International Journal of Antimicrobial Agents 62 (2023) 107007

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Caspofungin sequestration in a polyacrylonitrile-derived filter: Increasing the dose does not mitigate sequestration

Frédéric J. Baud[a,*], Vincent Jullien[b,c], Marie Desnos-Ollivier[d], Lionel Lamhaut[a], Olivier Lortholary[e]

[a] Département d'Anesthésie-Réanimation Adulte–SAMU de Paris, Hôpital Necker; Assistance Publique–Hôpitaux de Paris, University Paris Cité, Paris, France
[b] Université Sorbonne Paris Nord, IAME, INSERM, Paris, France
[c] UF de Pharmacologie, Hôpital Jean Verdier, APHP, Bondy, France
[d] Institut Pasteur, Université Paris Cité, Department of Mycology, Paris, France
[e] Necker Pasteur Centre for Infectious Diseases and Tropical Medicine, IHU Imagine, Necker Enfants Malades, University Hospital, Paris, France; Institut Pasteur, Université Paris Cité, Paris, France

ARTICLE INFO

Article history:
Received 13 December 2022
Accepted 29 September 2023

Editor: Dr A.M. Bal

Keywords:
Caspofungin
Echinocandins
Continuous renal replacement therapy
Pharmacokinetics
Sequestration
Treatment failures

ABSTRACT

Objectives: Critically ill patients frequently require continuous renal replacement therapy. Echinocandins are recommended as first-line treatment of candidemia. Preliminary results suggested echinocandin sequestration in a polyacrylonitrile filter. The present study aimed to determine whether increasing the dose might balance sequestration.

Methods: An STX filter (Baxter-Gambro) was used. A liquid chromatography–mass spectrometry method was used for dosage of caspofungin. In vitro drug disposition was evaluated by NeckEpur (Neckepur, Versailles, France) technology using a crystalloid medium instead of diluted/reconstituted blood, focusing on the disposition of the unbound fraction of drugs. Two concentrations were assessed.

Results: At the low dose, the mean measured initial concentration in the central compartment (CC) was 5.1 ± 0.6 mg/L. One hundred percent of the initial amount was eliminated from the CC within the 6-h session. The mean total clearance from the CC was 9.6 ± 2.5 L/h. The mean percentages of elimination resulting from sequestration and diafiltration were 96.0 ± 5.0 and 4.0 ± 5.2%, respectively. At high dose, the mean measured initial concentration in the CC was 13.1 mg/L. One hundred percent of the initial amount was eliminated from the CC within the 6-h session. The mean total clearance from the CC was 9.5 L/h. The mean percentages of elimination resulting from sequestration and filtration were 88.5% and 11.5%, respectively.

Conclusion: Increasing the dose does not mitigate caspofungin sequestration in the STX filter. The results raise caution about the simultaneous use of caspofungin and polyacrylonitrile-derived filters. Intermittent modes of renal replacement therapy might be considered. For sensitive species, fluconazole might be an alternative.

1. Introduction

Caspofungin has been consistently included in the list of drugs that do not need therapeutic adjustments during continuous renal replacement therapy (CRRT) [1], regardless of the CRRT method applied [2,3]. However, this assumption is supported by a limited number of clinical pharmacokinetics studies. Roger et al. and Aguilar et al. used polysulfone-derived filters. Roger et al. concluded that in adult patients requiring CRRT, higher than recommended loading doses of caspofungin are required to achieve pharmacokinetic/pharmacodynamic (PK/PD) targets in critically ill patients [2]. Additionally, Aguilar et al. determined that the licenced dosage regimen of caspofungin was not adequate to reach the PK/PD targets in some critically ill patients requiring CRRT [3]. As noted by several authors, data on caspofungin pharmacokinetics in critically ill patients under continuous renal replacement are limited, resulting in negative or inconclusive data regarding caspofungin adsorption [4–6], although only a few in vitro studies were reported.

Sequestration of caspofungin during CRRT is a matter of debate. Several authors made thorough reviews of clinical reports in the medical literature dealing with anidulafungin, caspofungin, and micafungin during CRRT and raised concern about the role of

* Corresponding author. Mailing address: Intensive Care Unit–Necker Hospital, Université Paris 7 Diderot: Universite de Paris, Rea Polyvalente Adulte, Hopital Necker 149, Rue de Sévres, Paris 75015, France.
E-mail address: baud.frederic@wanadoo.fr (F.J. Baud).

https://doi.org/10.1016/j.ijantimicag.2023.107007
0924-8579/

sequestration [4,7]. The authors concluded that 20% of echinocandin sequestration to membrane is not likely to be clinically relevant for anidulafungin and caspofungin, as the loading dose is greater than the maintenance dose [4]. However, this might be relevant for micafungin due to the lack of a loading dose. Honore et al. pointed out that only polysulfone filters were used in clinical studies, whereas other filters exhibit highly adsorptive properties. They suggested the need for further studies focusing on caspofungin using polyacrylonitrile-derived filters [5].

In vitro studies dealing with caspofungin sequestration in CRRT filters are scarce. Purohit et al. reported sequestration of caspofungin using a polysulfone filter filled with human whole blood in a close one-compartment model. In this model, mean fractional sequestration of caspofungin adds a clearance of 0.40 mL/min (0.024 L/h) [8]. Purohit et al. concluded that caspofungin had minimal circuit clearance and did not change with increasing flowrate. In contrast, we reported preliminary results of an in vitro study using the NeckEpur ((Neckepur, Versailles, France) method and a polyacrylonitrile-derived filter, showing that concentrations of unbound caspofungin and micafungin become undetectable in the central compartment (CC) within 4 h following initiation of sessions [9].

Later, we reported on a case of invasive candidiasis with candidemia efficiently treated using caspofungin. Caspofungin transiently failed when the patient required a long-lasting continuous hemofiltration using a polyacrylonitrile filter, while caspofungin regained full efficiency as soon as the continuous hemofiltration was withdrawn [10].

This case prompted us (1) to complete the in vitro assessment of caspofungin sequestration in a polyacrylonitrile filter and (2) to address whether increasing the dose of caspofungin might mitigate filter-induced sequestration.

2. Methods

2.1. Caspofungin

Caspofungin was supplied by Mylan, with one vial containing 50 mg of caspofungin (as acetate).

2.2. Measurements of caspofungin concentrations

The analytical method was a liquid chromatography–coupled mass spectrometry assay we previously published [11]. The chromatographic separation was performed on a Waters C18 BEH column (50 × 2.1 mm) with a mobile phase consisting of a mixture of water and acetonitrile, both containing 0.1% formic acid. In these conditions, the retention time of caspofungin was 1.58 min. The intra- and inter-day imprecision and inaccuracy were less than 20% for the limit of quantification (0.2 mg/L) and less than 15% for higher concentration levels.

We assigned the zero value to samples that had a caspofungin concentration below this threshold.

2.3. Aims of the study

The primary objective of the NeckEpur technology is to simultaneously assess the routes of elimination of drugs by filters used in CRRT by determining the respective contribution of filtration, dialysis, and adsorption over a period, resulting in elimination of 90% and more of the initial dose in the central compartment in an in vitro model [12–17].

There are three prerequisites for addressing the issue of the extent of adsorption in in vitro studies.

The first prerequisite is to use a medium that does not interfere with drug distribution in the CC. This prerequisite is addressed using crystalloid solution instead of blood. Indeed, as clearly stated by Maher [18] and Mac-Kay et al. [19] when using blood, the accurate calculation of clearance during RRT requires the measurements of plasma drug concentrations, the plasma protein concentrations at the same time, the measured fraction of drug bound to protein, and the intra-erythrocyte distribution coefficient. Noteworthy, Neri et al. recommended the use of water instead of blood to accurately determine the sieving coefficient and only in the filtration mode without any gradient of concentrations [20].

The second prerequisite is the need to assess stability of the drug in the crystalloid solution at room temperature during the study period. Indeed, the NeckEpur technology is based on the law of conservation of mass. In our very simple model, it is reasonable to assume that the law of conservation of mass holds true.

The third prerequisite results from the Gibbs-Donnan effect related to distribution of ionized molecule. To meet this requirement, the same crystalloid medium was used in the different compartments including the CC, the ultra-filtrate, and dialysate. Hemosol B0 (Baxter) was used in the present study.

2.4. Assessment of the stability of caspofungin in the CC

Stability of caspofungin in a 5-L bag of Hemosol B0 was assessed at room temperature and natural daylight at 0, 2, 4, 6, and 8 h following injection at two concentrations (low and high) in the CC.

2.5. Filter and dialyzer device

Prismaflex monitor and the ST150 filter derived from the AN-69 (Baxter-Gambro) was used. A new filter was used for each session.

2.5. Modes of exposure of the filter to caspofungin

A 5-L bag was used as the CC and loaded with caspofungin at the targeted concentration just before initiation of the session. This mode of exposure used in the NeckEpur technology initially exposes the filter to the maximal concentration and corresponds to a bolus dose as the maximal concentration occurs at T0. To our knowledge, this mode of exposure was used in all in vitro studies dealing with the assessment of drug adsorption in filters used in CRRT.

2.6. Mode of CRRT

At low dose, the ST filter was exposed to the filter in the diafiltration mode with diafiltration mode combining dialysis set to 2.5 L/h flow rate and filtration set to 0.5 L/h at predilution and 1 L/h at post-dilution ports. The total diafiltration flow rate was 4 L/h, as previously reported. The simulated blood flow rate was set to 200 mL/min. The net loss was set to zero. Duration of the session was set to 6 h.

At high dose, the ST filter was exposed to the filtration mode only with a flow rate set to 2.5 L/h in the post-dilution mode with simulated blood flow rate at 200 mL/min. As stated, previously, the filtration mode is the only one allowing accurate assessment of the sieving coefficient (Sc). The net loss was set to zero. Duration of session was set to 6 h.

2.7. Sampling

Samplings were performed in the CC at the inlet (C_{si}) and outlet (C_{so}) ports of the filter, at the effluent tubing, allowing access to instantaneous value of the concentration in the effluent (C_{effl}) at 0, +15, +30, +45, +60 min, and then at + 2, 3, 4, and 6 h.

Cumulative effluents were sampled at the time the bag was filled and needed to be changed, except at the end with incomplete filling.

2.8. NeckEpur technology

NeckEpur technology is designed to simultaneously determine the respective roles of dialysis, filtration, and adsorption of drugs in the filter. NeckEpur technology does not make any assumption about the time or concentration dependency of the PK in the CC. NeckEpur technology uses the fine-tuning measurement of volumes, flow rates, and concentrations in the different compartments, while measurements of quantities in the different compartments are based on the law of conservation of mass.

Volumes were assessed by measuring the weight of effluent bags using an electronic Salter scale range of measurements: 2 g to 10 000 g, (accuracy ± 2 g).

Precision of diafiltration flow rates was determined by measurement of the weight of crystalloid solute collected during the time elapsed when changing the effluent bags of solute. The filled bag weight was corrected by subtracting the weight of the empty dry bag.

In a previous study [12], precision of the 200-mL/min simulated blood flow rate was determined by measuring the weight of crystalloid solute collected over 10 min.

The clearance from the CC over the study period was calculated as $CL = (Dose_{initial} - Dose_X)/AUC_{0-X}$, where X denotes the end time of the session, and $Dose_X$ denotes the amount remaining in the CC at the end of the session.

Areas under the curve (AUCs) of concentrations were calculated using the trapezoidal method.

The extraction coefficient (EC) was calculated as recommended: $EC = ((C_{si} - C_{so})/C_{si})$ [21,22].

The clearance provided by the filter was calculated as $Clear_{filter} = EC \times Q_{simul}$, where Q_{simul} denotes the simulated blood flow rate set to 200 mL/min (12 L/h).

As stated previously, at each sampling time the Sc was assessed as recommended, only in the following filtration mode: $Sc = C_{effl\ instant}/C_{si}$.

The percentages of elimination by diafiltration/filtration and sequestration were calculated by means of the initial ($A_{initial}$) and final (A_{final}) amounts in the CC, and the total amounts were eliminated in the cumulated effluents ($A_{efflu\ cumul}$) according to the following equation: % eliminated from the CC by diafiltration/filtration = $(A_{efflu\ cumul})/(A_{initial} - A_{final})$

$$\%\,\text{sequestrated} = [A_{initial} - (A_{final} + A_{efflu})]/(A_{initial} - A_{final}) \times 100.$$

2.9. Presentation of results

The GraphPad Prism V9 software (GraphPad Software) was used for column statistics and regression analysis. At low dose, four sessions were made; the results are presented as mean ± standard deviation. At high dose, sessions were made in duplicate; the results are presented as the mean. The EC was calculated at each time of sampling in the CDF mode. In the filtration mode, we attempted to calculate instantaneous Sc.

2.10. Antifungal susceptibility

All clinical isolates of *Candida albicans* (*C. albicans*) received at the National Reference Centre for Mycoses and Antifungals as part of surveillance programmes or for expertise are identified according to an identical procedure [23]. For all isolates received between 1 January 2005 and 31 October 2022, MICs were determined for caspofungin using a modified version of the broth microdilution method from the European Committee on Antimicrobial Susceptibility Testing [24]. The AM3 medium (BD Difco, Reference 224320) was used for dilution [25]. Quality control strains (ATCC22019, ATCC6258) were included in each set. The concentration corresponding to the MIC that inhibited 50% (MIC50) and 90% (MIC90) of the isolates were determined.

3. Results

3.1. Stability

Stability of caspofungin was assessed in Hemosol B0 at room temperature and daylight over 8 h.

At low dose, the mean initial concentration was 5.26 mg/L. In comparison with T0, the percentages of variation at T+2, 6, and 8 h were − 8%, − 2%, and − 1%, respectively.

At high dose, the mean initial measured concentration was 17.7 mg/L. In comparison with T0, the percentages of variation at T+2, 6, and 8 h were − 5%, 0%, and − 2%, respectively.

3.2. Actual flow rate provided by the dialyser

During the four sessions at the diafiltration flow rate of 4 L/h, the filling time of the 5-L bags of effluent was recorded in 16 bags; the mean measured flow rate was 3.9 ± 0.1 L/h (coefficient of variation: 3.1%), which should be compared with the targeted 4 L/h one.

3.3. Low dose

The mean measured initial concentration of caspofungin in the CC was 5.1 ± 0.6 mg/L, corresponding to a mean initial amount of 25.0 ± 2.9 mg. One hundred percent of the initial amount was eliminated from the CC within the 6-h session. The time for caspofungin concentrations to become undetectable in the CC was 165 ± 90 min.

The mean AUC in the CC was 170 ± 50 mg/min/L. The mean clearance from the CC was 9.6 ± 2.5 L/h.

The mean EC was 81 ± 16%. The simulated flow rate was set to 12 L/h (200 mL/min). Accordingly, the clearance provided by the filter was equal to 9.7 L/h. As the concentrations in the instantaneous effluent was below the lower limit of quantitation (LLOQ), the value of the Sc cannot be calculated.

The mean values of the percentage of elimination resulting from sequestration and diafiltration were 96 ± 5 and 4 ± 5.2%, respectively. Table 1 includes the individual data collected in the four sessions. Fig. 1. shows the time courses of caspofungin in the CC, inlet, and outlet ports for the four sessions in the diafiltration mode.

3.4. High dose

The mean measured initial concentration of caspofungin in the CC was 13.1 mg/L, corresponding to a mean initial amount of 69.1 mg. One hundred percent of the initial amount was eliminated from the CC within the 6-h session. The time for caspofungin concentrations to become undetectable in the CC was 270 min.

The mean AUC in the CC was 453 mg/min/L. The mean clearance from the CC was 9.5 L/h. The mean EC was 62%. The simulated flow rate was set to 12 L/h. Accordingly, the clearance provided by the filter was equal to 7.4 L/h. The clearance provided by sequestration in the filter accounted for almost 80% of the total clearance from the CC.

The Sc could not be calculated at high concentration, as among the 18 samples in the two sessions, all concentrations in the instantaneous effluent were below the LLOQ.

Table 1
Pharmacokinetics parameters in the four sessions at low dose and the two at high dose.

Parameters	Low dose				High dose	
Session	1	2	3	4	1	2
Initial concentration[a] (mg/L)	4.94	4.34	5.47	5.6	13.9	12.4
AUC_{CC} (mg/min/L)	221.3	108.0	198.1	150.8	542.6	362.6
Time to < LLOQ (min)	240	60	180	120	180	360
Mean extraction coefficient (%)	100 ± 10	88 ± 15	65 ± 12	69 ± 25	52 ± 34	62 ± 13
Clearance from CC (L/h)	6.7	12.1	8.3	11.1	8.1	10.8
% eliminated by DF	0	0	9	9	13	10
% Sequestrated	100	100	91	91	90	89

AUC, area under the curve; CC, central compartment; DF, diafiltration; LLOQ, lower limit of quantitation.
[a] Denotes in the CC.

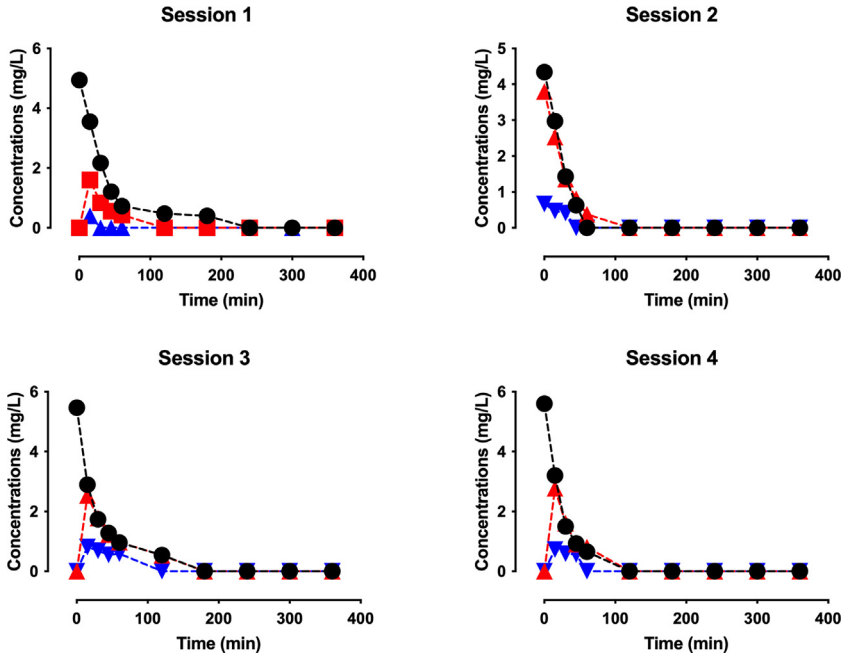

Fig. 1. Time course of caspofungin concentrations in the central compartment (black filled circles and dotted line), at the inlet (red filled squares and dotted line), and outlet ports (blue filled triangles and dotted line) for the four sessions in the diafiltration mode at low dose. There are four panels corresponding to the four sessions.

The mean percentages of elimination resulting from sequestration and filtration were 88.5 and 11.5%, respectively.

Individual data collected in the two sessions are displayed in Table 1.

Fig. 2 shows the time courses of caspofungin in the CC, inlet, and outlet ports of the two sessions in the filtration mode.

3.5. Relationship of the initial dose to the AUC_{0-360} at low and high doses in the CC

Figure 3 shows the linear relationship described by the following equation: $Y = 7.334\ X - 22.2$ ($R^2 = 0.8945$).

3.6. MIC of caspofungin for *Candida* species

The determination of MICs by broth microdilution using a modified version of the European Committee on Antimicrobial Susceptibility Testing method generated data for 3082 *C. albicans* and 610 *C. tropicalis* clinical isolates (Table 2). MIC50 and MIC90 are similar for both species: 0.03 and 0.06 mg/L, respectively.

4. Discussion

The results of the present study, in dealing with the PK of unbound caspofungin during sessions of CRRT, support the assumption of early-occurring and avid adsorption of caspofungin in a polyacrylonitrile-derived ST filter. Increasing the dose to frankly supra-therapeutic level results in only transient efficient concentrations, lasting less than 4 h. This finding supports the assumption that increasing the dose does not efficiently address sequestration induced by a polyacrylonitrile-derived filter. The use of low and high doses corresponding to low and high concentrations in the present study deserves some comments. Indeed, we studied the PK of elimination of the unbound concentrations of caspofungin. It should be pointed out that even at the highest recommended daily dose of 150 mg, assuming a linear relationship and according to data reported in the Stone et al. study [26], the peak unbound concentration of caspofungin would have been ca. 0.53 mg/L, which is far below the range of unbound concentrations of ca. 5 and 13 mg/L used in the present study.

Table 3 reports the clinical studies dealing with adsorption of echinocandins in critically ill patients receiving CRRT and in vitro studies of adsorption of caspofungin in filters used in CRRT.

Table 2
Range of MIC, MIC50, and MIC90 of caspofungin for isolates tested at the National Reference Centre for Mycoses and Antifungals using a modified version of the European Committee on Antimicrobial Susceptibility Testing broth microdilution method between 1 January 2005 and 31 October 2022.

Species	Number of isolates	MIC50 (mg/L)	MIC90 (mg/L)	Range of MICs (mg/L)
Candida albicans	3082	0.03	0.06	≤ 0.007 to 4.000
Candida tropicalis	610	0.03	0.06	≤ 0.007 to 2.000

Table 3
Clinical studies dealing with adsorption of echinocandins in critically ill patients receiving CRRT and in vitro studies of adsorption in filters used in CRRT.

Echinocandins	First author	Type of study	Filter	Mode of CRRT	Assessment of sequestration	Adsorption	Reference
Anidulafungin	Leitner	CT	PES	HF	Inlet-outlet differences and effluents	20%	[21]
Anidulafungin	Kölbinger	In vitro	PS	HD[a]	Clearance	99 - 60 - 35	[3]
Micafungin	Kishino	CT		HF	Inlet-outlet differences	0	[22]
Micafungin	Hirata	CT	PMMA	HDF	Not specific	No evidence	[23]
Micafungin	Baud	In vitro	PAN-PEI	CDF	CC and effluents	100%	[24]
Caspofungin	Weiler	CT	PS	HF and HD	Inlet-outlet differences and effluents	Ruled out adsorption	[27]
Caspofungin	Aguilar	CT	PS	HD	Inlet-outlet differences and effluents	Ruled out adsorption	[25]
Caspofungin	Roger	CT	PS	HF and HD	Inlet-outlet differences and effluents	No evidence	[26]
Caspofungin	Borsuk–De Moor	CT	NS	HF and HD	PKpop	Not discussed	[20]
Caspofungin	Baud	In vitro	PAN-PEI	CDF	CC and effluents	100%	[24]
Caspofungin	Purohit	In vitro	PS	CDF	Adsorption fraction	22 ± 4%	[17]
Caspofungin	Pérez-Pitarch	CT	NS	CDF	PKpop	Not discussed	[27]
Rezafungin	Jang	In vitro	PS and PAN	HF	Calculated from prefilter Conc and Sc	Unlikely to be adsorbed	[28]

CC, central compartment; CDF, continuous diafiltration; Conc, concentration; CRRT, continuous renal replacement therapy; CT, controlled trial; HD, haemodialysis; HDF, hemodiafiltration; HF, hemofiltration; NS, not specified; PAES, polyarylethersulfone; PAN, polyacrylonitrile; PAN-PEI, polyacrylonitrile covered by polyethyleneimine; PES, polyethylene sulfone; PMMA, polymethylmethacrylate; PKpop, population pharmacokinetics; PS, polysulfone; Sc, sieving coefficient.
[a] For HD, Kölbinger et al. used three media: saline, saline + albumin, and human blood.

In the present study, caspofungin concentrations in the different compartments are below the LLOQ within 6 h after initiation of exposure of the filter to the drug. We assigned the zero value to samples that had a caspofungin concentration below this threshold. The LLOQ reported in the present study, as well as in the preliminary report [9] of 0.2 mg/L, is equal to that reported in the literature [27], whereas Roger et al. reported a value of 0.1 mg/L [2]. In an in vitro study, using liquid chromatography–mass spectrometry, Purohit et al. reported a LLOQ for caspofungin of 1 mg/L [8]. Therefore, our results did not come from a lack of sensitivity of our method of measurement in comparison with the sensitivity of the different methods presently published in the medical literature.

Stability studies at both low and high doses ruled out sequestration in the plastic bag of Hemosol as well as spontaneous degradation of caspofungin, the latter having been evidenced in vivo [26,28].

Weiler et al. assessed caspofungin concentrations in arterial, prefilter/dialyzer, postfilter/dialyzer, and plasma samples as well as ultrafiltrate/dialysate concentration, which were quantified by high-performance liquid chromatography and mass spectrometry. Sieving/saturation coefficient and the corresponding extracorporeal clearances have been calculated form measured concentrations [27]. The comparisons of AUCs did not show evidence of significant differences. Therefore, membrane adsorption of caspofungin was ruled out by the authors. Our results about caspofungin and those of Kölbinger et al. about anidulafungin in saline medium [29] agree with the Weiler et al. results that extremely low values of concentrations in the instantaneous effluents, nearly at or below the LLOQ, preclude accurate assessment of the sieving coefficient while being suggestive of extensive adsorption. Indeed, drug adsorption occurs as soon as the drug in plasma (or crystalloid solution) meets the filter and during the time the ulfiltrate passes through the filter. One major consequence of adsorption is the early decrease in instantaneous ultrafiltrate concentrations. As a matter of fact, Rumpf et al. unveiled sequestration by unexpected early low ultrafiltrate concentrations of two adsorbed drugs in the RP6 dialyzer: gentamicin and doxycyclin [30]. Noteworthy, during the time course of adsorption of gentamicin and doxycyclin, there was a progressive increase in instantaneous ultrafiltrate concentrations suggestive of the completion of the phenomenon of adsorption. In our study, the extent of sequestration at the low and high doses resulted in non-quantifiable concentrations in the instantaneous effluents, except two samplings at high dose, and increasing the dose did not allow accurate calculation of Sc. In contrast, at the low and high doses, the cumulative effluents give access to quantifiable amounts.

To our knowledge, in vitro binding of caspofungin in filters used in CRRT has been poorly investigated. To address the use of caspofungin in the paediatric population, Purohit et al. studied sequestration of caspofungin in a polyarylethersulfone filter by means of a closed-loop model loaded with human blood. The Purohit et al. study aimed at mimicking sequential hemodiafiltration sessions at three flow rates: 0, 20, and 40 mL/kg/h [8]. Five sessions were performed to assess inter-run variability. Eighteen milligrams of caspofungin were added to the 1 L reservoir with a haematocrit of 35%. The mean fractional sequestration in the filter was assessed using a mathematical model with value of 22% of the initial dose corresponding to a clearance rate of 0.40 mL/min (0.024 L/h), which was not increased while doubling the flow rate [8]. The study deserved several comments [31]. Noteworthy, the authors reported a strong discrepancy between the extent of sequestration (22% of the initial dose) and the minute effect on the value of clearance added by significant sequestration (0.024 L/h). Despite this discrepancy, the authors concluded that caspofungin had minimal circuit clearance and did not change with increasing CRRT clearance rates [8].

The effect of protein binding on drug sequestration was studied by Kölbinger et al. using anidulafungin in three media: normal saline without and with albumin, and a mixture of human erythrocytes and fresh frozen plasma [29]. The sequestration rates were 99%, 60%, and 35%, respectively. It should be noted that the PK of drugs is based on the concentrations of the free fraction of drug in plasma and not on the total plasma concentrations. The values of anidulafungin sequestration in the different media, as shown by Kölbinger et al., shows the decreasing sequestration effect induced

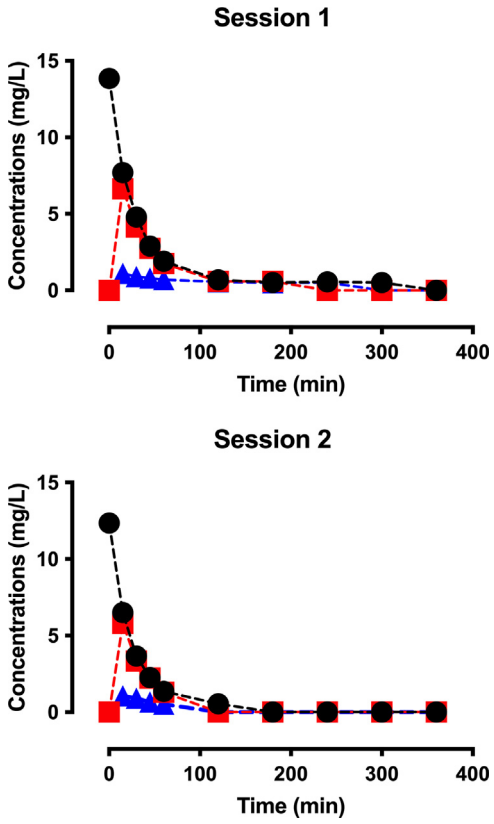

Fig. 2. Time course of caspofungin concentrations in the central compartment (black filled circles and dotted line), at the inlet (red filled squares and dotted line), and outlet ports (blue filled triangles and dotted line) of the two sessions in the filtration mode at high dose. There are two panels corresponding to the two sessions.

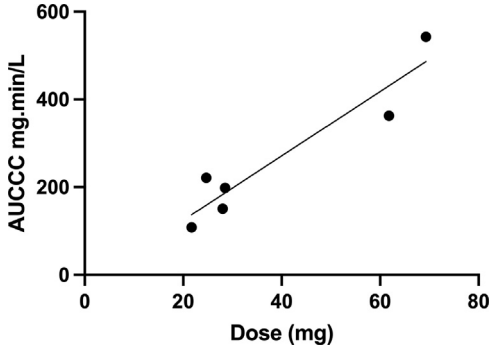

Fig. 3. Linear relationship between the dose and the area under the curve (AUC_{CC}) described by the following equation: Y = 7.334 X – 22.2 (R^2 = 0.8945).

by plasma and blood cells decreasing the ability of the drug to be presented to the filter. For drugs with low protein binding, the plasma concentration is an accurate surrogate of the free fraction. However, for drugs with high protein binding, the plasma concentration is no more an accurate surrogate of the free fraction. The blood-to-plasma ratio shows the additional factor resulting in drug sequestration in blood cells. The human blood-to-plasma partitioning ratio for caspofungin averages 0.74 and is independent of both incubation time and concentration [26]. Furthermore, during the life span of a filter, different types of proteins are adsorbed to membranes [32]. More proteins are adsorbed to polyacrylonitrile filters compared with other filters. For drugs exhibiting high protein binding, we cannot exclude that in addition to the direct drug-filter interaction, drug sequestration may also result from protein binding to filters [32]. We believe the NeckEpur technology allows one to study the direct drug-filter interaction, which allows the study of further interactions.

Even at high dose, we found caspofungin concentrations in the instantaneous effluents below the LLOQ, precluding any calculation of the Sc. In contrast, even in the filtration mode only, we found a calculable EC with a high value (81 ± 16%), resulting in an intrinsic clearance of the filter of 9.7 L/h, which strongly correlates with the value of the clearance assessed by means of the elimination of caspofungin from the CC, at 9.6 L/h. The values of the clearance of caspofungin from the CC at low and high doses were close together and far exceeded the values of the flow rates used in the two modes. We conclude that the ST150 adds a term of clearance not associated with diafiltration but likely resulting from sequestration of caspofungin in the filter.

We tested the hypothesis about whether a 3-fold increase in the concentration of caspofungin in the CC might mitigate sequestration. As a matter of fact, tripling the dose of caspofungin resulted in almost tripling the cumulative elimination of caspofungin in effluents that rose from 4% to 11.5%. Note that the concentrations of caspofungin presently studied correspond to the free fraction of caspofungin in plasma. Assuming a value of 11.6% of the unbound fraction in patients suffering from candidemia, the initial amount of “unbound” caspofungin in the CC of 25.0 and 69.1 mg would require a daily dose of 216 and 596 mg, respectively—doses above the maximal recommended dose of 150 mg/d [33,34].

There is a gap between concentrations of echinocandins lower than the LLOQ and concentrations lower than the MIC of *Candida* isolates. Indeed, the MIC of caspofungin towards various isolates of *Candida* is about 1 order of magnitude below the LLOQ or more. The MIC50 and MIC90 values are identical for *C. albicans* and *C. tropicalis* (0.03/0.06 mg/L) and like the values described previously [35] and in the literature [36]. This finding is of major importance and concentrations below the LLOQ does not mean inefficiency of “undetectable” caspofungin concentrations. As a matter of fact, we reported on a case of invasive candidiasis efficiently treated with 50 mg caspofungin [10]. Because of fluid overload and oliguric renal failure, continuous veno-venous hemofiltration (CVVHF) using the ST150 filter and Prismaflex dialyzer was initiated 2 d after intensive care unit admission. Three days after CVVHF initiation, blood cultures became positive with the same species of *Candida* and remained positive for 2 additional days, while caspofungin was given at an intravenous daily dose of 50 mg. Because the experimental in vitro results suggested elimination by CVVHF of the free fraction of caspofungin [9], CVVHF was stopped while caspofungin was given at the same dose. Blood cultures became negative again. This case illustrates the competition between daily administration of the drug as a 1-h infusion and as a continuous process of elimination by sequestration operating 24 h a day, including the hour required for caspofungin administration. Indeed, in experimental models of *C. albicans* infection, the PK/PD target of free caspofungin concentration is fAUC area under the curve of concentrations (fAUC)/Minimal inhibitory concentration (MIC) = 20 [37]. For a MIC = 0.06 mg/L, this makes a target fAUC = 1.2 mg.h/L, corresponding to a target 24-h average free concentration ($C_{average}$ [38,39]) of 0.05 mg/L. We hypothesise that caspofungin release from protein binding and tissue redistribution would have been able to maintain the unbound fraction above the MIC up to 72 h after CRRT initiation.

We can question whether there is any chemical interaction between caspofungin and polyacrylonitrile promoting sequestration. The parameters determining drug-filter interactions are poorly understood.

According to Purohit et al. [8], the adsorption studies of other antimicrobials have shown that drug-circuit adsorption is affected by properties of both medication and circuit.

- Medication properties affecting adsorption include protein binding, molecular weight, molecular charge, hydration radius, and concentration.
- The circuit properties affecting adsorption are the filter and the circuit material (polyacrylonitrile, polyamide, or polysulfone) and surface area. Recently, in the class of aminoglycosides, we added the polar surface area as a major physico-chemical parameter determining the extent of sequestration: the lower the polar surface area, the greater the extent of sequestration [13].

In our experience using NeckEpur technology, aminoglycosides are avidly bound to polyacrylonitrile. The molecular weight of the tested aminoglycosides ranged from ca. 467 to 585 g/mol. They are a cationic drug, whereas polyacrylonitrile-derived filters are negatively charged. The polar surface area of gentamicin, the most avidly sequestrated aminoglycoside, is 213.72 $Å^2$. Caspofungin molecular weight is 1093.331 g/mol with two cationic charges and a polar surface area of 412.03 $Å^2$. Protein binding of aminoglycosides is less than or equal to 11%, whereas that of caspofungin is ca. 96.5%.

The most evident parameter shared by aminoglycosides and caspofungin is their cationic structure regarding interaction with the polyacrylonitrile-derived filter. Interestingly, the ratio of the polar surface area to molecular weight of the most avidly bound aminoglycoside, gentamicin, is 0.418, whereas that of caspofungin is 0.377.

Our study presents several limitations. Only one type of filter was studied, although three main types of filters are presently used in the intensive care unit, including polysulfone- and polyamide-derived filters and the polyacrylonitrile filter. However, Kölbinger et al. and Leitner et al. reported anidulafungin sequestration using a polysulfone-derived filter [29,40].

The LLOQ of the methods of measurements used to assess caspofungin concentrations is significantly greater than the MIC. Therefore, increasing the sensitivity of analytical methods would be of value for better analysis of this major issue and a more precise assessment of the value of caspofungin Sc facing different filters.

The present study showed that increasing the dose far above the recommended highest dose does not significantly mitigate caspofungin sequestration. Further studies are needed to refine the dosage regimen resulting in the greatest mitigation of caspofungin sequestration. In vitro studies may provide a significant contribution to address this major issue before clinical trials. While waiting for this issue to be addressed, caution is necessarily while simultaneously using caspofungin and CRRT with the ST150 filters.

We did not assess the effect of exposure of the same filter to repeated daily dose of caspofungin. In a previous study dealing with exposure of the same filter to three daily doses of gentamicin, sequestration resulted in underdosing, with findings suggestive of a progressive saturation of the filter [15].

Immediate measures mitigating sequestration should be considered. One measure would be to limit the CRRT session using polyacrylonitrile-derived filters to less than 2 days. The simultaneous use of caspofungin and RRT with a polyacrylonitrile filter should not be advised. We should consider shifting from a polyacrylonitrile to a polysulfone filter. However, in an in vitro study using human blood, Purohit et al. reported a mean fractional adsorption of caspofungin of 22% in a polysulfone filter without any warning conclusion [8]. Further studies are needed before proposing a definitive alternative.

CRRT has been promoted instead of intermittent haemodialysis (IHD) because of fewer unfavourable hemodynamic effects and continuous control of the fluid balance. Currently used RRT modalities include conventional IHD, CRRT, and prolonged intermittent RRT [41]. Based on international surveys, CRRT remains the preferred technique in Europe, Asia, and Australasia, whereas IHD is more commonly prescribed in North America. In light of previous clinical studies reporting caspofungin PK to be unaffected by CRRT and the superiority of CRRT in critically ill patients, a shift to IHD is a questionable option. Indeed, there are neither in vitro nor in vivo data supporting this assumption.

Simultaneous use of caspofungin and RRT with a polyacrylonitrile filter should not be advised. We should consider shifting from a polyacrylonitrile to a polysulfone filter. In an in vitro study using human blood, Purohit et al. reported a mean fractional adsorption of caspofungin of 22% in a polysulfone filter without any warning conclusion [8]. As stated, previously, Kölbinger et al. studied the adsorption of anidulafungin in a polysulfone filter using three media: normal saline without and with albumin, and a mixture of human erythrocytes and fresh frozen plasma. The sequestration rates were 99%, 60%, and 35%, respectively [29]. We are presently testing the sequestration of caspofungin and micafungin in a polysulfone-derived filter using the NeckEpur technology. Further studies are needed before proposing a definitive alternative.

Rezafungin is a promising echinocandin allowing a weekly administration. Jang et al. performed an ex vivo study of rezafungin adsorption and clearance during CRRT using a polyether sulfone- and a polyacrylonitrile-derived filter [42]. Bovine whole blood was used in a closed-loop system, as previously reported. The authors concluded that, based on the Sc observed in this ex vivo study, rezafungin is unlikely to be adsorbed nor cleared by any form of CRRT. The methodology and the results deserve comments. The study lasted only 60 min, during which the effect of three flow rates were studied, resulting in samplings in less than 15 min after modification of flow rate. Adsorption is a time-dependent phenomenon with maximum values occurring within a few hours. The major determinant of the Sc is the unbound fraction of drugs. The LLOQs of the method used in previous in vitro and in vivo PK of caspofungin were in the range of 0.1 to 0.2 mg/L, and the value of 1 mg/L reported by Jang et al. does not meet the requirements for assessing the Sc of rezafungin, which is 99.2% bound to proteins. The initial 30-mg/L concentration would have resulted in an initial concentration of 0.24 mg/L in the instantaneous effluent, far below the LLOQ.

Despite many efforts, patients receiving fluconazole under CRRT did not easily attain the PK/PD target [43,44]. The difficulty in reaching targeted concentrations raises questions about possible sequestration in filters [45]. As there was no previous in vitro study, we considered it mandatory to address this major issue using the NeckEpur technology [16]. Adsorption of intravenous formulation of fluconazole was studied using the AV1000 polysulfone- and ST150 polyacrylonitrile-derived filters. The mode of CRRT was filtration with post-dilution only at flow rates of 1.5 and 2.5 L/h. Filtration allows accurate calculation of the sieving coefficient. Sessions were performed in duplicate at 2.5 L/h and triplicate using 1.5 L/h and lasted 6 h, allowing elimination of 90% and more of the initial amount in the central compartment at the 2.5-L/h flow rate. At the 2.5-L/h flowrate, the sieving coefficients provided by the AV1000 and ST150 filters were 0.94–0.91 and 0.99–0.91, respectively. The clearances from the CC were 2.5–2.6 and 2.4–2.3 L/h, respectively. The percentages of the amount eliminated from the CC by filtration/adsorption were 100/0%–95/5% and 100/0%–100/0%, respectively. At the 1.5-L/h flowrate, using the ST150 polyacrylonitrile-derived filters, the percentages of the amount eliminated from the CC by filtration/adsorption in the three sessions were 99/1%, 100/0% and 100/0%, respectively. Numerous PK parameters of fluconazole allow comparison of in vivo studies with the results obtained in our in vitro model. Indeed, fluconazole has a small molecular weight (306 g/mol) and is nonionized. Protein binding is dependent on the condition of the patients

with values in the range of 11%–13% in healthy volunteers that rose to 23% in special populations. Fluconazole is merely excreted unchanged by the renal route. The apparent volume of distribution of fluconazole, about that of water in the body (60% of body weight), is far greater than the 5-L bag of our CC. Nonetheless, we believe our findings support the assumption that in patients suffering from candidemia involving sensitive species to fluconazole and requiring CRRT, fluconazole is a valuable alternative to echinocandins. In oligo-anuric patients requiring CRRT, data from the literature show that the clearance of fluconazole, expressed in L/h, is strongly and linearly correlated with the diafiltration flow rate, whatever the mode of CRRT [16]. Therefore, in oligo-anuric patients, this parameter and its modification should be considered when administering the daily dose of fluconazole. We believe fluconazole, not being sequestrated in the ST filter, may be an alternative to caspofungin in sensitive species.

In the future, clinical trials dealing with the PK of caspofungin in critically ill patients receiving CRRT should avoid the simultaneous use of polyacrylonitrile-derived filters in light of these data.

We advocate clinical decision making, although it would be better when based on the results of clinical studies of PK during CRRT.

5. Conclusions

This study provides evidence of extensive sequestration of unbound caspofungin in the ST filter during session of CRRT lasting 6 h. Until an efficient dosage regimen of caspofungin under CRRT has been identified, we advise caution when using simultaneously CRRT with the polyacrylonitrile filter and caspofungin during sessions lasting more than 2 d. Intermittent modes of RRT might address caspofungin sequestration. In sensitive species, fluconazole is a credible alternative.

Competing interests: FJB and LL are inventors of the NeckEpur technology patented by Assistance Publique–Hôpitaux de Paris and Université de Paris Cité. FJB is a stock owner of the NeckEpur company.

Ethical approval: Not required.

Acknowledgements: The authors thank Anne Villepelet-Castot, MD, for her thorough review and revision of the manuscript, and Solange Corriol-Rohou, MD, for her review of the manuscript and, in particular, for language editing.

References

[1] Martin-Loeches I, Antonelli M, Cuenca-Estrella M, Dimopoulos G, Einav S, De Waele JJ, et al. ESICM/ESCMID task force on practical management of invasive candidiasis in critically ill patients. Intensive Care Med 2019;45:789–805.
[2] Roger C, Wallis SC, Muller L, Saissi G, Lipman J, Brüggemann RJ, et al. Caspofungin population pharmacokinetics in critically ill patients undergoing continuous veno-venous haemofiltration or haemodiafiltration. Clin Pharmacokinet 2017;56:1057–68.
[3] Aguilar G, Ferriols R, Lozano A, Ezquer C, Carbonell JA, Jurado A, et al. Optimal doses of caspofungin during continuous venovenous hemodiafiltration in critically ill patients. Crit Care 2017;21:17.
[4] Tomasa Irriguible TM. Echinocandins and continuous renal replacement therapies: the role of adsorption. Arch Clin Nephrol 2018:9–11.
[5] Honore PM. Adsorption and caspofungin dosing during continuous renal replacement therapy. Crit Care 2019;23:240.
[6] Borsuk-De Moor A, Sysiak-Sławecka J, Rypulak E, Borys M, Piwowarczyk P, Raszewski G, et al. Nonstationary pharmacokinetics of caspofungin in ICU patients. Antimicrob Agents Chemother 2020;64:e00345 –20.
[7] González de Molina F, Martínez-Alberici Á, Ferrer R. Treatment with echinocandins during continuous renal replacement therapy. Crit Care 2014;18:218.
[8] Purohit PJ, Elkomy MH, Frymoyer A, Sutherland SM, Drover DR, Hammer GB, et al. Antimicrobial disposition during pediatric continuous renal replacement therapy using an ex vivo model. Crit Care Med 2019;47:e767–73.
[9] Baud FJ, Jullien V, Secrétan P-H, Houzé P, Lamhaut L. Are we correctly treating invasive candidiasis under continuous renal replacement therapy with echinocandins? Preliminary in vitro assessment. Anaesth Crit Care Pain Med 2021;40:100640.
[10] Raphalen J-H, Marçais A, Parize P, Pilmis B, Lillo-Lelouet A, Lamhaut L, et al. Is caspofungin efficient to treat invasive candidiasis requiring continuous veno-venous hemofiltration? A case report. Therapies 2021;76:512–15.
[11] Toussaint B, Lanternier F, Woloch C, Fournier D, Launay M, Billaud E, et al. An ultra performance liquid chromatography-tandem mass spectrometry method for the therapeutic drug monitoring of isavuconazole and seven other antifungal compounds in plasma samples. J Chromatogr B Analyt Technol Biomed Life Sci 2017;1046:26–33.
[12] Houze P, Baud FJ, Raphalen JH, Winchenne A, Moreira S, Gault P, et al. Continuous renal replacement therapy in the treatment of severe hyperkalemia: an in vitro study. Int J Artif Organs 2020;43:87–93.
[13] Baud FJ, Houze P, Carli P, Lamhaut L. Alteration of the pharmacokinetics of aminoglycosides by adsorption in a filter during continuous renal replacement therapy. An in vitro assessment. Therapie 2021;76:415–24. doi:10.1016/j.therap.2020.10.005.
[14] Baud FJ, Houze P, Raphalen JH, Winchenne A, Philippe P, Carli P, et al. Diafiltration flowrate is a determinant of the extent of adsorption of amikacin in renal replacement therapy using the ST150((R))-AN69 filter: an in vitro study. Int J Artif Organs 2020;43:758–66.
[15] Baud FJ, Seif V, Houzé P, Raphalen J-H, Pilmis B, Carli P, et al. Elimination of three doses of gentamicin over three consecutive days using a polyacrylonitrile-derived filter: an in vitro assessment. Int J Artif Organs 2021;44:641–50.
[16] Baud FJ, Jullien V, Abarou T, Pilmis B, Raphalen JH, Houze P, et al. Elimination of fluconazole during continuous renal replacement therapy. An in vitro assessment. Int J Artif Organs 2021;44:453–64.
[17] Le Ven J, Pellan C, Maulet V, Le Monnier A, Baud FJ. Elimination of cefotaxime using polysulfone and polyacrylonitrile-derived filters: an in vitro assessment. Int J Artif Organs 2023;46:113–19.
[18] Maher JF. Principles of dialysis and dialysis of drugs. Am J Med 1977;62:475–81.
[19] Mac-Kay MV, Fernandez IP, Herrera Carranza J, Sancez Burson J. An in vitro study of the influence of a drug's molecular weight on its overall (Clt), diffusive (Cld) and convective (Clc) clearance through dialysers. Biopharm Drug Dispos 1995;16:23–35.
[20] Neri M, Villa G, Garzotto F, Bagshaw S, Bellomo R, Cerda J, et al. Nomenclature for renal replacement therapy in acute kidney injury: basic principles. Crit Care 2016;20:318.
[21] Rowland M, Tozer TN. Elimination. In: Rowland M, Tozer TN, editors. Clinical pharmacokinetics. Concepts and applications. Baltimore, MD: Williams & Wilkins; 1995. p. 156–83.
[22] Derendorf H, Schmidt S. Plasma-to-blood concentration ratio. In: Derendorf H, Schmidt S, editors. Rowalnd and Tozer's clinical pharamcokinetics and pharmacodynamics. Concepts and applications. Philadelphia: Wolters Kluwer; 2020. p. 775–6.
[23] Bretagne S, Sitbon K, Desnos-Ollivier M, Garcia-Hermoso D, Letscher-Bru V, Cassaing S, et al. Active surveillance program to increase awareness on invasive fungal diseases: the French RESSIF Network (2012 to 2018). mBio 2022;13:e00920–2.
[24] Determination of minimum inhibitory concentrations (MICs) of antibacterial agents by broth dilution. Clin Microbiol Infect 2003;9:ix–xv.
[25] Dannaoui E, Lortholary O, Raoux D, Bougnoux ME, Galeazzi G, Lawrence C, et al. Comparative in vitro activities of caspofungin and micafungin, determined using the method of the European Committee on Antimicrobial Susceptibility Testing, against yeast isolates obtained in France in 2005–2006. Antimicrob Agents Chemother 2008;52:778–81.
[26] Stone JA, Xu X, Winchell GA, Deutsch PJ, Pearson PG, Migoya EM, et al. Disposition of caspofungin: role of distribution in determining pharmacokinetics in plasma. Antimicrob Agents Chemother 2004;48:815–23.
[27] Weiler S, Seger C, Pfisterer H, Stienecke E, Stippler F, Welte R, et al. Pharmacokinetics of caspofungin in critically ill patients on continuous renal replacement therapy. Antimicrob Agents Chemother 2013;57:4053–7.
[28] Kofla G, Ruhnke M. Pharmacology and metabolism of anidulafungin, caspofungin and micafungin in the treatment of invasive candidosis—review of the literature. Eur J Med Res 2011;16:159.
[29] Kolbinger P, Gruber M, Roth G, Graf BM, Ittner K-P. Filter adsorption of anidulafungin to a polysulfone-based hemofilter during CVVHD in vitro. Artif Organs 2018;42:200–7.
[30] Rumpf KW, Rieger J, Ansorg R, Doht B, Scheler F. Binding of antibiotics by dialysis membranes and its clinical relevance. Proc Eur Dial Transpl Assoc 1977;14:607–9.
[31] Baud FJ, Houze P, Raphalen J-H, Lamhaut L. Does pharmacokinetics in the central compartment evidence routes of elimination during continuous renal replacement therapy in ex vivo model? Crit Care Med 2020;48:e163–4.
[32] Michikoshi J, Matsumoto S, Miyawaki H, Morita M, Niu H, Seo K, et al. Evaluation of proteins and cells that adsorb to dialysis membranes used in continuous hemodiafiltration: comparison of AN69ST, polymethylmethacrylate, and polysulfone membranes. Blood Purif 2019;48:358–67.
[33] Cornely OA, Lasso M, Betts R, Klimko N, Vazquez J, Dobb G, et al. Caspofungin for the treatment of less common forms of invasive candidiasis. J Antimicrob Chemother 2007;60:363–9.
[34] Betts RF, Nucci M, Talwar D, Gareca M, Queiroz-Telles F, Bedimo RJ, et al. A multicenter, double-blind trial of a high-dose caspofungin treatment regimen

versus a standard caspofungin treatment regimen for adult patients with invasive candidiasis. Clin Infect Dis 2009;48:1676–84.
[35] Desnos-Ollivier M, Bretagne S, Lortholary O, Dromer F, Group French Mycoses Study. Echinocandins susceptibility patterns of 2,787 yeast isolates: importance of the thresholds for the detection of FKS mutations. Antimicrob Agents Chemother 2022;66:e0172521.
[36] Pfaller MA, Boyken L, Hollis RJ, Messer SA, Tendolkar S, Diekema DJ. In vitro susceptibilities of Candida spp. to caspofungin: four years of global surveillance. J Clin Microbiol 2006;44:760–3.
[37] Andes D, Diekema DJ, Pfaller MA, Bohrmuller J, Marchillo K, Lepak A. In vivo comparison of the pharmacodynamic targets for echinocandin drugs against Candida species. Antimicrob Agents Chemother 2010;54:2497–506.
[38] Roberts JA, Bellomo R, Cotta MO, Koch BCP, Lyster H, Ostermann M, et al. Machines that help machines to help patients: optimising antimicrobial dosing in patients receiving extracorporeal membrane oxygenation and renal replacement therapy using dosing software. Intensive Care Med 2022;48:1338–51.
[39] John J, Loo A, Mazur S, Walsh TJ. Therapeutic drug monitoring of systemic antifungal agents: a pragmatic approach for adult and pediatric patients. Expert Opin Drug Metab Toxicol 2019;15:881–95.
[40] Leitner JM, Meyer B, Fuhrmann V, Saria K, Zuba C, Jager W, et al. Multiple-dose pharmacokinetics of anidulafungin during continuous venovenous haemofiltration. J Antimicrob Chemother 2011;66:880–4.
[41] Roberts JA, Joynt G, Lee A, Choi G, Bellomo R, Kanji S, et al. The effect of renal replacement therapy and antibiotic dose on antibiotic concentrations in critically ill patients: data from the multinational SMARRT Study. Clin Infect Dis 2021;72:1369–78. doi:10.1093/cid/ciaa224.
[42] Jang SM, Hough G, Mueller BA. Ex vivo rezafungin adsorption and clearance during continuous renal replacement therapy. Blood Purif 2018;46:214–19.
[43] Sinnollareddy MG, Roberts JA, Lipman J, Akova M, Bassetti M, De Waele JJ, et al. Pharmacokinetic variability and exposures of fluconazole, anidulafungin, and caspofungin in intensive care unit patients: data from multinational Defining Antibiotic Levels in Intensive care unit (DALI) patients study. Crit Care 2015;19:33.
[44] Pea F, Viale P, Pavan F, Furlanut M. Pharmacokinetic considerations for antimicrobial therapy in patients receiving renal replacement therapy. Clin Pharmacokinet 2007;46:997–1038.
[45] Muhl E, Martens T, Iven H, Rob P, Bruch HP. Influence of continuous veno-venous haemodiafiltration and continuous veno-venous haemofiltration on the pharmacokinetics of fluconazole. Eur J Clin Pharmacol 2000;56:671–8.