Antibiotics Removal by Continuous Venovenous Hemofiltration with a Novel Asymmetric Triacetate Membrane Hemofilter: An in vitro Study

Andreas Körtge^{a, b} Jolanta Majcher-Peszynska^c Benjamin Heskamp^{a, b}
Reinhold Wasserkort^{a, b} Steffen Mitzner^{a, b}

^aDepartment of Extracorporeal Immunomodulation EXIM, Fraunhofer Institute for Cell Therapy and Immunology IZI, Rostock, Germany; ^bDivision of Nephrology, Centre for Internal Medicine, University Medicine Rostock, Rostock, Germany; ^cInstitute for Pharmacology and Toxicology, University Medicine Rostock, Rostock, Germany

Keywords

Continuous renal replacement therapy · Hemofiltration · Acute kidney injury · Sepsis · Antibiotics removal

Abstract

Introduction: Continuous renal replacement therapies (CRRTs) are essential in the treatment of critically ill patients with acute kidney injury and are also discussed as a supporting sepsis therapy. CRRT can affect antibiotics plasma concentrations. **Objective:** The effect of continuous venovenous hemofiltration (CVVH) with an asymmetric triacetate (ATA) membrane hemofilter on concentrations of antibiotics with low (meropenem), medium (vancomycin), and high (daptomycin) protein binding (PB) was investigated. **Methods:** 1 L human whole blood supplemented with antibiotics was recirculated and filtrated for 6 h in vitro. Clearances and sieving coefficients (SC) were determined from antibiotics concentrations measured at filter inlet, outlet, and filtrate side. Reservoir concentration data were fitted using a first-order kinetic model. **Results:** Meropenem and vancomycin concentrations decreased to 5–10% of the initial plasma level, while only 50% of daptomycin were removed. Clearances and SCs were (10.8 [10.8–17.4] mL/min, SC = 0.72 [0.72–1.16]) for me-

roperenem, (13.4 [12.3–13.7] mL/min, 0.89 [0.82–0.92]) for vancomycin, and (2.1 [1.8–2.1] mL/min, 0.14 [0.12–0.14]) for daptomycin. Removal by adsorption was negligible. **Conclusions:** The clearances and SCs presented are comparable with findings of other authors. Meropenem and vancomycin, which exhibit low and medium PB, respectively, were strongly removed, while considerably less daptomycin was removed because of its high PB. Our results suggest that in clinical use of the tested antibiotics during CRRT with the ATA hemofilter, the same factors have to be considered for determining the dosing strategy as with filters with other commonly applied membrane materials.

© 2021 The Author(s)
Published by S. Karger AG, Basel

Introduction

Continuous renal replacement therapies (CRRTs) are indispensable means for the treatment of critically ill patients with acute kidney injury and are moreover discussed among experts as a supporting therapy of sepsis [1]. CRRTs and other blood purification methods as for instance hemoperfusion aim to remove inflammatory cytokines and other mediators in order to downregulate the

excessive inflammatory response which promotes the progression of both diseases [2–4]. The plasma concentrations of antibiotics and other treatment-relevant drugs, of which the former are particularly essential for the therapy of critically ill patients with bacterial infections [5–7], can be affected by blood purification treatments. High antibiotic clearances may result in subtherapeutic concentrations which in turn may result in insufficient treatment of the bacterial infection. This raises the risk of clinical failure with an increase in morbidity and mortality [6]. Furthermore, removal of important substances, namely trace elements, vitamins, electrolytes, and amino acids, may contribute to cause further harm to the patient [8]. Generally, drug dosage in patients with impaired renal and nonrenal clearance undergoing CRRTs is difficult because of the numerous factors affecting the pharmacokinetics, especially the total clearance, of the respective drug. For this reason, a KDIGO statement on the subject “Drug dosing consideration in patients with acute and chronic kidney disease” [9] recommends suitable in vitro studies to evaluate the most relevant antibiotic and other drug clearances for new renal replacement therapies, dialysis membranes, and devices in order to support the clinician with regard to potential drug dosage adjustments.

In the present study, the effect of continuous venovenous hemofiltration (CVVH) using a novel asymmetric triacetate (ATA) membrane hemofilter on plasma levels of antibiotics specifically relevant in acute kidney injury and sepsis was investigated in an in vitro model. Two properties of the ATA membrane are of particular interest regarding the potential removal of antibiotics: first, Sunohara and Masuda [10] described that the initial removal of plasma proteins in a CVVH setup was considerably lower than with a polysulfone dialyzer, presumably also resulting in a reduced removal of protein-bound antibiotics. This effect was ascribed to the asymmetrical structure of the ATA membrane, that is, compared to conventional symmetric cellulose triacetate membranes, the asymmetric structures facilitates higher hydraulic permeability, and less pressure-induced increase in pore diameter leading to albumin loss. Second, the authors describe in the same study that the modified membrane has a smoother surface compared to conventional CTA membrane, resulting in less protein adsorption [10]. For the present work, this could entail that water-soluble and protein-bound antibiotics are not removed as much by adsorption. Three different antibiotics with low, medium, and high degrees of protein binding (PB) were tested, namely meropenem (PB $\approx$ 2%), vancomycin (PB $\approx$ 55%),

Fig. 1. In vitro experimental setup. 1 L of human whole blood was recirculated (100 mL/min) and filtrated (15 mL/min) for 6 h. Filtrate was collected in a separate bag, and the fluid loss was compensated with a calcium-free dialysis replacement solution. Samples were taken from the reservoir bag, at the inlet, outlet, and filtrate outlet.

and daptomycin (PB $\approx$ 92%) [5]. Meropenem is a carbapenem antibiotic often applied as initial therapy in sepsis because of its broad-spectrum activity against gram-positive and gram-negative pathogens, including *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. As a β -lactam antibiotic, bactericidal activity of meropenem is correlated with the time that concentrations remain above the minimum inhibitory concentration (MIC) of the pathogen during the dosing interval. For carbapenems, concentrations above the MIC for approximately 40% of the dosing interval T are needed for bactericidal effects. In most studies under CVVH conditions, the normal dose of meropenem (1-h infusion of 1,000 mg every 8 h) may be sufficient to retain optimal pharmacokinetic/pharmacodynamic exposure of 40% $T > 2$ mg/L for the most susceptible bacteria [11]. To achieve the more stringent 100% $T > 2$ mg/L, target requires higher doses of meropenem (2 g every 8 h) administered in a prolonged (3 h) infusion [12]. Vancomycin is a glycopeptide antibiotic used as a first-line agent for treating methicillin-resistant *Staphylococcus aureus* and other gram-positive bacteria. Its efficacy is related to its correct dosing according to optimal pharmacokinetic/pharmacodynamic parameters, defined as an area under the curve (AUC) to

Table 1. List of antibiotics added to the test blood

	Target peak level, mg/L	Effective trough level, mg/L	Study level, mg/L	PB, %	VOD, L/kg	MW, Da	MIC, mg/L
Meropenem	40 (Refs. [30, 32])	4 (Refs. [5, 30])	40	2	0.25	383	2 (<i>Enterobacterales</i>)
Vancomycin	40 (Ref. [33])	10–20 (Refs. [5, 14])	40	55	0.7	1,450	2 (<i>Staphylococcus aureus</i>)
Daptomycin	90–110 (Refs. [29, 34, 35])	3.2 (Ref. [17])	100	92	0.13	1,620	1 (<i>Staphylococcus aureus</i>)

Degrees of PB and VOD according to reference [5]. MIC values are according to reference [31]. PB, protein binding; VOD, volumes of distribution; MIC, minimum inhibitory concentration.

MIC ratio ≥ 400 and trough vancomycin concentrations of 10–15 (20) mg/L [5, 13, 14]. Daptomycin is a lipopeptide antibiotic with bactericidal activity against multi-drug-resistant gram-positive pathogens. According to pharmacokinetic/pharmacodynamic relationships, higher doses of daptomycin are needed in critically ill patients with frequently augmented daptomycin clearance to maximize its concentration-dependent activity (higher AUC/MIC and $C_{\max}/\text{MIC}$) [15]. The clinical target for daptomycin efficacy in critically ill patients is an AUC_{0–24}/MIC ratio of ≥ 666 [16]. A trough level of <3.2 mg/L was found to be associated with poor clinical outcomes in patients with various gram-positive infections [17].

Materials and Methods

Experiments were performed using the SOLACEA-15H hemofilter (1.5 m² membrane surface; Nipro Corporation, Osaka, Japan) (for performance and other data please refer to [10, 18]). The experimental setup is shown in Figure 1. The test solution was citrate-anticoagulated human whole blood (1,000 mL mixed from 2 AB0-compatible 500-mL donations donated max 24 h prior to the experiments and stored at 4°C; Haema Blutspende Service, Munich, Germany). Warming of rinsing solution and blood to 37°C was performed with a Fluido[®] Infrared Fluid & Blood Warmer (The Surgical Co., GmbH, Kleve, Germany). Antibiotics were dissolved in distilled water to obtain 5-mg/L stock solutions. Therapeutic plasma concentrations of meropenem (Meropenem Dr. Eberth 500 mg, powder; Dr. Friedrich Eberth Arzneimittel GmbH, Ursensollen, Germany), vancomycin (Vanco-saar[®] 500 mg, powder; MIP Pharma GmbH, Blieskastel, Germany), and daptomycin (Cubicin[®] 500 mg, powder; Merck Sharp & Dohme B.V., Haarlem, Netherlands) were adjusted by adding the stock solution under consideration of the blood hematocrit to the blood reservoir (see Table 1 for target concentrations). Uniform distribution of the antibiotics in the blood was ensured by gently agitating the reservoir for 15 min on a rocking shaker (Rocker 2D digital; IKA-Werke GmbH & CO., KG, Staufen im Breisgau, Germany). Prior to the test, the hemofilter was rinsed with physiological saline solution according to the manufacturer's instructions. The blood was

pumped into the arterial inlet of the device at a flow rate of 100 mL/min. The venous line was connected to the reservoir bag so that the blood recirculated. The filtrate was collected in a separate filtrate bag, and the fluid loss was compensated using a calcium-free dialysis replacement solution (Ci-Ca Dialysate K4; Fresenius Medical Care, Bad Homburg, Germany). Filtrate and substitution solution were pumped with a flow rate of 15 mL/min.

The experiment duration was 360 min. Samples were taken from the blood reservoir bag directly after start of the experiments (0 min) and after 5, 30, 180, and 360 min; at the filter inlet, outlet, and filtrate outlet after 30 min; and from the filtrate collection bag after 360 min. The samples were immediately centrifuged at 1,500 rcf for 10 min after collection. The plasma was carefully collected and immediately stored at -80°C . Control samples (taken from the test reservoir after addition of the antibiotics and kept in a water bath at 37°C during the experiments) were centrifuged and stored after termination of the experiments.

The concentrations of meropenem in plasma and filtrate were determined at the Center for Pharmacology and Toxicology (Institute for Clinical Pharmacology, University Medicine Rostock, Germany) by a validated isocratic high-pressure liquid chromatography HPLC method with ultraviolet detection and ceftazidime as internal standard (in reference to [19]). The assay was validated according to standard procedures with precisions (coefficient of variance) and accuracies (relative error) of better than $\pm 15\%$. The LLOQ was calculated as 0.5 mg/L and the calibration curve was linear with $r^2 > 0.999$ in the range of 1–60 mg/L.

Vancomycin concentrations were determined by nephelometric measurements with a biochemistry analyzer (Cobas Mira; Roche, Basel, Switzerland) using a homogeneous enzyme immunoassay (Emit 2000 Vancomycin Assay; Beckman Coulter, Brea, CA, USA) and tri-level, serum-based assayed control samples (LiquichekTM Therapeutic Drug Monitoring Quality Control; Bio-Rad Laboratories GmbH, Munich, Germany). The sensitivity level of the vancomycin assay is 2.0 $\mu\text{g/mL}$. This level represents the lowest concentration of vancomycin that can be distinguished from 0 $\mu\text{g/mL}$ (blank) with a confidence level of 95%. The assay accurately quantitates vancomycin concentrations in human plasma containing 2.0–50 $\mu\text{g/mL}$ vancomycin.

Daptomycin was determined by a validated liquid chromatography-tandem mass spectrometry method at the medical laboratory MVZ Labor Dr. Limbach & Kollegen (Heidelberg, Germany). The lower limit of quantification was calculated as 0.5 mg/L (precision coefficient of variance and accuracy relative error better than $\pm 10\%$). The detailed method has not yet been published for proprietary reasons.

Fig. 2. Meropenem (a), vancomycin (b), daptomycin (c), and total protein and albumin (d) concentration-time curves in the blood reservoir during recirculation and filtration through the ATA hemofilter. The dashed horizontal lines represent the effective trough levels (meropenem 4 mg/L [30], vancomycin 10 mg/L [5, 14], daptomycin 3.2 mg/L [17]). The dotted lines represent the fitted exponential concentration-time curves assuming first-order kinetics. ATA, asymmetric triacetate.

Albumin and total protein (TP) concentrations were determined with an automated analyzer (Cobas Mira Plus, Roche, Basel, Switzerland) and commercially available diagnostic kits LT-AB0103 (bromocresol green assay; LT-SYS, Berlin, Germany) and LT-TP 0253 (biuret assay; LT-SYS, Berlin, Germany). The limit of detection of both assays was 2.0 g/L.

To determine the amount of adsorbed antibiotics to the membrane surface, the mass balance (MB) was calculated as follows:

$$MB = \frac{m(t_{\text{end}})}{m(t_0)} = \frac{c_r(t_{\text{end}}) \times V_B \times (1 - \text{Hct}) + c_{\text{fb}}(t_{\text{end}}) \times V_{\text{fb}}(t_{\text{end}})}{c_r(t_0) \times V_B \times (1 - \text{Hct})} [\%]$$

with m total mass of the respective antibiotic, c_r plasma concentration of the antibiotic in the reservoir bag, c_{fb} antibiotic concentration in the filtrate collection bag c_{fb} measured at the end of the

experiments, V_B total blood volume V_B , V_{fb} volume of the filtrate collected in the filtrate bag, Hct hematocrit.

In order to fit the concentration-time curves $c(t)$, a first-order kinetic approach was applied resulting in the following equation [20]:

$$c(t) = c_0 \times \exp(-kt)$$

with the initial concentration c_0 and the elimination rate constant k . k was determined by plotting the natural logarithm of the antibiotic plasma concentration as a function of time, which gives a straight line with a slope equal to $-k$. The pharmacokinetic clearance CL_{KIN} was calculated as follows:

$$CL_{\text{KIN}} = k \times VOD = (k \times V_{\text{reservoir}})$$

with the volume of distribution (VOD) of the respective drug. It is of note that in the present study, the VOD equals the volume of the

blood reservoir because all antibiotics have VODs that result in an even distribution in the test blood.

Sieving coefficients (SCs) were calculated as follows:

$$SC = \frac{2 c_f}{(c_{in} + c_{out})}$$

with c_{in} concentration of solute at the blood inlet of the filter, c_{out} concentration of solute at the blood outlet of the filter, c_f concentration of solute at the filtrate outlet of the filter.

Clearances (CL_{HF} , convective removal by hemofiltration only) were calculated as follows:

$$CL_{HF} = SC \times Q_F$$

with the filtration flow rate Q_F .

Results

The concentration-time curves of the antibiotics, TP, and albumin in the blood reservoir are depicted in Figure 2. Meropenem and vancomycin plasma concentrations (Fig. 2a, b) decreased to values below the effective trough levels of 4 and 10 mg/L after 139 and 87 min, respectively (times were calculated from the fitted concentration-time curves). Plasma concentrations fell below the respective MIC after 184 min (meropenem; *Enterobacteriales* MIC: 2 mg/L) and 204 min (vancomycin; *Staphylococcus aureus* MIC: 2 mg/L). The daptomycin plasma concentration (Fig. 2c) decreased to 50% of the initial value after 360 min. The fits of the first-order kinetic model (dotted lines) yielded good approximations with elimination rate constants and clearances of $k = 0.0155 \text{ min}^{-1}$ and $CL_{KIN} = 15.5 \text{ mL/min}$ for meropenem ($r^2 = 0.9982$), 0.0139 min^{-1} and 13.9 mL/min for vancomycin ($r^2 = 0.9988$), and 0.0019 min^{-1} and 1.9 mL/min for daptomycin ($r^2 = 0.9758$), respectively. TP and albumin concentrations in the blood reservoir are decreased by 8% (4.7 g) and 10% (3.3 g), respectively, during the experiments (Fig. 2d).

Figure 3 shows the convective clearances CL_{HF} calculated from the antibiotic concentrations measured after 30 min of recirculation and filtration in the in vitro model at the filter inlet, outlet, and filtrate outlet. With 10.8 (10.8–17.4) mL/min (meropenem), 13.4 (12.3–13.7) mL/min (vancomycin), and 2.1 (1.8–2.1) mL/min (daptomycin), the convective clearances calculated from these independent measurements agreed well with the values obtained from the fits of the reservoir concentrations. The corresponding SCs were 0.72 (0.72–1.16) (meropenem), 0.89 (0.82–0.92) (vancomycin), and 0.14 (0.12–0.14)

Fig. 3. SCs and convective clearances of the ATA hemofilter calculated from plasma and filtrate concentrations measured in samples taken at the inlet and outlet and the filtrate side after 30 min (median). ATA, asymmetric triacetate; SC, sieving coefficient.

(daptomycin). Mass balance values were 96 (74–117)% for meropenem, 111 (104–120)% for vancomycin, and 114 (113–117)% for daptomycin. Values are given as median (range).

Discussion/Conclusion

This is the first in vitro study comparing the elimination of antibiotics using CRRT with a novel ATA membrane hemofilter. The purpose of this study was to examine the elimination of selected antibiotics to avoid incorrect dosage in clinical use. These antibiotics, which are often used in critically ill patients, have different physicochemical, pharmacokinetic, and pharmacodynamic properties and are discussed separately.

Meropenem

Because of its very low degree of PB, meropenem is strongly removed by conventional hemodialysis and hemofiltration. This is reflected by high SCs in the range between 0.63 and 1.0 stated in the literature [21]. The SC for meropenem determined in the present study with the ATA membrane hemofilter (0.72 [0.72–1.16]) is in accordance with the results obtained by other authors.

Vancomycin

Despite its higher degree of PB of approximately 55%, vancomycin is similarly removed by CVVH with the ATA hemofilter as compared to meropenem. This may be partly attributed to albumin loss observed during the

experiments. However, it should be noted that the degree of PB is not the only factor determining removal. Rather, other factors as for instance molecular charge distribution and size, and the drug-membrane interaction have impact on the membrane permeability for a specific drug [22]. Since the molecular weight of vancomycin is almost 4 times higher than that of meropenem, which would be supposed to impede membrane passage, we suggest that the high clearance is attributed to a more favorable interaction of vancomycin with the ATA membrane. The SC of 0.89 (0.82–0.92) determined in the present in vitro study is comparable to those observed by a number of authors. Macias et al. [23] determined a SC of 0.8 for vancomycin using polysulfone hemofilters in anuric critically ill patients. Boereboom et al. [24] determined vancomycin SCs in the range of 0.73–0.86 for polyacrylonitrile hemofilters. In a recent study of Li et al. [25], the mean SC for vancomycin was 0.72 ± 0.02 in severe pneumonia patients undergoing CVVH using a polysulfone hemofilter.

Daptomycin

Based on the large molecular weight (1,620 Da) and the high degree of PB (90–92%), minor removal of daptomycin by hemodialysis is basically expected, and 2 in vitro studies have confirmed this. In good agreement with the results from the present study, Churchwell et al. [26] determined daptomycin SCs for AN69 and polysulfone hemodiafilters in the range from 0.14 to 0.20. Wagner et al. [27] determined a considerably higher SC of 0.40 ± 0.03 for a polyethersulfone dialyzer in a CVVH in vitro model. The lower SCs of daptomycin determined in the present study suggests a lower elimination rate with the ATA hemofilter in comparison with other hemofilters. However, it should be taken into consideration that especially critically ill patients may exhibit hypoalbuminemia resulting in considerably decreased albumin levels and a higher fraction of unbound daptomycin which in turn can be removed more effectively by hemodialysis. Kielstein et al. [28] observed daptomycin clearances of >60 mL/min in patients with low serum albumin levels who underwent extended dialysis (treatment times ~ 8 h). Falcone et al. [29] suggested that the significant decrease in plasma levels of daptomycin in patients undergoing continuous venovenous hemodiafiltration in their study may be ascribed to an increase in the volume of distribution which was due to administration of large volumes of resuscitation fluids. For these patients, higher doses of daptomycin may be necessary to avoid subtherapeutic concentrations.

To conclude, because the SCs obtained in this in vitro study are comparable with results obtained for other hemofilters and removal by adsorption to the membrane was negligible, it can be assumed that the same dose recommendations can be used for clinical use of the antibiotics under CVVH conditions with the ATA membrane hemofilter. Basically, it should be noted that early therapeutic drug monitoring is indicated when applying blood purification therapies. Further clinical studies are necessary to confirm these findings.

Acknowledgements

The work of Helga Weiss-Reining (measurement of albumin and total protein) and Katrin Kroesche (measurement of meropenem) is gratefully acknowledged.

Statement of Ethics

Prior to blood donation, all donors have given their written informed consent that their blood can be used for research purposes. The experimental use of donor blood was approved by the Ethics Committee of the University of Rostock (No. A 2018-0087).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This study was financially supported by Nipro Corporation. ATA membrane hemofilters were provided by Nipro Corporation.

Author Contributions

Andreas Körtge designed the in vitro experiments and contributed substantially to the making of the manuscript. Benjamin Heskamp contributed substantially to the development of the experimental design. Jolanta Majcher-Peszyńska provided expertise in clinical pharmacology and contributed to the making of the manuscript. Reinhold Wasserkort contributed to drafting of the manuscript and the discussion of the study. Steffen Mitzner provided clinical expertise for the design of the experiments and the discussion of the study.

References

- Ronco C, Ricci Z, De Backer D, Kellum JA, Taccone FS, Joannidis M, et al. Renal replacement therapy in acute kidney injury: controversy and consensus. *Crit Care*. 2015;19:146.
- Akay A, Nguyen Q, Edelstein CL. Mediators of inflammation in acute kidney injury. *Mediators Inflamm*. 2009;2009:137072.
- Ronco C, Tetra C, Mariano F, Wratten ML, Bonello M, Bordon V, et al. Interpreting the mechanisms of continuous renal replacement therapy in sepsis: the peak concentration hypothesis. *Artif Organs*. 2003;27(9):792–801.
- de Vriese AS, Colardyn FA, Philippe JJ, Vanholder RC, de Sutter JH, Lameire NH. Cytokine removal during continuous hemofiltration in septic patients. *J Am Soc Nephrol*. 1999;10(4):846–53.
- Trotman RL, Williamson JC, Shoemaker DM, Salzer WL. Antibiotic dosing in critically ill adult patients receiving continuous renal replacement therapy. *Clin Infect Dis*. 2005;41(8):1159–66.
- Lewis SJ, Mueller BA. Antibiotic dosing in critically ill patients receiving CRRT: underdosing is overprevalent. *Semin Dial*. 2014;27(5):441–5.
- Bodmann KF, Grabein B, Kresken M. Kalkulierte Parenterale Initialtherapie Bakterieller Erkrankungen Bei Erwachsenen: PEG S2k Leitlinie, Paul-Ehrlich-Gesellschaft für Chemotherapie e.V. 2019.
- Kielstein JT, David S. Pro: renal replacement trauma or Paracelsus 2.0. *Nephrol Dial Transplant*. 2013;28(11):2728–31.
- Matzke GR, Aronoff GR, Atkinson AJ, Bennett WM, Decker BS, Eckardt K-U, et al. Drug dosing consideration in patients with acute and chronic kidney disease: a clinical update from kidney disease: improving global outcomes (KDIGO). *Kidney Int*. 2011;80(11):1122–37.
- Sunohara T, Masuda T. Fundamental characteristics of the newly developed ATA™ membrane dialyzer. *Contrib Nephrol*. 2017;189:215–21.
- Onichimowski D, Będzowska A, Ziółkowski H, Jaroszewski J, Borys M, Czuczwar M, et al. Population pharmacokinetics of standard-dose meropenem in critically ill patients on continuous renal replacement therapy: a prospective observational trial. *Pharmacol Rep*. 2020;72(3):719–29.
- Nowak-Kózka I, Polok KJ, Górka J, Fronczek J, Gielicz A, Seczyńska B, et al. Concentration of meropenem in patients with sepsis and acute kidney injury before and after initiation of continuous renal replacement therapy: a prospective observational trial. *Pharmacol Rep*. 2020;72(1):147–55.
- Alvarez R, Lopez Cortes LE, Molina J, Cisneros JM, Pachon J. Optimizing the clinical use of vancomycin. *Antimicrob Agents Chemother*. 2016;60(5):2601–9.
- Rybak M, Lomaestro B, Rotschafer JC, Moellering R, Craig W, Billeter M, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm*. 2009;66(1):82–98.
- Falcone M, Russo A, Venditti M, Novelli A, Pai MP. Considerations for higher doses of daptomycin in critically ill patients with methicillin-resistant *Staphylococcus aureus* bacteremia. *Clin Infect Dis*. 2013;57(11):1568–76.
- Abdul-Aziz MH, Alffenaar J-WC, Bassetti M, Bracht H, Dimopoulos G, Marriott D, et al. Antimicrobial therapeutic drug monitoring in critically ill adult patients: a position paper. *Intensive Care Med*. 2020;46(6):1127–53.
- Galar A, Muñoz P, Valerio M, Cercenado E, García-González X, Burillo A, et al. Current use of daptomycin and systematic therapeutic drug monitoring: clinical experience in a tertiary care institution. *Int J Antimicrob Agents*. 2019;53(1):40–8.
- Kim TR, Hadidi M, Motevalian SP, Sunohara T, Zydney AL. Transport characteristics of asymmetric cellulose triacetate hemodialysis membranes. *Blood Purif*. 2018;45(1–3):46–52.
- Dailly E, Bouquie R, Deslandes G, Joliet P, Le Floch R. A liquid chromatography assay for a quantification of doripenem, ertapenem, imipenem, meropenem concentrations in human plasma: application to a clinical pharmacokinetic study. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2011;879(15–16):1137–42.
- Sprenger KB, Kratz W, Lewis AE, Stadtmüller U. Kinetic modeling of hemodialysis, hemofiltration, and hemodiafiltration. *Kidney Int*. 1983;24(2):143–51.
- Bilgrami I, Roberts JA, Wallis SC, Thomas J, Davis J, Fowler S, et al. Meropenem dosing in critically ill patients with sepsis receiving high-volume continuous venovenous hemofiltration. *Antimicrob Agents Chemother*. 2010;54(7):2974–8.
- Golper TA, Bennett WM. Drug removal by continuous arteriovenous hemofiltration. A review of the evidence in poisoned patients. *Med Toxicol Adverse Drug Exp*. 1988;3(5):341–9.
- Macias WL, Mueller BA, Scarim SK. Vancomycin pharmacokinetics in acute renal failure: preservation of nonrenal clearance. *Clin Pharmacol Ther*. 1991;50(6):688–94.
- Boereboom FT, Ververs FF, Blankestijn PJ, Savelkoul TJ, van Dijk A. Vancomycin clearance during continuous venovenous haemofiltration in critically ill patients. *Intensive Care Med*. 1999;25(10):1100–4.
- Li Q, Liang F, Sang L, Li P, Lv B, Tan L, et al. Pharmacokinetics of and maintenance dose recommendations for vancomycin in severe pneumonia patients undergoing continuous venovenous hemofiltration with the combination of predilution and postdilution. *Eur J Clin Pharmacol*. 2020;76(2):211–7.
- Churchwell MD, Pasko DA, Mueller BA. Daptomycin clearance during modeled continuous renal replacement therapy. *Blood Purif*. 2006;24(5–6):548–54.
- Wagner CC, Steiner I, Zeitlinger M. Daptomycin elimination by CVVH in vitro: evaluation of factors influencing sieving and membrane adsorption. *Int J Clin Pharmacol Ther*. 2009;47(3):178–86.
- Kielstein JT, Eugbers C, Bode-Boeger SM, Martens-Lobenhoffer J, Haller H, Joukhadar C, et al. Dosing of daptomycin in intensive care unit patients with acute kidney injury undergoing extended dialysis—a pharmacokinetic study. *Nephrol Dial Transplant*. 2010;25(5):1537–41.
- Falcone M, Russo A, Cassetta MI, Lappa A, Tritapepe L, Fallani S, et al. Daptomycin serum levels in critical patients undergoing continuous renal replacement. *J Chemother*. 2012;24(5):253–6.
- Krueger WA, Neeser G, Schuster H, Schroeder TH, Hoffmann E, Heininger A, et al. Correlation of meropenem plasma levels with pharmacodynamic requirements in critically ill patients receiving continuous veno-venous hemofiltration. *Chemotherapy*. 2003;49(6):280–6.
- The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. version 10.0. 2020.
- Mouton JW, Touzw DJ, Horrevorts AM, Vinks AA. Comparative pharmacokinetics of the carbapenems: clinical implications. *Clin Pharmacokinet*. 2000;39(3):185–201.
- Saunders N. Why monitor peak vancomycin concentrations? *Lancet*. 1994;344(8939–40):1748.
- Vilay AM, Griot M, Depestel DD, Sowinski KM, Gao L, Heung M, et al. Daptomycin pharmacokinetics in critically ill patients receiving continuous venovenous hemodialysis. *Crit Care Med*. 2011;39(1):19–25.
- Dvorchik BH, Brazier D, DeBruin MF, Arbeit RD. Daptomycin pharmacokinetics and safety following administration of escalating doses once daily to healthy subjects. *Antimicrob Agents Chemother*. 2003;47(4):1318–23.