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

3

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## 1 **Introduction**

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

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

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## 2 **Patients and Methods**

### 3 *Design*

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

### 11 *Data*

12 The following data were collected for all patients: age, gender, weight and body mass index,  
13 admission date and ICU admission diagnosis, date of intubation and extubation and the  
14 mortality date. With the therapeutic drug monitoring (TDM), the following data were also  
15 collected: weight; temperature; heart rate; mean arterial pressure; respiratory rate; inspiratory  
16 oxygen fraction; the following biological factors: partial pressure of arterial oxygen (PaO<sub>2</sub>),  
17 pH, potassium and sodium levels, lactic acid, leukocytes, haematocrit, serum proteins, renal  
18 function parameters: serum creatinine, urine output, creatininuria (creatinine clearance was  
19 calculated from the 24-h urine using the formula:  $CL_{Cr} \text{ mL/min} = [(\text{urine Cr, mg/dL}) \times (\text{urine}$   
20  $\text{output, mL})] / [(\text{serum Cr, mg/dL}) \times (\text{time of urine collection, min})]$ ), presence of continuous  
21 renal replacement therapy (cRRT) (initiation time of cRRT, dialysate and ultrafiltrate rate);  
22 data concerning antibiotic therapy, type of drugs, initiation time, posology, type of infusion  
23 (continuous, extended or bolus infusion), infusion time, number of doses received before  
24 TDM, exact time of the last infusion; data related to ECMO: indication, initiation time, type  
25 of ECMO, cannulation site, ECMO course before TDM, ECMO parameters the day of the  
26 TDM; data related to the sepsis: pathogens and infection type.

### 27 *Extracorporeal life support circuit and management*

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

1 Crystalloids and/or colloids were used for the priming volume. ECMO parameters were  
2 adjusted by the physician to ensure blood oxygen level, the CO<sub>2</sub> removal and an appropriate  
3 blood flow. All patients received ECMO circuits anticoagulation with heparin.

#### 4 *Antibiotic treatment, measurements and pharmacokinetic (PK) analysis*

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

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

28 Chromatographic analysis was performed with a TLX-1 chromatographic system with two  
29 UltiMate 3000 LC pumps. The extraction was performed in Focus Technical mode with an  
30 online turbulent flow SPE TurboFlow® MCX-2 column (60  $\mu$ m, 0.5x50 mm, Thermo  
31 Scientific). Analytical separation was carried out at room temperature in gradient mode with  
32 0.1% of formic acid (v/v) in water (A) or 0.1% of formic acid (v/v) in acetonitrile (B), on a

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

#### 7 *Statistical analysis*

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

#### 12 *Ethical considerations*

13 The study was approved by an independent National Research Ethics Committee (Comité de  
14 Protection des Personnes Ile de France VI, N°2014-A00043-44), registered in EudraCT  
15 (2011-003292-10) and clinicaltrials.gov (NCT03131063).

16

17

## 1 **Results**

2 Forty-four patients were prospectively included on a twelve-month period (May 2014-April  
3 2015), which allowed 68 inclusions. Patient characteristics are shown in Table 1. Some of the  
4 patients had been included several times for different antibiotic therapies. Inclusions were  
5 made with a minimum interval of 48 hours in case of antibiotics of the same class. All the  
6 patients who had been included required mechanical ventilation and the use of a support by  
7 catecholamines. The median length of ICU stay was 25 days [17-39]. Among the 68  
8 inclusions, 34 (50%) died during ICU hospitalisation. Patients and ECMO characteristics are  
9 shown in Table 1.

### 10 *Bacteriological data*

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

### 15 *Pharmacological analysis*

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

### 20 *$\beta$ -lactams*

21 Cefotaxime was dosed in 12 cases. CT50 and Cmin median were respectively 64.7 mg.L<sup>-1</sup>  
22 [20.2-97.5] and 28.6 mg.L<sup>-1</sup> [7.3-42.1] for a median dose of 7 grams per day [6-8].  
23 Considering a target MIC of 1mg.L<sup>-1</sup>, corresponding to the MIC of the enterobacterias to  
24 cefotaxime, the pharmacokinetic goals (4 mg.L<sup>-1</sup> for CT50 and 1 mg.L<sup>-1</sup> for Cmin) were  
25 achieved in 100% of the cases for CT50 and in 81.8% of the cases for Cmin.

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

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

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

### 13 *Aminoglycosides*

14 In our study, 8 patients were treated with aminoglycosides. One was treated with gentamycin,  
15 another with tobramycin and six with amikacin. The gentamycin peak reached 38.2 mg.L<sup>-1</sup> for  
16 a dose of 11.1 mg.kg<sup>-1</sup>. This peak was considered as being in the therapeutic range of 30 and  
17 40 mg.L<sup>-1</sup>. The tobramycin peak reached 13.7 mg.L<sup>-1</sup> with a dosage of 7.1 mg.kg<sup>-1</sup>, which is  
18 below the target concentration. Regarding amikacin, six plasmatic peaks were measured. Four  
19 doses (66.7%) were infra-therapeutics by taking a therapeutic zone ranging between 60 and  
20 80 mg.L<sup>-1</sup>.

21

22



## 1 **Discussion**

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

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

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

14

15 Nowadays, there are no formal recommendations regarding the pK objectives to obtain  
16 an optimum efficiency. If animal studies define as necessary a fT>MIC between 40% and  
17 70%, several studies suggested that an exposure to higher doses would be necessary. Roberts  
18 and al.<sup>[29]</sup> recently demonstrated that fT>MIC of 100% of the inter-doses interval was  
19 necessary. This important concept supported our choices of the pK objectives we wanted to  
20 achieve. Indeed, our initial hypothesis was that a probability antibiotic therapy should cater to  
21 the most adverse situations involving microorganisms with the higher MIC to antibiotics  
22 given.

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

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

3

4

5

1 **Conclusion**

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

1 **Figure 1 legend:**

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

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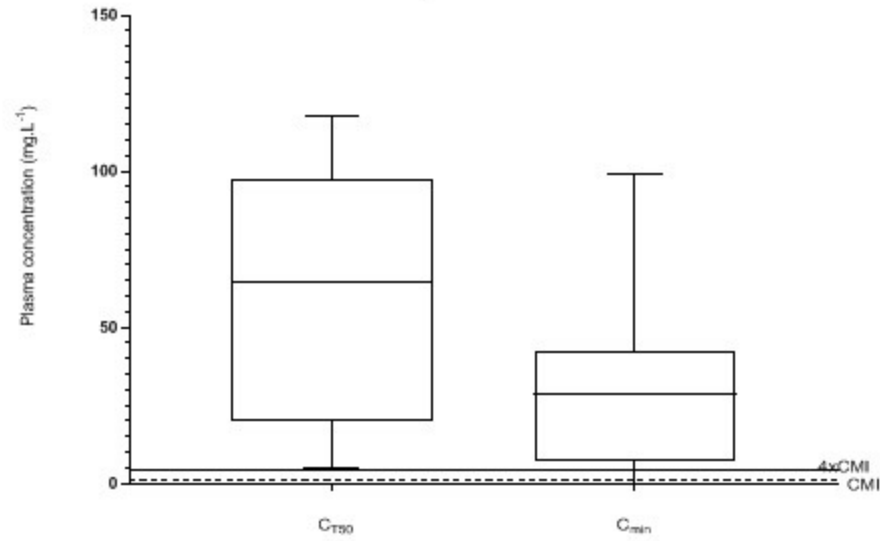
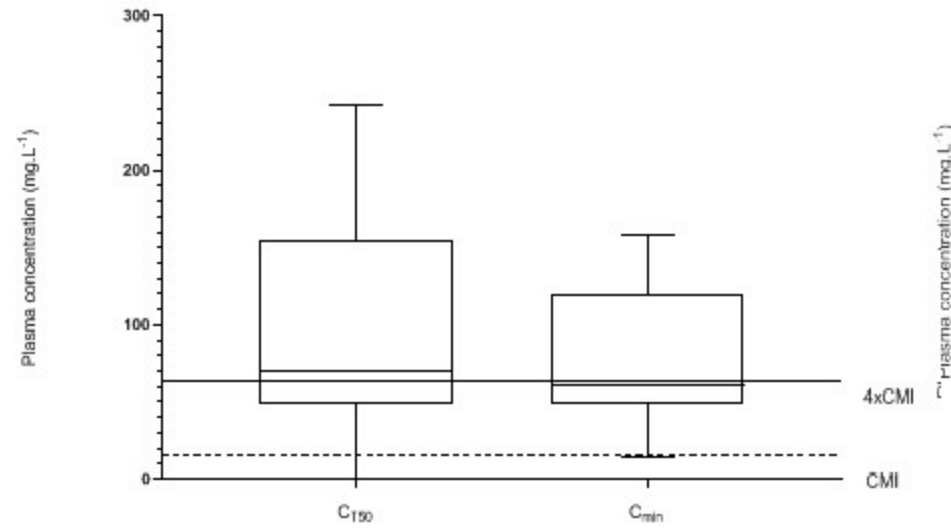
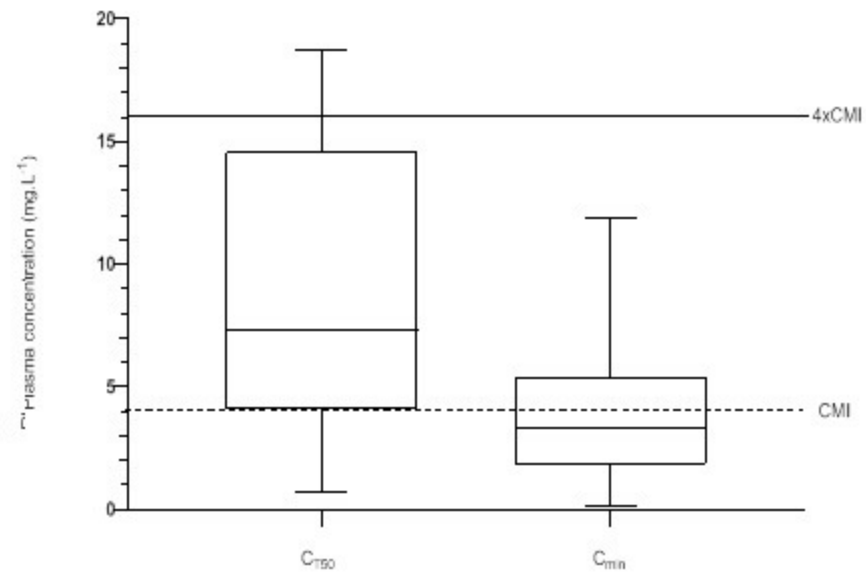
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**Cefotaxime****Piperacillin****Imipenem**



**Table 1:** Demographic and Clinical Characteristics of Patients

<b>Patient characteristic</b>	<b>n (%) or median [IQR]</b>
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 ( $\mu\text{mol/L}$ )	78 [60-133]
Creatinine clearance (mL/min)	20 [0-69]
CRRT	28 (41)
<b>Indication for ECMO</b>	
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)
<b>Type of ECMO</b>	
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

<b>Infected Sites</b>	<b>n (%)</b>
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

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

**Table 4:** Therapeutic drug monitoring

	n	Dosing regimen (g.d <sup>-1</sup> )	MIC	Proportions of adequates
Amoxicillin	6	6	8	66.6
Piperacillin	19	16	16	80.5
Cefotaxime	12	7	1	91.3
Ceftazidime	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