ascites fluid was observed at echinocandin concentrations achieved in our study population.

## DISCUSSION

Echinocandin plasma pharmacokinetics in our study population were comparable with previously published data (17–22). In ascites fluid, AFG kinetics were similar to those reported from 24 critically ill patients with peritonitis and to those we previously

**TABLE 1** Study population information

| Patient | Body wt (kg) | Main diagnosis[a] | Cumulative dose (mg) | Drug | Sampling of ascites fluid[b] |
|---|---|---|---|---|---|
| 1 | 40 | *Candida* peritonitis, larynx carcinoma, liver cirrhosis, chronic hepatitis C, HIV infection | 200 | AFG | Ascites drain |
| 2 | 74 | Septic shock, pneumonia, methotrexate-induced acute liver failure, cholangitis | 1,000 | AFG | Ascites drain |
| 3 | 90 | Acute on chronic liver failure, liver cirrhosis, hemochromatosis | 200 | AFG | Ascites drain |
| 4 | 39 | Decompensated liver cirrhosis, renal failure, opioid addiction | 500 | AFG | Ascites drain |
| 5 | 70 | Acute on chronic liver failure, alcoholic liver disease | 700 | AFG | Ascites drain |
| 6 | 59 | Gastric cancer | 300 | AFG | Ascites drain |
| 7 | 80 | Septic shock, *Candida dubliniensis*, *Enterococcus faecium* peritonitis, pulmonary aspergillosis, st. p. LTX | 300 | AFG | Paracentesis |
| 8 | 61 | Peritonitis (*E. faecium*), st. p. LTX, hypersplenism | 200 | AFG | Paracentesis |
| 9 | 90 | Incisional hernia, idiopathic thrombocytopenic purpura | 800 | AFG | Paracentesis |
| 10 | 66 | Bile duct adenoma | 300 | AFG | Paracentesis |
| 11[c] | 85 | Cystectomy, prostatectomy, ileal conduit, urothelial carcinoma, pneumonia, CHD | 200 | AFG | Ascites drain |
| 11[c] | 85 | | 100 | MFG | Ascites drain |
| 12 | 76 | MVR, papillary muscle rupture after MI, septic shock, VAP (*Stenotrophomonas maltophilia*) | 900 | MFG | Ascites drain |
| 13 | 98 | Peritonitis, st. p. distal pancreatectomy, pneumonia | 100 | MFG | Ascites drain |
| 14 | 51 | Peritonitis, post-ERCP pancreatitis, Peutz-Jeghers syndrome | 300 | MFG | Ascites drain |
| 15 | 75 | Cholestatic graft failure, st. p. LTX, candidemia (*C. dubliniensis*), MOF, pulmonary *Rhizopus oryzae* mycosis (diagnosed at autopsy) | 1,000 | MFG | Paracentesis |
| 16 | 30 | Cystic fibrosis, st. p. LTX, graft dysfunction | 1,000 | MFG | Paracentesis |
| 17 | 85 | Peritonitis, st. p. cholecystectomy complicated by bile duct and hepatic artery laceration, st. p. hemihepatectomy | 370 | CAS | Ascites drain |
| 18 | 75 | Peritonitis, gastric carcinoma, st. p. gastric perforation, hemorrhagic shock | 170 | CAS | Ascites drain |
| 19 | 90 | Septic shock, cholecystitis, peritonitis (*C. glabrata*, *E. faecium*), gastric cancer | 220 | CAS | Ascites drain |
| 20 | 75 | LTX (acute liver failure), septic shock, MOF | 170 | CAS | Ascites drain |
| 21 | 70 | Perforated gastric ulcer, peritonitis, alcoholic liver disease | 470 | CAS | Ascites drain |
| 22 | 65 | Small intestine perforation, peritonitis, incarcerated umbilical hernia, liver cirrhosis | 170 | CAS | Ascites drain |
| 23 | 75 | Liver cirrhosis, hemothorax after multiple rib fractures | 170 | CAS | Ascites drain |
| 24 | 81 | Peritonitis from sigmoid colon perforation | 220 | CAS | Ascites drain |
| 25 | 50 | Peritonitis, small bowel anastomotic leak, uterine leiomyosarcoma, pelvic abscess | 220 | CAS | Ascites drain |
| 26 | 85 | Bile duct perforation after laparoscopic cholecystectomy, peritonitis | 170 | CAS | Paracentesis |
| 27 | 65 | Septic shock, diffuse large B-cell lymphoma, liver cirrhosis | 470 | CAS | Paracentesis |
| 28 | 73 | Lithogenic pancreatitis, hemorrhagic shock | 400 | CAS | Paracentesis |
| 29 | 98 | Lymphohistiocytic syndrome | 350 | CAS | Paracentesis |

[a]HIV, human immunodeficiency virus; st. p., status post; LTX, liver transplantation; CHD, coronary heart disease; MVR, mitral valve replacement; MI, myocardial infarction; VAP, ventilator-associated pneumonia; ERCP, endoscopic retrograde cholangiopancreatography; MOF, multiorgan failure; AFG, anidulafungin; MFG, micafungin; CAS, caspofungin.
[b]When ascites fluid was sampled via drainage, the collection bags were changed before (0 h) as well as 1, 4, 8, 12, 18, and 24 h after the start of the echinocandin infusion and kept for echinocandin measurement. During paracentesis, single-sample pairs (ascites fluid and plasma) were taken at different times from echinocandin infusion.
[c]Patient 11 was initially treated with AFG and switched to MFG after 6 days by the treating physician.

determined in a smaller group of critically ill patients (22, 23). During peritonitis, MFG had achieved peritoneal fluid concentrations comparable with our findings (24). Concentrations of CAS in ascites fluid have not been reported so far.

The ratio of the area under the echinocandin concentration-time curve over 24 hours to the MIC of the pathogen ($AUC_{0-24}$/MIC) has been shown to correlate with the antifungal efficacy of echinocandin treatment. In a murine model, a fungistatic effect of AFG on *C. albicans* and *C. glabrata* was reached by $AUC_{0-24}$/MIC ratios of 2,782 and 1,366, respectively. For MFG, the respective ratios were 5,299 and 1,542, and the $AUC_{0-24}$/MIC ratios of CAS amounted to 748 and 96 for *C. albicans* and *C. glabrata*, respectively (25). MICs of AFG of 0.008 to 0.25 $\mu$g/ml were reported for *C. albicans* and 0.015 to 1.0 $\mu$g/ml for

**TABLE 2** Echinocandin pharmacokinetics in ascites fluid obtained from ascites drains and in plasma with 24-h sampling period[a]

| Patient | Sample | Drug | Day of therapy | Dose (mg/kg/d) | $C_{max}$ ($\mu$g/ml) | $C_{min}$ ($\mu$g/ml) | $T_{max}$ (h) | $AUC_{0-24}$ ($\mu$g × 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 | |

[a]$C_{max}$, echinocandin peak concentration; $C_{min}$, echinocandin trough concentration; $T_{max}$, time to $C_{max}$; $AUC_{0-24}$, area under the echinocandin concentration-time curve over 24 h; $t_{1/2}$, echinocandin plasma half-life; PR, penetration ratio ($AUC_{0-24\ ascites\ fluid}$/$AUC_{0-24\ plasma}$); AFG, anidulafungin; MFG, micafungin; CAS, caspofungin.

*C. glabrata*. MICs of MFG and CAS were 0.008 to 1.0 $\mu$g/ml, respectively, for *C. albicans* and ≤0.008 to 1.0 $\mu$g/ml and ≤0.008 to 0.25 $\mu$g/ml, respectively, for *C. glabrata* (26). Based on these data, in our study population, only CAS would have reached fungistatic ascites fluid concentrations for *C. albicans* with MIC values of ≤0.06 to 0.1 $\mu$g/ml and for *C. glabrata* with MICs of ≤0.008 to 0.5 $\mu$g/ml.

However, the relevance of *in vitro* MIC of echinocandins is not yet known for ascites fluid. Therefore, we assessed the antifungal activity of AFG, MFG, and CAS in ascites fluid by *in vitro* simulations in echinocandin-spiked ascites fluid and by *ex vivo*

**TABLE 3** Echinocandin pharmacokinetics in ascites fluid obtained from ascites drains and in plasma with <24-h sampling period[a]

| Patient | Sample | Drug | Day of therapy | Dose (mg/kg/d) | $C_{max}$ ($\mu$g/ml) | $C_{min}$ ($\mu$g/ml) | $T_{max}$ (h) | $AUC_{0-n}$ ($\mu$g × h/ml) | $T_{sampling}$ (h) | PR |
|---|---|---|---|---|---|---|---|---|---|---|
| 6 | Ascites fluid | AFG | 2 | 1.69 | 0.38 | 0.26 | 4 | 5.7 | 18 | 0.13 |
| | Plasma | | | | 3.07 | 1.60 | 1 | 44.9 | 18 | |
| 11 | Ascites fluid | MFG | 1 | 1.18 | 0.11 | 0.04 | 4 | 0.6 | 8 | 0.02 |
| | Plasma | | | | 5.15 | 1.36 | 1 | 28.1 | 8 | |
| 12 | Ascites fluid | MFG | 5 | 2.63 | 2.38 | 1.75 | 0 | 24.3 | 12 | 0.31 |
| | Plasma | | | | 9.71 | 5.39 | 1 | 78.5 | 12 | |
| 19 | Ascites fluid | CAS | 4 | 0.56 | 0.97 | 0.31 | 1.5 | 10.8 | 18 | 0.08 |
| | Plasma | | | | 10.67 | 3.84 | 1.5 | 127.4 | 18 | |
| 20 | Ascites fluid | CAS | 3 | 0.67 | 1.54 | 0.31 | 8 | 13.2 | 12 | 0.46 |
| | Plasma | | | | 5.71 | 0.85 | 1 | 28.7 | 12 | |
| 24 | Ascites fluid | CAS | 4 | 0.62 | 1.37 | 1.10 | 0 | 9.2 | 8 | 0.14 |
| | Plasma | | | | 10.40 | 3.82 | 1 | 63.9 | 8 | |
| 25 | Ascites fluid | CAS | 5 | 1.00 | 3.46 | 1.46 | 18[b] | 40.7 | 18 | 0.30 |
| | Plasma | | | | 11.30 | 3.38 | 1 | 137.7 | 18 | |

[a]$C_{max}$, echinocandin peak concentration; $C_{min}$, echinocandin trough concentration; $T_{max}$, time to $C_{max}$; $AUC_{0-n}$, area under the time-concentration curve from start of echinocandin infusion to the last sampling; PR, penetration ratio ($AUC_{0-n\ ascites\ fluid}$/$AUC_{0-n\ plasma}$); AFG, anidulafungin; MFG, micafungin; CAS, caspofungin; $T_{sampling}$, sampling interval, when <24 h.

[b]The CAS concentration increased over the entire sampling interval of 18 h.

**TABLE 4** Echinocandin concentrations in single samples obtained during paracentesis[a]

| Patient | Drug | Day of therapy | Dose (mg/kg/d) | Conc. in ascites fluid ($\mu$g/ml) | Conc. in plasma ($\mu$g/ml) | Time from infusion (h) | PR |
|---|---|---|---|---|---|---|---|
| 7 | AFG | 2 | 1.25 | 0.28 | 2.72 | 4 | 0.10 |
| 7 | | 4 | 1.25 | 0.42 | 1.92 | 14 | 0.22 |
| 8 | AFG | 1 | 3.28 | 0.04 | 6.28 | 1.5 | 0.01 |
| 8 | | 4 | 1.64 | 1.18 | 3.68 | 4 | 0.32 |
| 9 | AFG | 8 | 1.11 | 0.99 | 2.87 | 0 | 0.34 |
| 10 | AFG | 3 | 1.52 | 0.20 | 2.11 | 1 | 0.09 |
| 15 | MFG | 9 | 1.33 | 1.23 | 6.01 | 8 | 0.20 |
| 16 | MFG | 16 | 1.67 | 1.32 | n.a. | 24 | n.a. |
| 16 | MFG | 20 | 1.67 | 1.03 | n.a. | 1 | n.a. |
| 26 | CAS | 3 | 0.59 | 0.70 | 7.31 | 12 | 0.10 |
| 26 | | 3 | 0.59 | 1.37 | 5.37 | 24 | 0.26 |
| 27 | CAS | 9 | 0.77 | 0.98 | 8.42 | 4 | 0.12 |
| 27 | | 14 | 0.77 | 2.16 | 7.02 | 8 | 0.31 |
| 27 | | 16 | 0.77 | 2.59 | 7.14 | 9 | 0.36 |
| 28 | CAS | 7 | 0.68 | 1.66 | 13.90 | 1.5 | 0.12 |
| 29 | CAS | 5 | 0.71 | 1.31 | 2.06 | 4 | 0.64 |

[a]AFG, anidulafungin; MFG, micafungin; CAS, caspofungin; Conc., echinocandin concentration; Time from infusion, time from start of echinocandin infusion; PR, penetration ratio ($C_{ascites\ fluid}/C_{plasma}$); n.a., not available (plasma sampling was missed).

simulations in ascites fluid samples of some of our study patients. In ascites fluid, the proliferation of *C. albicans* was slow and the growth of *C. glabrata* was lacking, even in the absence of antifungals. This finding might be ascribed to the variable availability of nutrients or to the presence of constituents with antimicrobial activity in ascites fluid. Peritoneal immunity has been shown to be influenced by numerous conditions, such as underlying disease and genetic polymorphisms (27, 28). Notably, we had removed any cells from ascites fluid by sterile filtration before inoculation with *Candida*.

*In vitro*, we observed a moderate decline in fungal CFU counts in ascites fluid spiked with CAS, whereas spiking with AFG or MFG had no relevant effect on fungal growth. In ascites fluid of our study patients, echinocandin concentrations achieved by therapeutic doses did not result in a consistent eradication of *C. albicans* or *C. glabrata*. Thus, AFG and MFG were largely ineffective, and the antifungal activity of CAS was variable in this compartment, probably depending on the susceptibility of the pathogen and on the individual properties of the ascites fluid, e.g., the pH value. The stability of AFG has been reported to decline at pH of >8 (29).

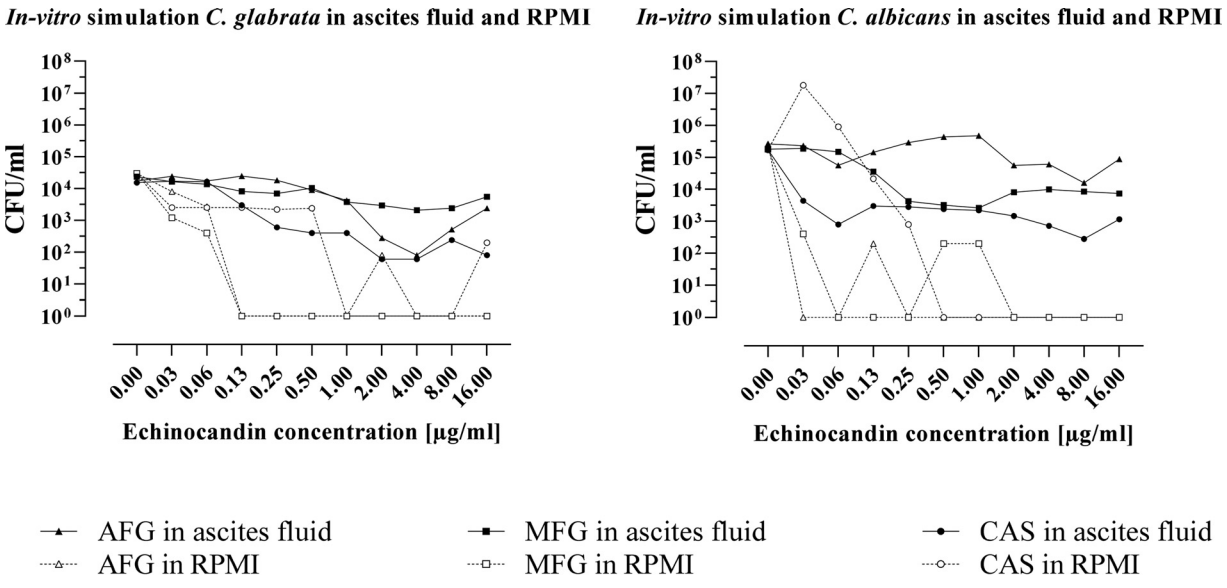


**FIG 1** *In vitro* simulation of growth of *C. glabrata* (left panel) and *C. albicans* (right panel) in ascites fluid and in RPMI media treated with anidulafungin (AFG), micafungin (MFG), and caspofungin (CAS). Samples were incubated for 24 h.

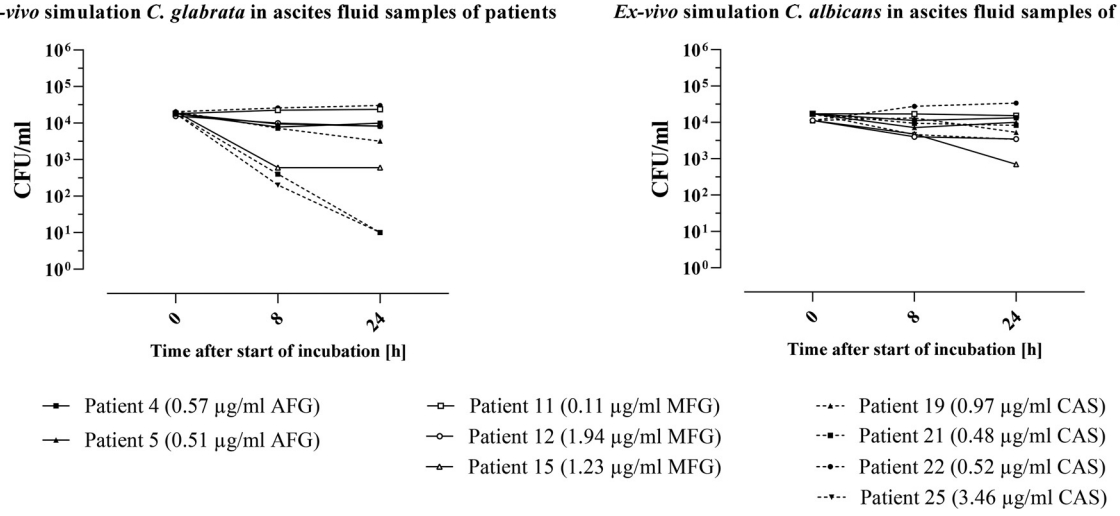


**FIG 2** *Ex vivo* simulation of growth of *C. glabrata* (left panel) and *C. albicans* (right panel) in ascites fluid of patients treated with standard doses of anidulafungin (AFG), micafungin (MFG), and caspofungin (CAS). Ascites drains had been inserted in patients 4, 5, 11, 12, 19, 21 22, and 25. The collections bags were changed before (0 h) as well as 1, 4, 8, 12, 18, and 24 h after the start of infusion and kept for echinocandin measurement and for *ex vivo* simulation when the sample volume was sufficient. For *ex vivo* simulation, seven samples were obtained from patients 4, 5, 21, and 22; six samples from patients 19 and 25; four samples from patient 11; and two samples from patient 12. For sake of clarity of the figure, the growth curves are displayed for $C_{max}$ values only. From patient 15, a single sample was taken during paracentesis 8 h after MFG administration.

Echinocandins inhibit the synthesis of 1,3-$\beta$-D-glucans, which are essential constituents of fungal cell walls required during cellular proliferation. Consequently, echinocandin exposure caused lysis of exponentially growing *C. albicans* cells but not of stationary cells (30). Accordingly, we observed moderate or even a lack of antifungal activity of echinocandins in ascites fluid, where fungal proliferation was slower than in culture medium or was even absent. In plasma, protein binding of AFG and MFG exceeds that of CAS, resulting in lower free AFG and MFG plasma levels. Protein binding of echinocandins in ascites fluid is unknown. Notably, a positive correlation between serum albumin concentrations and the probability of pharmacokinetic/pharmacodynamic target attainment has been reported for MFG (24). Observational clinical studies revealed a favorable outcome of 57% to 77% of patients suffering from *Candida* peritonitis treated with CAS (31, 32) and of 79% of peritonitis patients on AFG therapy (33). Thirteen of our 29 patients suffered from peritonitis. Echinocandin penetration into ascites fluid of patients with and without peritonitis was similar throughout our study population (PR of 0.17 versus 0.22; $P = 0.374$). Similar AFG and MFG concentrations in the ascites fluid of patients with peritonitis have been reported previously (22, 24). Therefore, peritonitis probably does not promote the intraperitoneal penetration of echinocandins.

Little data are available on ascites fluid penetration of antifungals. High concentrations approaching the simultaneous plasma levels are achieved by 5-flucytosine and by fluconazole (34, 35). Ascites fluid concentrations of amphotericin B were below 0.5 $\mu$g/ml after administration of conventional or lipid-formulated amphotericin B (34, 36). The antifungal activity of these drugs in human ascites fluid is not yet known.

The limited size and the heterogeneity of our study population are clear limitations. Medical and surgical patients presenting with ascites caused by different underlying diseases were enrolled. However, there was no patient on peritoneal dialysis in our study population although this group of patients is at high risk of *Candida* peritonitis. Furthermore, we did not separately determine free and protein-bound echinocandin levels in ascites fluid or in plasma. The antifungal activity of AFG, MFG, and CAS in ascites fluid at concentrations achieved by therapeutic doses was assessed only for *C. albicans* and *C. glabrata* isolates because these species are the most frequent pathogens associated with fungal peritonitis (31–33). Other *Candida* species might present different growth and echinocandin susceptibility in human ascites fluid. Furthermore, the

use of a standard EUCAST MIC test was not applicable for ascites fluid in our simulation experiments. Further methodological studies (e.g., on sample preparation) will be required for establishing this approach. *Ex vivo* simulation in patient ascites fluid samples was hampered by the loss of echinocandins during sterile filtration that necessitated spiking of the samples for restoring of the original echinocandin concentrations. Thus, *ex vivo* simulations were similar with *in vitro* simulations but allowed for the evaluation of individual ascites fluid samples taken during echinocandin treatment. Nevertheless, we observed a considerable interpatient and interisolate variability of *Candida* growth and echinocandin activity in ascites fluid. This variability will limit the predictability of fungal eradication from ascites fluid by echinocandins. Along with antifungal treatment, patient-specific factors might be crucial for fungal eradication during *Candida* peritonitis. These factors, however, are hardly predictable for the individual patient. Timely and effective treatment is therefore mandatory in this life-threatening condition, although the optimal antifungal regimen remains to be established.

In conclusion, echinocandin concentrations in ascites fluid were lower than the simultaneous plasma levels, and *Candida* proliferation in ascites fluid was slower than that in culture medium. The echinocandin susceptibility of *Candida* in ascites fluid is variable but lower than that in culture medium. Treatment with standard doses of AFG, MFG, or CAS which is based on candidemia studies will result in ascites fluid concentrations preventing relevant proliferation of *C. albicans* and *C. glabrata* but does not warrant reliable eradication. Further studies on the clinical efficiency of antifungals against fungal peritonitis are required.

## MATERIALS AND METHODS

**Patient enrollment.** The protocol of this open-label pharmacokinetic study was approved by the local ethics committees (EudraCT no. 2013-005065-38), and the study was performed in accordance with the Declaration of Helsinki and with Austrian law. Written informed consent was granted by competent patients. *Post hoc* consent was obtained from patients who were incompetent at the time of enrollment. We enrolled consecutive critically ill adults treated with AFG, MFG, or CAS for proven or suspected invasive fungal infections who had an indication for peritoneal drainage or paracentesis. AFG (Ecalta; Pfizer, Sandwich, Kent, UK), MFG (Mycamine; Astellas, Leiderdorp, the Netherlands), and CAS (Cancidas; Merck Sharp and Dohme, Hertfordshire, UK) were administered at the discretion of the treating physician. Ascites fluid was obtained from ascites drains or during paracentesis. When an ascites drain had been inserted, the collection bags were changed before (0 h) as well as 1, 4, 8, 12, 18, and 24 h after the start of infusion and kept for echinocandin measurement. Paracentesis was scheduled according to clinical requirements. Two-milliliter blood samples were drawn into heparinized vials (Sarstedt, Nümbrecht, Germany) simultaneously with paracentesis or with the changes of the collection bags and were centrifuged at 350 × *g* for 10 min. Plasma and ascites fluid samples were stored at −80°C.

**Echinocandin quantification.** AFG and MFG in ascites fluid and in plasma were quantified with high-performance liquid chromatography and UV detection (HPLC-UV) as described previously (37).

CAS concentrations were measured by liquid chromatography-tandem mass spectrometry (LC-MS/MS). Aliquots of 25 $\mu$l of the samples were mixed with 25 $\mu$l of an internal standard solution (caspofungin [$C_{52}H_{84}D_4N_{10}O_{15}$]; 1.0 $\mu$g/ml; Toronto Research Chemicals, North York, Canada). Subsequently, 100 $\mu$l of 0.1% formic acid in acetonitrile was added for protein precipitation. After 5 minutes of ultrasonication, samples were centrifuged for 5 minutes at 1,900 × *g*, and 160 $\mu$l of the supernatant was mixed with 150 $\mu$l of 0.1% formic acid in acetonitrile.

The LC-MS/MS system comprised a 1100 series HPLC pump (Agilent, Waldbronn, Germany), a CTC-PAL autosampler (CTC Analytics AG, Zwingen, Switzerland), and a QTrap 4000 mass spectrometer (Sciex, Framingham, MA, USA). Separation was performed on a Zorbax SB-$C_{18}$ column (2.1 by 150 mm, 5 $\mu$m) protected by an SB-$C_{18}$ guard column (4.6 by 12.5 mm, 5 $\mu$m; both Agilent Technologies, Vienna, Austria). Separation was accomplished with a linear gradient of 5% to 100% acetonitrile in aqueous 0.5% acetic acid solution within 10 minutes. The flow rate was set to 300 $\mu$l/min, and the column temperature and the injection volume amounted to 50°C and 10 $\mu$l, respectively. Mass spectrometry detection was performed with electrospray ionization in positive ion mode. Multiple reaction monitoring was carried out using the precursor-to-product ion transitions *m/z* 547.5 to 131.1 (quantifier) and 547.5 to 137.1 (qualifier) for CAS as well as 549.5 to 131.1 for caspofungin-D4.

For calibration, matrix-matched standards were used (range, 0.05 to 10.0 mg/liter), with a lower limit of quantitation (LLOQ) of 0.1 mg/liter. The fitness of the method was confirmed by validation experiments. Bias and relative standard deviations were <15%. The process efficiencies were 70% to 80%. Plasma samples of patients 17 to 20 and 23 and 27 were quantified with a previously described LC-MS/MS method (38).

**Pharmacokinetic and statistical calculations.** When serial samples had been obtained from an ascites drainage, the penetration ratio (PR) was defined as the ratio between the area under the echinocandin concentration-time curve over the sampling period ($AUC_{0-n}$) in ascites fluid and the $AUC_{0-n}$ in

plasma ($AUC_{0-n\ ascites\ fluid}/AUC_{0-n\ plasma}$; with sampling periods of 8 h, 12 h, 18 h, or 24 h). When single samples had been drawn during paracentesis, the PR was the ratio between the echinocandin concentration in ascites fluid and in the simultaneously taken plasma sample ($C_{ascites\ fluid}/C_{plasma}$).

Echinocandin pharmacokinetics in ascites fluid and in plasma were calculated by a noncompartmental model using Kinetica 2000 (InnaPhase Corp., Champs-sur-Marne, France). The $AUC_{0-n}$ was calculated using the log-linear method whenever the concentration in a trapezoid decreased or with the trapezoidal method when the concentration increased. The significance of the difference between the echinocandin concentrations in ascites fluid and in plasma was assessed by the Wilcoxon signed-rank test. Differences between the PR of the echinocandins were assessed with the Mann-Whitney U test and done with Bonferroni correction. Statistical calculations were performed with SPSS Statistics 24.0 (IBM Corporation, New York, USA).

**Pharmacodynamic assessment by *in vitro* and *ex vivo* simulation.** Clinical isolates of *C. albicans* and *C. glabrata*, stored at −80°C, were thawed and grown on Sabouraud (SAB) agar plates (Difco, Vienna, Austria) for 24 h at 37 ± 1°C. Ascites fluid was filtered twice (Filtropur S; 0.2- and 0.45-$\mu$m pore size; Sarstedt, Nümbrecht, Germany) in order to avoid bacterial or fungal contamination and subsequently inoculated with $2 \times 10^4$ *Candida* cells per ml. Controls were grown in RPMI 1640 culture medium (Sigma-Aldrich, St. Louis, USA). Samples were incubated at 37 ± 1°C and gently shaken at 170 rpm. After 24 and 48 h, aliquots were drawn and diluted 10-fold or 100-fold in double-distilled water. Aliquots of 50 $\mu$l of these dilutions were plated in duplicate onto SAB agar plates with an automatic spiral plater (model WASP 2; Don Whitley Scientific, Shipley, UK). The plates were incubated at 37 ± 1°C for 24 h, and the number of fungal CFUs was counted. *In vitro* simulation was also tried using standard EUCAST MIC tests. By applying this approach, however, numerous ascites fluid samples were unevaluable because of the highly variable color and turbidity of ascites fluid.

*In vitro* simulations were performed in filtered ascites fluid obtained from patients not on antifungal treatment. Ascites fluid was spiked with AFG, MFG, or CAS at final concentrations of 0.03, 0.06, 0.125, 0.25, 0.50, 1.00, 2.00, 4.00, 8.00, and 16.00 $\mu$g/ml. For this purpose, we used stock solutions comprising 1 mg/ml of AFG, MFG, or CAS dissolved in 90% methanol (vol/vol in water). Echinocandin-spiked samples were inoculated with $2 \times 10^4$ cells of *C. albicans* or *C. glabrata* per ml and incubated for 24 h at 37 ± 1°C. The sample volume amounted to 3 ml during incubation. Subsequently, aliquots were drawn and plated in duplicity undiluted or diluted 10-fold or 100-fold. After 24 h of incubation at 37 ± 1°C, the number of CFUs was assessed, considering the dilution.

*Ex vivo* simulation was performed in ascites fluid samples of selected study patients taken for measurement of echinocandin concentrations via ascites drains before (0 h), as well as 4, 8, 12, 18, and 24 h after, the start of the echinocandin infusion or during paracentesis scheduled at different times after infusion according to clinical requirements. Ascites fluid samples of patients 4, 5, 19, 21, 22, and 25 were inoculated with *C. albicans* or *C. glabrata* and exposed to the echinocandin concentrations measured in these samples. AFG, MFG, and CAS were not detectable in the ascites fluid samples after sterile filtration, probably because of absorption by the filter. Therefore, the samples were spiked with echinocandins at the previously measured concentrations and subsequently inoculated with $2 \times 10^4$ cells of *C. glabrata* or *C. albicans* per ml using the respective stock solutions mentioned above. *Ex vivo* simulations were performed with a final sample volume of 1.5 ml of ascites fluid and RPMI, respectively. Samples were incubated for 24 h at 37 ± 1°C. After 8 and 24 hours, respectively, 100 $\mu$l of each sample was plated in duplicate onto SAB agar plates with an automatic spiral plater. Plates were incubated at 37 ± 1°C for 24 hours, and then CFUs were counted as described above.

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## REFERENCES

1. Matuszkiewicz-Rowinska J. 2009. Update on fungal peritonitis and its treatment. Perit Dial Int 29:S161–S165.
2. Hasibeder W, Halabi M. 2014. Candida peritonitis. Minerva Anestesiol 80:470–481.
3. Al Bshabshe A, Joseph MRP, Battayah ES, Hamid ME. 2019. Fungal peritonitis caused by Pichia kudriavzevii following sleeve gastrectomy. Ann Saudi Med 39:205–208. https://doi.org/10.5144/0256-4947.2019.205.
4. Wawrysiuk S, Rechberger T, Futyma K, Miotła P. 2018. A case report of an intraperitoneal infection. Prz Menopauzalny 17:94–96. https://doi.org/10.5114/pm.2018.77310.
5. Szeto CC, Li PK. 2019. Peritoneal dialysis-associated peritonitis. Clin J Am Soc Nephrol 14:1100–1105. https://doi.org/10.2215/CJN.14631218.
6. Tong R, Hu S, Yang H. 2018. Peritoneal dialysis related fungal peritonitis caused by Candida krusei: the first reported case. Nephrology (Carlton) 23:703–704. https://doi.org/10.1111/nep.13167.
7. Hu S, Tong R, Bo Y, Ming P, Yang H. 2019. Fungal peritonitis in peritoneal dialysis: 5-year review from a North China center. Infection 47:35–43. https://doi.org/10.1007/s15010-018-1204-7.
8. Emami S, Lew SQ. 2018. PD-associated peritonitis: a case report. Perit Dial Int 38:391–392. https://doi.org/10.3747/pdi.2018.00044.
9. Tariq T, Irfan FB, Farishta M, Dykstra B, Sieloff EM, Desai AP. 2019. Spontaneous fungal peritonitis: micro-organisms, management and mortality in liver cirrhosis—a systematic review. World J Hepatol 11:596–606. https://doi.org/10.4254/wjh.v11.i7.596.

10. Maraolo AE, Buonomo AR, Zappulo E, Scotto R, Pinchera B, Gentile I. 2019. Unsolved issues in the treatment of spontaneous peritonitis in patients with cirrhosis: nosocomial versus community-acquired infections and the role of fungi. Rev Recent Clin Trials 14:129–135. https://doi.org/10.2174/1574887114666181204102516.
11. Shizuma T. 2018. Spontaneous bacterial and fungal peritonitis in patients with liver cirrhosis: a literature review. World J Hepatol 10:254–266. https://doi.org/10.4254/wjh.v10.i2.254.
12. Verma N, Singh S, Taneja S, Duseja A, Singh V, Dhiman RK, Chakrabarti A, Chawla YK. 2019. Invasive fungal infections amongst patients with acute-on-chronic liver failure at high risk for fungal infections. Liver Int 39:503–513. https://doi.org/10.1111/liv.13981.
13. Jindal N, Arora S, Pathania S. 2015. Fungal culture positivity in patients with perforation peritonitis. J Clin Diagn Res 9:DC01–DC03. https://doi.org/10.7860/JCDR/2015/13189.6050.
14. de Ruiter J, Weel J, Manusama E, Kingma WP, van der Voort PH. 2009. The epidemiology of intra-abdominal flora in critically ill patients with secondary and tertiary abdominal sepsis. Infection 37:522–527. https://doi.org/10.1007/s15010-009-8249-6.
15. Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, Reboli AC, Schuster MG, Vazquez JA, Walsh TJ, Zaoutis TE, Sobel JD. 2016. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis 62:e1–e50. https://doi.org/10.1093/cid/civ933.
16. Chen SC, Slavin MA, Sorrell TC. 2011. Echinocandin antifungal drugs in fungal infections: a comparison. Drugs 71:11–41. https://doi.org/10.2165/11585270-000000000-00000.
17. Dupont H, Massias L, Jung B, Ammenouche N, Montravers P. 2017. Pharmacokinetic study of anidulafungin in ICU patients with intra-abdominal candidiasis. J Antimicrob Chemother 72:1429–1432. https://doi.org/10.1093/jac/dkw568.
18. Wasmann RE, Muilwijk EW, Burger DM, Verweij PE, Knibbe CA, Bruggemann RJ. 2018. Clinical pharmacokinetics and pharmacodynamics of micafungin. Clin Pharmacokinet 57:267–286. https://doi.org/10.1007/s40262-017-0578-5.
19. Muilwijk EW, Schouten JA, van Leeuwen HJ, van Zanten AR, de Lange DW, Colbers A, Verweij PE, Burger DM, Pickkers P, Bruggemann RJ. 2014. Pharmacokinetics of caspofungin in ICU patients. J Antimicrob Chemother 69:3294–3299. https://doi.org/10.1093/jac/dku313.
20. Hiemenz J, Cagnoni P, Simpson D, Devine S, Chao N, Keirns J, Lau W, Facklam D, Buell D. 2005. Pharmacokinetic and maximum tolerated dose study of micafungin in combination with fluconazole versus fluconazole alone for prophylaxis of fungal infections in adult patients undergoing a bone marrow or peripheral stem cell transplant. Antimicrob Agents Chemother 49:1331–1336. https://doi.org/10.1128/AAC.49.4.1331-1336.2005.
21. Brüggemann RJ, Middel-Baars V, de Lange DW, Colbers A, Girbes AR, Pickkers P, Swart EL. 2017. Pharmacokinetics of anidulafungin in critically ill intensive care unit patients with suspected or proven invasive fungal infections. Antimicrob Agents Chemother 61:e01894-16. https://doi.org/10.1128/AAC.01894-16.
22. Perez Civantos DV, Robles Marcos M, Azanza Perea JR, Pazos Pacheco C, Garcia-Montoto Perez F, Jerez Gomez-Coronado V. 2019. Pharmacokinetics of anidulafungin in critically ill patients with Candida peritonitis. Int J Infect Dis 86:142–146. https://doi.org/10.1016/j.ijid.2019.07.008.
23. Welte R, Eller P, Lorenz I, Joannidis M, Bellmann R. 2018. Anidulafungin pharmacokinetics in ascites fluid and pleural effusion of critically ill patients. Antimicrob Agents Chemother 62:e02326-17. https://doi.org/10.1128/AAC.02326-17.
24. Grau S, Luque S, Campillo N, Samsó E, Rodríguez U, García-Bernedo CA, Salas E, Sharma R, Hope WW, Roberts JA. 2015. Plasma and peritoneal fluid population pharmacokinetics of micafungin in post-surgical patients with severe peritonitis. J Antimicrob Chemother 70:2854–2861. https://doi.org/10.1093/jac/dkv173.
25. Andes D, Diekema DJ, Pfaller MA, Bohrmuller J, Marchillo K, Lepak A. 2010. In vivo comparison of the pharmacodynamic targets for echinocandin drugs against Candida species. Antimicrob Agents Chemother 54:2497–2506. https://doi.org/10.1128/AAC.01584-09.
26. Pfaller MA, Messer SA, Rhomberg PR, Castanheira M. 2017. CD101, a long-acting echinocandin, and comparator antifungal agents tested against a global collection of invasive fungal isolates in the SENTRY 2015 Antifungal Surveillance Program. Int J Antimicrob Agents 50:352–358. https://doi.org/10.1016/j.ijantimicag.2017.03.028.
27. Nieto JC, Perea L, Soriano G, Zamora C, Cantó E, Medina A, Poca M, Sanchez E, Roman E, Julià G, Navarro F, Gely C, Alvarado EA, Guarner C, Juarez C, Vidal S. 2018. Ascitic fluid regulates the local innate immune response of patients with cirrhosis. J Leukoc Biol 104:833–841. https://doi.org/10.1002/JLB.3A0218-072R.
28. Mai M, Stengel S, Al-Herwi E, Peter J, Schmidt C, Rubio I, Stallmach A, Bruns T. 2017. Genetic variants of TRAF6 modulate peritoneal immunity and the risk of spontaneous bacterial peritonitis in cirrhosis: a combined prospective-retrospective study. Sci Rep 7:4914. https://doi.org/10.1038/s41598-017-04895-z.
29. Norris T, VanAlsten J, Hubbs S, Ewing M, Cai W, Jorgensen ML, Bordner J, Jensen GO. 2008. Commercialization and late-stage development of a semisynthetic antifungal aft anidulafungin/D-fructose (Eraxis). Org Process Res Dev 12:447–455. https://doi.org/10.1021/op800055h.
30. Cassone A, Mason RE, Kerridge D. 1981. Lysis of growing yeast-form cells of Candida albicans by echinocandin: a cytological study. Med Mycol 19:97–110. https://doi.org/10.1080/00362178185380161.
31. Cornely OA, Lasso M, Betts R, Klimko N, Vazquez J, Dobb G, Velez J, Williams-Diaz A, Lipka J, Taylor A, Sable C, Kartsonis N. 2007. Caspofungin for the treatment of less common forms of invasive candidiasis. J Antimicrob Chemother 60:363–369. https://doi.org/10.1093/jac/dkm169.
32. Montravers P, Mira JP, Gangneux JP, Leroy O, Lortholary O, AmarCand Study Group. 2011. A multicentre study of antifungal strategies and outcome of Candida spp. peritonitis in intensive-care units. Clin Microbiol Infect 17:1061–1067. https://doi.org/10.1111/j.1469-0691.2010.03360.x.
33. Maseda E, Rodríguez-Manzaneque M, Dominguez D, González-Serrano M, Mouriz L, Álvarez-Escudero J, Ojeda N, Sánchez-Zamora P, Granizo JJ, Giménez MJ, GTIPO-SEDAR. 2016. Intraabdominal candidiasis in surgical ICU patients treated with anidulafungin: a multicenter retrospective study. Rev Esp Quimioter 29:32–39.
34. van der Voort PH, Boerma EC, Yska JP. 2007. Serum and intraperitoneal levels of amphotericin B and flucytosine during intravenous treatment of critically ill patients with Candida peritonitis. J Antimicrob Chemother 59:952–956. https://doi.org/10.1093/jac/dkm074.
35. Pea F, Righi E, Cojutti P, Carnelutti A, Baccarani U, Soardo G, Bassetti M. 2014. Intra-abdominal penetration and pharmacodynamic exposure to fluconazole in three liver transplant patients with deep-seated candidiasis. J Antimicrob Chemother 69:2585–2586. https://doi.org/10.1093/jac/dku169.
36. Weiler S, Bellmann-Weiler R, Dunzendorfer S, Joannidis M, Bellmann R. 2008. Levels of amphotericin B lipid formulations in ascites. J Antimicrob Chemother 62:1163–1164. https://doi.org/10.1093/jac/dkn306.
37. Welte R, Oberacher H, Schwärzler B, Joannidis M, Bellmann R. 2020. Quantification of anidulafungin and micafungin in human body fluids by high performance-liquid chromatography with UV-detection. J Chromatogr B Analyt Technol Biomed Life Sci 1139:121937. https://doi.org/10.1016/j.jchromb.2019.121937.
38. Weiler S, Seger C, Pfisterer H, Stienecke E, Stippler F, Welte R, Joannidis M, Griesmacher A, Bellmann R. 2013. Pharmacokinetics of caspofungin in critically ill patients on continuous renal replacement therapy. Antimicrob Agents Chemother 57:4053–4057. https://doi.org/10.1128/AAC.00335-13.