PHARMECMO: Therapeutic drug monitoring and adequacy of current dosing regimens of antibiotics in patients on Extracorporeal Life Support

Adrien Bouglé, Olivier Dujardin, Victoria Lepere, Nora Ait Hamou, Charles Vidal, Guillaume Lebreton, Joe-Elie Salem, Najoua El-Helali, Grégoire Petijean, Julien Amour

PHARMECMO: Therapeutic drug monitoring and adequacy of current dosing regimens of antibiotics in patients on Extracorporeal Life Support

Adrien Bouglé[1], Olivier Dujardin[1], Victoria Lepère[1], Nora Ait Hamou[1], Charles Vidal[1], Guillaume Lebreton[2], Joe-Elie Salem[3], Najoua El-Helali[4], Grégoire Petijean[4], Julien Amour[1]

[1] Sorbonne Université, UMR INSERM 1166, IHU ICAN, Assistance Publique - Hôpitaux de Paris (AP-HP), Department of Anaesthesiology and Critical Care Medicine, Institute of Cardiology, Pitié-Salpêtrière Hospital, Paris, France

[2] Sorbonne Université, UMR INSERM 1166, IHU ICAN, Assistance Publique - Hôpitaux de Paris (AP-HP), Department of Cardio-Vascular and Thoracic Surgery, Institute of Cardiology, Pitié-Salpêtrière Hospital, Paris, France

[3] Sorbonne Université, UMR INSERM 1166, IHU ICAN, Assistance Publique - Hôpitaux de Paris (AP-HP), Department of Pharmacology, Pitié-Salpêtrière Hospital, Paris, France

[4] Department of Clinical Microbiology and Therapeutic Monitoring of Anti-infective drugs, Hospital Group Paris Saint-Joseph, Paris, France

Introduction

ECMO (Extracorporeal Membrane Oxygenation) is a life-support technique used to treat patients with cardiorespiratory failure refractory to conventional therapies. Major advances in device technology and the publication of the Conventional Ventilatory Support versus Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure (CESAR) trial[1] or the ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial [2] have led to a significant expansion of ECMO use worldwide. Survival for adults supported with ECMO showed continuous improvement over time, with survival rates reported in The Extracorporeal Life Support Organisation's (ELSO) registry[3] of 50% in patients with veno-arterial ECMO and up to 70% in patients with veno-venous ECMO. However, more than 60% of adult patients receiving ECMO will develop nosocomial infections, that are associated with longer durations of mechanical ventilation, ECMO support, and hospital stays[4]. Hence, optimisation of antibiotic therapy for ECMO patients remains a pharmacological challenge. Increase in the volume of distribution (Vd), altered clearance or drug extraction by the circuit could induce significant changes in antibiotics pharmacokinetics under ECMO assistance, as shown in paediatric populations[5]. However, recent studies in an adult population did not confirm these previous results[6,7,8,9,10].

The objective of this prospective pilot study was to observe the plasma concentrations of commonly used antibiotics (ß-lactams, glycopeptides, fluoroquinolones and aminoglycosides) in intensive care for adult patients treated with extracorporeal membrane oxygenation.

Patients and Methods

Design

The PHARMECMO study was a pilot prospective observational study, conducted in an eighteen-bed adult cardiac surgery intensive care unit at La Pitié-Salpêtrière University Hospital, Paris, France. Adult patients admitted in the ICU for veno-venous (VV ECMO) or veno-arterial ECMO (VA ECMO) assistance with known or suspected sepsis and receiving antibiotic therapy were included. Exclusion criteria were known allergy to studied antibiotics, pregnancy, patients with burns or cystic fibrosis, therapeutic plasma exchanges in the preceding 24 hours. All patients or relatives provided written informed consent to participate.

Data

The following data were collected for all patients: age, gender, weight and body mass index, admission date and ICU admission diagnosis, date of intubation and extubation and the mortality date. With the therapeutic drug monitoring (TDM), the following data were also collected: weight; temperature; heart rate; mean arterial pressure; respiratory rate; inspiratory oxygen fraction; the following biological factors: partial pressure of arterial oxygen (PaO2), pH, potassium and sodium levels, lactic acid, leukocytes, haematocrit, serum proteins, renal function parameters: serum creatinine, urine output, creatininuria (creatinine clearance was calculated from the 24-h urine using the formula: CL_{Cr} mL/min = [(urine Cr, mg/dL) x (urine output, mL)]/[(serum Cr, mg/dL) x (time of urine collection, min)]), presence of continuous renal replacement therapy (cRRT) (initiation time of cRRT, dialysate and untrafiltrate rate); data concerning antibiotic therapy, type of drugs, initiation time, posology, type of infusion (continuous, extended or bolus infusion), infusion time, number of doses received before TDM, exact time of the last infusion; data related to ECMO: indication, initiation time, type of ECMO, cannulation site, ECMO course before TDM, ECMO parameters the day of the TDM; data related to the sepsis: pathogens and infection type.

Extracorporeal life support circuit and management

All ECMO equipment was implanted surgically with peripheral or central heparin-coating cannulation. The ECMO circuits used were comprised of a centrifugal blood pump (ROTAFLOW, Centrifugal Pump; Maquet), an oxygenator and cannulas (Edward Lifesciences, Irvine, CA). In case of peripheral VA cannulation, an anterograde catheter was placed to avoid limb ischaemia. A heat exchanger was also used to maintain normothermia.

Crystalloids and/or colloids were used for the priming volume. ECMO parameters were adjusted by the physician to ensure blood oxygen level, the CO_2 removal and an appropriate blood flow. All patients received ECMO circuits anticoagulation with heparin.

Antibiotic treatment, measurements and pharmacokinetic (PK) analysis

The decision to initiate antibiotic therapy was made by the physician taking care of the patient according to clinical, biological and microbiological findings. For β-lactams infused in an intermittent or extended way, two successive TDM were performed respectively at 50% (C_{T50}) at 100% (C_{min}) of the dose interval. For glycopeptides and β-lactams infused in a continuous way, only one TDM was performed to measure the steady state concentration. To be sure to perform therapeutic drug monitoring in a steady state phase, samples were collected after at least 48 hours from the start of antibiotic therapy, at 8:00 a.m. For aminoglycosides and fluoroquinolones, the maximum concentration (C_{max}) was measured 30 minutes after the end of a 30 minutes infusion time. Blood samples were directly sent to the emergency chemistry laboratory to be centrifuged and kept at -80°C. Those samples were then sent to the microbiological laboratory of Saint-Joseph Hospital. Plasma concentration of the antibiotics was determined using a high-performance liquid chromatography connected to mass-spectrometry.

The pharmacokinetic (pK) objectives chosen for β-lactams were: an antibiotic plasma concentration above 4 times the minimum inhibitory concentration (MIC) during 50% of the dose interval[6,7,11] and an antibiotic plasma concentration above the MIC during 100%[12] of the dose interval. The target MIC was defined by the clinical breakpoints for *Pseudomonas aeruginosa* as defined by the European Committee on Antimicrobial Susceptibility Testing (EUCAST). Vancomycin steady state plasma concentrations were considered adequate if between 20 $mg.L^{-1}$ and 30 $mg.L^{-1}$ [13]. Concerning aminoglycoside, C_{max} were considered adequate between 60 $mg.L^{-1}$ and 80 $mg.L^{-1}$ [14,15] for amikacin and between 30 $mg.L^{-1}$ and 40 $mg.L^{-1}$ for gentamicin and tobramycin. Regarding fluroquinolones, a $C_{max}/CMI > 8$[16] was considered adequate.

Chromatographic analysis was performed with a TLX-1 chromatographic system with two UltiMate 3000 LC pumps. The extraction was performed in Focus Technical mode with an online turbulent flow SPE TurboFlow® MCX-2 column (60 µm, 0.5x50 mm, Thermo Scientific). Analytical separation was carried out at room temperature in gradient mode with 0.1% of formic acid (v/v) in water (A) or 0.1% of formic acid (v/v) in acetonitrile (B), on a

Hypersil® GoldAq column (5 µm, 50×3mm, Thermo Scientific). The detection was performed with a High Resolution Mass Spectrometric (HRMS) analyser (Exactive Plus, Thermo Scientific) equipped with a heated electrospray ionization source (h-ESI-II). Amikacin analysis was performed with an immuno-turbidimetric method on Indiko Plus analyser (Thermo Fisher) with absorbance determination. The entire methodology was validated following the validation guidelines of the European Medicines Agency (EMA).

Statistical analysis

Discrete variables were expressed as counts (%) and continuous variables as median and interquartile range. The data distribution of TDM was depicted with the use of boxplots (R Software, version 3.3). The comparison between the categorical variables was assessed using Fisher's exact test. A *P*-value of <0.05 was considered statistically significant.

Ethical considerations

The study was approved by an independent National Research Ethics Committee (Comité de Protection des Personnes Ile de France VI, N°2014-A00043-44), registered in EudraCT (2011-003292-10) and clinicaltrials.gov (NCT03131063).

Results

Forty-four patients were prospectively included on a twelve-month period (May 2014-April 2015), which allowed 68 inclusions. Patient characteristics are shown in Table 1. Some of the patients had been included several times for different antibiotic therapies. Inclusions were made with a minimum interval of 48 hours in case of antibiotics of the same class. All the patients who had been included required mechanical ventilation and the use of a support by catecholamines. The median length of ICU stay was 25 days [17-39]. Among the 68 inclusions, 34 (50%) died during ICU hospitalisation. Patients and ECMO characteristics are shown in Table 1.

Bacteriological data

More than half of the infections were ventilator-associated pneumonias, followed by bacteraemia and operating site infections (table 2). Almost a quarter of suspected infections were not documented. *Pseudomonas aeruginosa* was the most frequent isolated microorganism (29.4%) (See table 3).

Pharmacological analysis

A total of 115 measures of plasma concentration were made using high-pressure liquid chromatography and mass spectrometry. Among the 68 inclusions, 53 (77.9%) concerned ß-lactams. The main studied ß-lactams were piperacillin (n=19), cefotaxime (n=12) and imipenem (n=10).

β-lactams

Cefotaxime was dosed in 12 cases. CT50 and Cmin median were respectively 64.7 $mg.L^{-1}$ [20.2-97.5] and 28.6 $mg.L^{-1}$ [7.3-42.1] for a median dose of 7 grams per day [6-8]. Considering a target MIC of 1$mg.L^{-1}$, corresponding to the MIC of the enterobacterias to cefotaxime, the pharmacokinetic goals (4 $mg.L^{-1}$ for CT50 and 1 $mg.L^{-1}$ for Cmin) were achieved in 100% of the cases for CT50 and in 81.8% of the cases for Cmin.

Piperacillin was the most represented molecule in our study, with a total of 19 inclusions. The median dose was 4 grams four times a day given using an extended infusion. CT50 and Cmin median were respectively 87 $mg.L^{-1}$ [52.8-155.1] and 61.2 $mg.L^{-1}$ [35.4-109.6]. Taking into account the MIC of the *Pseudomonas aeruginosa* to the piperacillin, the pharmacokinetic goals were 64 $mg.L^{-1}$ for CT50 and 16 $mg.L^{-1}$ for Cmin. Thus, 68.7% of CT50 and 93.7% of Cmin reached the pharmacokinetic goals defined.

Ten patients treated with the association imipenem/cilastatin were included in our study. The median dose of imipenem was 1 gram three times a day. CT50 and Cmin median plasma concentration were respectively 7.3 $mg.L^{-1}$ [4.0-14.6] and 3.3 $mg.L^{-1}$ [1.8-5.4]. Based on the MIC of *Pseudomonas aeruginosa* to imipenem according to the EUCAST (4 $mg.L^{-1}$), the pharmacokinetic goals were 16 $mg.L^{-1}$ for the CT50 and 4 $mg.L^{-1}$ for the Cmin. Only one CT50 was above 16 $mg.L^{-1}$. For the Cmin, 60% of the doses did not reached the target concentration of one time the MIC. In our 10 patients cohort, only one patient was considered as reaching the pharmacokinetic goals. Considering a median dose of 1 gram three times a day, 90% of the pair of doses performed were considered as subtherapeutic.

Twelve cases dealing with other ß-lactams were included. The results of the pharmacological therapeutic follow-ups are summarized in table 4. Figure 1 represents plasma concentrations for cefotaxime, piperacillin and imipenem.

Aminoglycosides

In our study, 8 patients were treated with aminoglycosides. One was treated with gentamycin, another with tobramycin and six with amikacin. The gentamycin peak reached 38.2 $mg.L^{-1}$ for a dose of 11.1 $mg.kg^{-1}$. This peak was considered as being in the therapeutic range of 30 and 40 $mg.L^{-1}$. The tobramycin peak reached 13.7 $mg.L^{-1}$ with a dosage of 7.1 $mg.kg^{-1}$, which is below the target concentration. Regarding amikacin, six plasmatic peaks were measured. Four doses (66.7%) were infra-therapeutics by taking a therapeutic zone ranging between 60 and 80 $mg.L^{-1}$.

Discussion

The ß-lactams, which are the most frequently used antibiotics in the ICU, were the main category studied in this work. The three main ß-lactams studied showed very different results in terms of achievement of the pK objectives. In the case of cefotaxime, the achievement of the objectives was mostly fulfilled. For piperacillin, the pK objectives also seemed mostly achieved. The concentrations were kept in 88,2% (15/17) of the cases above the *Pseudomonas aeruginosa* MIC. On the other hand, for imipenem, with a dosage of three grams per day, the pharmacokinetic goals were reached only in 10% of the cases. Regarding the aminoglycosides, 62,5% of the peak concentration were sub-therapeutic.

The results of this preliminary study could constitute a first observation of the pK of antibiotics in an adult population under circulatory assistance by VA ECMO in a context of postoperative cardiac surgery. As far as we know, there are no data in this context. Ex vivo studies has shown that the use of ECMO could alter drug pharmacokinetics. Drugs sequestration result of the adsorption of drugs on the PVC tubing and/or the membrane oxygenator[17]. Lipophilicity and protein binding are the main determinants of circuit adsorption[18,19,20,21]. Increased volume of distribution and decreased clearance are also involved in pk alteration during ECMO. Indeed, the different studies available were conducted on heterogeneous groups of patients, made of medical and surgical patients or patients under VV and VA ECMO in variable proportion. The Ashman and al. study[22] conducted on children or newborns showed that usual doses of cefotaxime enabled sufficient plasma concentrations for an effective treatment. Our results seem to confirm the conclusions of this study in the adult population. Other teams draw different results than ours for piperacillin. In a study published by Donadello and al.[23], the goal of keeping a concentration of piperacillin between 4 and 8 times the MIC during 50% of the time of the inter-doses interval was completed in less than 50% of cases. These results are contradictory with the ones found in our study. Several reasons can explain the difference. First, the population they studied was different, an exclusive respiratory assistance by VV ECMO was used in 65% of the cases, and the prevalence of the renal dysfunction was below than the one in our study. Unlike our study, the doses of piperacillin were adjusted to the renal function. Finally, pharmacological measurements were not always conducted in a steady state plasma concentration, which made the interpretation of their results more delicate considering the frequency of under-dosing during the initial phase of antibiotic therapy. There are no data in regard of the pK of the imipenem under ECMO except for two cases reports[24]. Couffignal and

al.[25] noticed than an administration every 6 hours in ICU patients without ECMO was better able to reach the objectives than an administration three times a day. However, even at the highest studied dosages (1g/6h), f T>MIC of 100% was reached in only 45% of the cases. These results confirmed our observations and implied the necessity to increase doses. The two studies focusing on the pK of meropenem in patients under ECMO seems to indicate that a dose of 1g/8h would maintain a sufficient plasma concentration. In these studies, neither the ECMO, neither extra-renal dialysis seemed to significantly influence pharmacokinetic of meropenem. Likewise, for the amikacin, the study of Gélisse and al.[8] showed that ECMO did not influence the pK of the amikacin, with, however, non-strictly identical groups. In this study, we could notice insufficient peak concentrations in more than 25% of the cases with a dose of 25 mg/kg. Finally, like in all the studies, which had been made on the pK of thee antibiotics under ECMO, a wild inter-individual variability was observed. This concept is a major argument for the use of a pharmacological therapeutic management.

Nowadays, there are no formal recommendations regarding the pK objectives to obtain an optimum efficiency. If animal studies define as necessary a fT>MIC between 40% and 70%, several studies suggested that an exposure to higher doses would be necessary. Roberts and al.[29] recently demonstrated that fT>MIC of 100% of the inter-doses interval was necessary. This important concept supported our choices of the pK objectives we wanted to achieve. Indeed, our initial hypothesis was that a probability antibiotic therapy should cater to the most adverse situations involving microorganisms with the higher MIC to antibiotics given.

Our preliminary study shows several limits. First of all, it could not conclude on the specific role of the ECMO in terms of impact on the pK of the different antibiotics studied given the lack of control groups. However, the main objective was to assess in which measures antibiotic therapy in patients under ECMO achieves the pK objectives. Our initial hypothesis was that an optimisation of the antibiotic therapy was possible using a pharmacological and therapeutic monitoring in this population with a severe pathology. This work was carried out in the cardiac surgery ICU treating patients with long term circulatory support and heart transplant. The studied population was made of surgical patients in need of a circulatory support by peripheral or central VA ECMO, sometimes associated with another circulatory device. Complications associated with a support by ECMO were different depending on the type of assistance; this could constitute a limit to the external validity of our

results. Finally, for some of the antibiotics under study, the low number of patients was a limit for the interpretation of the results.

Conclusion

These preliminary results suggest that therapeutic drug monitoring could optimize the achievement of pharmacokinetic objectives associated with an effective antibiotic therapy. These data also suggest, that, for most patients, the recommended doses of imipenem at 1g three times a day and amikacin at 20 to 25mg/kg, do not achieve the pK targets reported in the literature.

Figure 1 legend:

Plasma concentration at 50% (CT50) and 100% (Cmin) of the dosing interval. Dotted line indicates MIC and the solid line indicates the objective of 4xMIC.

1 References

[1] Peek GJ[1], Mugford M, Tiruvoipati R, Wilson A, Allen E, Thalanany MM, Hibbert CL, Truesdale A, Clemens F, Cooper N, Firmin RK, Elbourne D; CESAR trial collaboration. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. Lancet. 2009 Oct 17;374(9698):1351-63.

[2] Alain Combes, M.D., Ph.D., David Hajage, M.D., Ph.D., Gilles Capellier, M.D., Ph.D., Alexandre Demoule, M.D., Ph.D., Sylvain Lavoué, M.D., Christophe Guervilly, M.D., Daniel Da Silva, M.D., Lara Zafrani, M.D., Ph.D., Patrice Tirot, M.D., Benoit Veber, M.D., Ph.D., Eric Maury, M.D., Ph.D., Bruno Levy, M.D., Ph.D., Yves Cohen, M.D., Ph.D., Christian Richard, M.D., Ph.D., Pierre Kalfon, M.D., Ph.D., Lila Bouadma, M.D., Ph.D., Hossein Mehdaoui, M.D., Gaëtan Beduneau, M.D., Ph.D., Guillaume Lebreton, M.D., Ph.D., Laurent Brochard, M.D., Ph.D., Niall D. Ferguson, M.D., Eddy Fan, M.D., Ph.D., Arthur S. Slutsky, M.D., Daniel Brodie, M.D., and Alain Mercat, M.D., Ph.D. for the EOLIA Trial Group, REVA, and ECMONet*. Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome. N Engl J Med. 2018 May 24;378(21):1965-1975. doi: 10.1056/NEJMoa1800385.

[3] Thiagarajan RR, Barbaro RP, Rycus PT, Mcmullan DM, Conrad SA, Fortenberry JD, Paden ML; ELSO member centers. Extracorporeal Life Support Organization Registry International Report 2016. ASAIO J. 2017 Jan/Feb;63(1):60-67.

[4] Schmidt M, Bréchot N, Hariri S, Guiguet M, Luyt CE, Makri R, Leprince P, Trouillet JL, Pavie A, Chastre J, Combes A. Nosocomial infections in adult cardiogenic shock patients supported by venoarterial extracorporeal membrane oxygenation. Clin Infect Dis. 2012 Dec;55(12):1633-41

[5] Sherwin J, Heath T, Watt K. Pharmacokinetics and Dosing of Anti-infective Drugs in Patients on Extracorporeal Membrane Oxygenation: A Review of the Current Literature. Clin Ther. 2016 Sep;38(9):1976-94.

[6] Donadello K, Antonucci E, Cristallini S, Roberts JA, Beumier M, Scolletta S, Jacobs F, Rondelet B, de Backer D, Vincent JL, Taccone FS. β-Lactam pharmacokinetics during extracorporeal membrane oxygenation therapy: A case-control study. Int J Antimicrob Agents. 2015 Mar;45(3):278-82.

[7] Shekar K, Fraser JF, Taccone FS, Welch S, Wallis SC, Mullany DV, Lipman J, Roberts JA; ASAP ECMO Study Investigators. The combined effects of extracorporeal membrane oxygenation and renal replacement therapy on meropenem pharmacokinetics: a matched cohort study. Crit Care. 2014 Dec 12;18(6):565.

[8] Gélisse E, Neuville M, de Montmollin E, Bouadma L, Mourvillier B, Timsit JF, Sonneville R. Extracorporeal membrane oxygenation (ECMO) does not impact on amikacin pharmacokinetics: a case-control study. Intensive Care Med. 2016 May;42(5):946-8.

[9] Donadello K, Roberts JA, Cristallini S, Beumier M, Shekar K, Jacobs F, Belhaj A, Vincent JL, de Backer D, Taccone FS. Vancomycin population pharmacokinetics during extracorporeal membrane oxygenation therapy: a matched cohort study. Crit Care. 2014 Nov 22;18(6):632.

[10] Touchard C, AubPredictors of insufficient peak amikacin concentration in critically ill patients on extracorporeal membrane oxygenation.ry A, Eloy P, Bréchot N, Lebreton G, Franchineau G, Besset S, Hékimian G, Nieszkowska A, Leprince P, Luyt CE, Combes A, Schmidt M. Predictors of insufficient peak amikacin concentration in critically ill patients on extracorporeal membrane oxygenation. Crit Care. 2018 Aug 19;22(1):199

[11] Li C, Du X, Kuti JL, Nicolau DP. Clinical pharmacodynamics of meropenem in patients with lower respiratory tract infections. Antimicrob Agents Chemother. 2007 May;51(5):1725-30. Epub 2007 Feb 16.

[12] Roberts JA, Paul SK, Akova M, Bassetti M, De Waele JJ, Dimopoulos G, Kaukonen KM, Koulenti D, Martin C, Montravers P, Rello J, Rhodes A, Starr T, Wallis SC, Lipman J; DALI Study. DALI: defining antibiotic levels in intensive care unit patients: are current β-lactam antibiotic doses sufficient for critically ill patients? Clin Infect Dis. 2014 Apr;58(8):1072-83

[13] Elbarbry, F. Eur J Drug Metab Pharmacokinet (2018) 43: 259. https://doi.org/10.1007/s13318-017-0456-4

[14] Moore RD, Lietman PS, Smith CR. Clinical response to aminoglycoside therapy: importance of the ratio of peak concentration to minimal inhibitory concentration. J Infect Dis. 1987 Jan;155(1):93-9.

[15] Agence française sanitaire des produits de santé. Mise au point sur le bon usage des aminosides administrés par voie injectable: gentamicine, tobramycine, nétilmicine, amikacine. 2011 Mar

[16] Conil JM, Georges B, de Lussy A, Khachman D, Seguin T, Ruiz S, Cougot P, Fourcade O, Houin G, Saivin S. Ciprofloxacin use in critically ill patients: pharmacokinetic and pharmacodynamic approaches. Int J Antimicrob Agents. 2008 Dec;32(6):505-10. doi: 10.1016/j.ijantimicag.2008.05.019

[17] Lemaitre F, Hasni N, Leprince P, Corvol E, Belhabib G, Fillâtre P, Luyt CE, Leven C, Farinotti R, Fernandez C, Combes A. Propofol, midazolam, vancomycin and cyclosporine therapeutic drug monitoring in extracorporeal membrane oxygenation circuits primed with whole human blood. Crit Care. 2015 Feb 12;19:40

[18] Shekar K, Roberts JA, Mcdonald CI, Fisquet S, Barnett AG, Mullany DV, Ghassabian S, Wallis SC, Fung YL, Smith MT, Fraser JF. Sequestration of drugs in the circuit may lead to therapeutic failure during extracorporeal membrane oxygenation. Crit Care. 2012 Oct 15;16(5):R194

[19] Wildschut ED, Ahsman MJ, Allegaert K, Mathot RA, Tibboel D. Determinants of drug absorption in different ECMO circuits. Intensive Care Med. 2010 Dec;36(12):2109-16

[20] Shekar K, Roberts JA, Mcdonald CI, Ghassabian S, Anstey C, Wallis SC, Mullany DV, Fung YL, Fraser JF. Protein-bound drugs are prone to sequestration in the extracorporeal membrane oxygenation circuit: results from an ex vivo study. Crit Care. 2015 Apr 14;19:164.

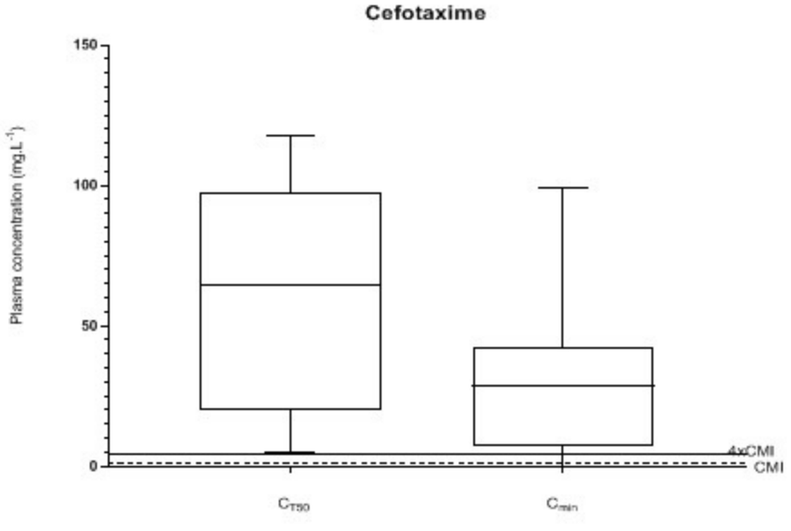
[21] Shekar K, Roberts JA, Barnett AG, Diab S, Wallis SC, Fung YL, Fraser JF. Can physicochemical properties of antimicrobials be used to predict their pharmacokinetics during extracorporeal membrane oxygenation? Illustrative data from ovine models. Crit Care. 2015 Dec 15;19:437.

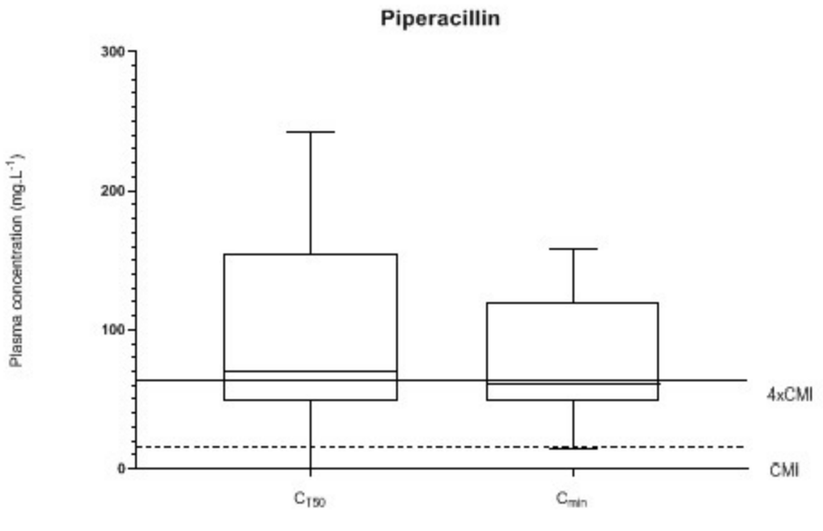
[22] Ahsman MJ, Wildschut ED, Tibboel D, Mathot RA. Pharmacokinetics of cefotaxime and desacetylcefotaxime in infants during extracorporeal membrane oxygenation. Antimicrob Agents Chemother. 2010 May;54(5):1734-41.

[23] Donadello K, Antonucci E, Cristallini S, Roberts JA, Beumier M, Scolletta S, Jacobs F, Rondelet B, de Backer D, Vincent JL, Taccone FS. β-Lactam pharmacokinetics during extracorporeal membrane oxygenation therapy: A case-control study. Int J Antimicrob Agents. 2015 Mar;45(3):278-82.

[24] C. Welsch, P. Augustin,J. Allyn, L. Massias, P. Montravers, N. Allou. Alveolar and serum concentrations of imipenem in two lung transplant recipients supported with extracorporeal membrane oxygenation. Transpl Infect Dis 2015: 17: 103–105.

[25] Couffignal C, Pajot O, Laouénan C, Burdet C, Foucrier A, Wolff M, Armand-Lefevre L, Mentré F, Massias L. Population pharmacokinetics of imipenem in critically ill patients with suspected ventilator-associated pneumonia and evaluation of dosage regimens. Br J Clin Pharmacol. 2014 Nov;78(5):1022-34


Cefotaxime
Plasma concentration (mg.L-1)
150
100
50
0
4xCMI
CMI
CT50
Cmin


Piperacillin
Plasma concentration (mg.L-1)
300
200
100
0
4xCMI
CMI
CT50
Cmin

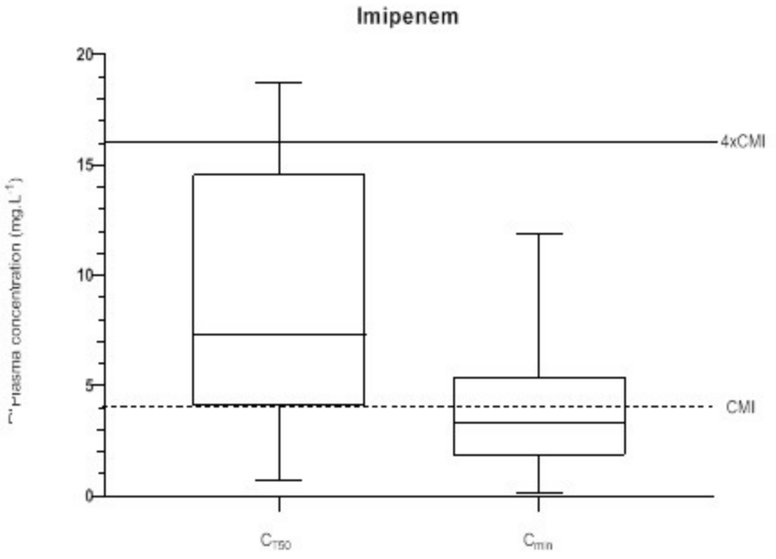

Imipenem
Plasma concentration (mg.L-1)
20
15
10
5
0
4xCMI
CMI
CT50
Cmin

Table 1: Demographic and Clinical Characteristics of Patients

Patient characteristic	**n (%) or median [IQR]**
Age (years)	62.5 [58-67]
Female	10 (14.7)
BMI	25.2 [23.4-28.2]
IGS 2	52 [43-67]
Time from ECMO to inclusion	6 [4-14.7]
Duration of ECMO	20 [12-25]
Mortality	34 (50)
Serum proteins (g/L)	48 [44-52]
Plasma creatinine concentration (µmol/L)	78 [60-133]
Creatinine clearance (mL/min)	20 [0-69]
CRRT	28 (41)
Indication for ECMO	
Post cardiotomy	19 (27.90)
Dilated cardiomyopathy	17 (25.0)
infective endocarditis	10 (14.7)
Acute myocardial infarction	8 (11.7)
Heart transplantation	6 (8.8)
Other	8 (11.7)
Type of ECMO	
VV	2 (2.9)
VA Peripheral	50 (73.5)
VA central	4 (5.8)
RA - PA	12 (17.6)

BMI: body mass index; IGS 2: index de gravité simplifié 2; COPD: chronic obstructive pulmonary disease; CRRT: continuous renal replacement therapy; ECMO: extracorporeal membrane oxygenation; VA: venoarterial ; VV: venovenous; RA-PA : right atrium – Pulmonary artery. The biochemical indices were measured on day of pharmacokinetic sampling.

Table 2 Infected Sites

Infected Sites	**n (%)**
VAP	35 (51.5%)
Bloodstream infections	6 (8.9%)
Infective endocarditis	4 (5.8%)
Catheter infection	4 (8.8%)
Mediastinitis and local infection of the cannulation site	6 (8.9%)
Urinary tract infection	3 (4.4%)
Not documented	16 (23.5%)

VAP : Ventilator-associated pneumonia

Table 3 : Bacteriological data

Pathogens	**n (%)**
Pseudomonas aeruginosa	20 (29.4%)
Klebsiella pneumoniae	13 (19.1%)
E. Coli	11 (16.2%)
Enterobacter cloacae	5 (7.3%)
Morganella morganii	2 (2.9%)
Citrobacter koseri	1 (1.5%)
Other gram negative bacteria	2 (2.9%)
Streptococcus	5 (7.3%)
Staphylococcus epidermidis	4 (5.9%)
Staphylococcus aureus	1 (1.5%)
Enterococcus	1 (1.5%)
Stenotrophomonas maltophilia	1 (1.5%)
Listeria monocytogene	1 (1.5%)

Table 4: Therapeutic drug monitoring

	n	Dosing regimen ($g.d^{-1}$)	MIC	Proportions of adequates
Amoxicillin	6	6	8	66.6
Piperacillin	19	16	16	80.5
Cefotaxime	12	7	1	91.3
Ceftazidine	3	6	8	100
Cefepime	1	6	8	100
Meropenem	2	3-6	2	100
Iminpenem	10	3	4	25
Vancomycin	5	2	4	80
Ciprofloxacin	2	0.8	0.5	50