# Exploring the impact of extracorporeal membrane oxygenation (ECMO) therapy on piperacillin pharmacokinetics: do general intensive care unit models perform similarly to ECMO models?

Ibrahim El-Haffaf[1], David Williamson[1,2], Rosalie Voyer[1], Yiorgos Alexandros Cavayas[2], Marc-Alexandre Duceppe[3], Chantale Simard[4], Han Ting Wang[5], Zoé Thiboutot[5], Amélie Marsot[1,6]

[1]Faculty of pharmacy, Université de Montréal, Montreal, QC, Canada; [2]Hôpital du Sacré-Cœur de Montréal, Montreal, QC, Canada; [3]Centre universitaire de santé McGill, Montreal, QC, Canada; [4]Faculty of pharmacy, Université Laval, Quebec City, QC, Canada; [5]Centre hospitalier de l'Université de Montréal, Montreal, QC, Canada ; [6]Research center, CHU Sainte-Justine, Montreal, QC, Canada

Contact: ibrahim.el-haffaf@umontreal.ca

## INTRODUCTION

- Extracorporeal membrane oxygenation (ECMO) therapy is a last-resort therapy to support the heart and/or lungs of critically ill patients in intensive care units (ICU)[1].

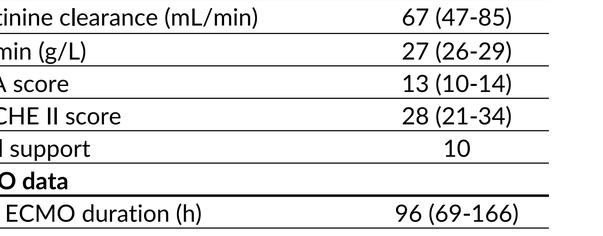



Figure 1. ECMO circuit using a veno-venous (VV) mode

- ECMO circuit may impact the pharmacokinetics (PK) of drugs according to their physicochemical properties, but data remains limited for antimicrobials[1].
- Patients under ECMO are at higher risk of acquiring infections and are thus often prescribed broad-spectrum antimicrobials such as piperacillin/tazobactam[1,2].
- Many piperacillin population pharmacokinetic (popPK) models have been published in the literature, but no external evaluations have been performed to assess their transferability in ECMO patients[3].

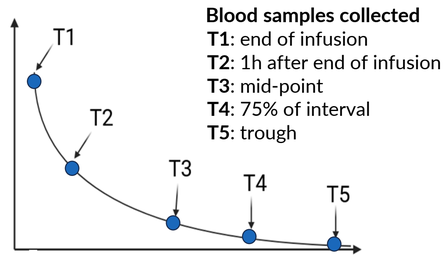
## OBJECTIVES

**Evaluate the predictive performance of piperacillin popPK models and compare the performance of general ICU models to ECMO models**

## METHODS

**External evaluation dataset (prospective study)**

- Critically ill adult patients under ECMO
- Piperacillin/tazobactam
- Ø pregnancy




**Literature review and external evaluation process**

- Literature review on Pubmed to identify piperacillin popPK models developed with critically ill patient data (non-ECMO and ECMO)
- Use of NONMEM v7.6 to calculate **population- and individual-predicted concentrations (PRED/IPRED).**
- Prediction error (PE) was calculated as: $PE\ (\%) = \frac{C_{predicted} - C_{observed}}{C_{observed}} \times 100\%$
- Model bias $MDPE\ (\%) = median\ (PE)$
- Model imprecision $MDAPE\ (\%) = median\ |PE|$
- Model had acceptable performance if bias was between ±20% and if imprecision ≤30%[3]
- ECMO-specific models were re-estimated if *a priori* (PRED) model performance was not satisfactory (MAXEVAL=9999).

## RESULTS

Table 1. ECMO patient data (N=24)

| Demographic data | Median (IQR) or N |
|---|---|
| Men/women | 18/6 |
| Age (years) | 55 (41-65) |
| Weight (kg) | 89 (81-100) |
| **Clinical data** | |
| Serum creatinine (µmol/L) | 154 (97-181) |
| Creatinine clearance (mL/min) | 67 (47-85) |
| Albumin (g/L) | 27 (26-29) |
| SOFA score | 13 (10-14) |
| APACHE II score | 28 (21-34) |
| Renal support | 10 |
| **ECMO data** | |
| Total ECMO duration (h) | 96 (69-166) |
| *Modes* | |
| Veno-venous | 14 |
| Veno-arterial | 10 |
| ECMO flow rate (L/min) | 4.0 (3.1-4.3) |
| **PK data** | |
| *Administered doses* | 24 |
| 2250 mg q8h | 1 |
| 3375 mg q6h | 11 |
| 4500 mg q6h | 11 |
| 4500 mg q4h | 1 |
| Intermittent infusion | 18 |
| Prolonged infusion | 6 |
| $C_{50\%}$(mg/L) | 80 (52-162) |
| $C_{min}$ (mg/L) | 68 (26-102) |

Table 2. Parameters of initial vs re-estimated ECMO models

| Parameter | Fillâtre et al. | | Kim et al. | |
|---|---|---|---|---|
| | Initial model | Re-estimated | Initial model | Re-estimated |
| CL | 5.01 (9%) | 4.93 (12.4%) | 5.05 (6.67%) | 3.38 (14.5%) |
| V1 | 17.5 (9%) | 14.5 (9.5%) | 7.38 (15.0%) | 10.1 (12.2%) |
| V2 | 10.4 (22%) | 6.95 (44.5%) | 6.27 (16.2%) | 4.39 (20.2%) |
| Q | 7.01 (29%) | 3.49 (22.6%) | 6.28 (23.9%) | 2.95 (41.7%) |
| IIV CL (CV%) | 65.8 (11%) | 79.3 (19.6%) | 33.7 (11.8%) | 71.2 (19.5%) |
| IIV V1 (CV%) | 33.9 (16%) | 38.3 (23.9%) | 45.9 (17.4%) | 39.2 (27.8%) |
| IIV V2 (CV%) | 101.3 (27%) | 1369.9 (316%) | NA | NA |
| IIV Q (CV%) | NA | NA | NA | NA |
| Covariate effect | NA | NA | eGFR: 0.00932 (14%) | eGFR: 0.0119 (36%) |

**For Kim et al., allometric scaling was used for all parameters and their CL was calculated as: $CL = 5.01*(Weight/70)^{0.75} * e^{(0.00932*(eGFR-50.6))}$**
**Data presented as Parameter (%Relative standard error)**
CL: clearance, CV: coefficient of variation, eGFR: estimated glomerular filtration rate, IIV: interindividual variability, NA: not applicable Q: inter-compartmental clearance, V: volume of distribution

**Literature review**

20 articles included

- 3 ECMO popPK models
  - Two-compartment models: n=3
- 17 non-ECMO popPK models
  - One-compartment models: n=6
  - Two-compartment models: n=11

**Covariates**

- Renal function marker: n=2
- Allometric scaling: n=1
- ECMO: n=1

- Renal function marker: n=9
- Bodyweight: n=6
- Renal replacement therapy: n=5
- Mean arterial pressure: n=1

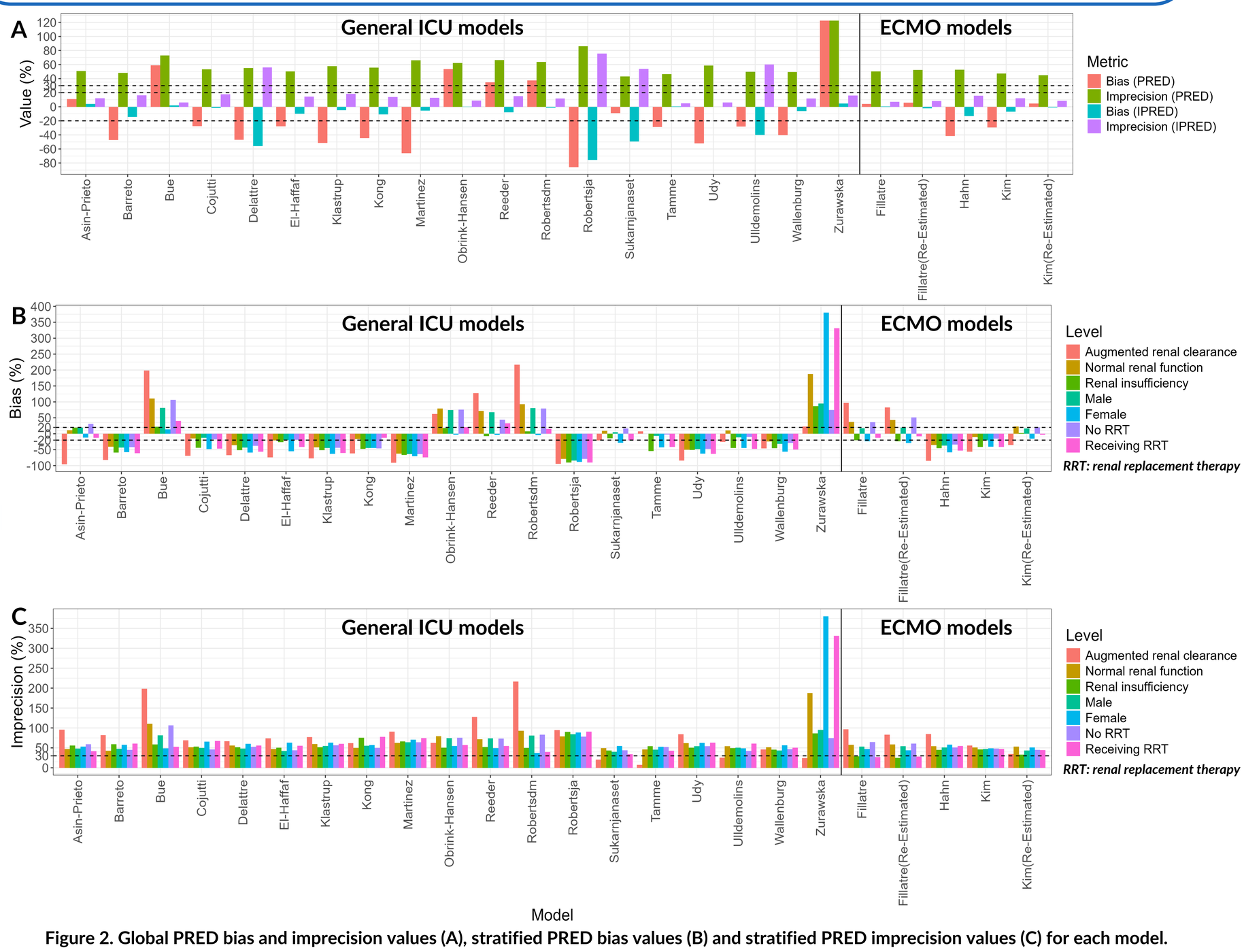



Figure 2. Global PRED bias and imprecision values (A), stratified PRED bias values (B) and stratified PRED imprecision values (C) for each model.

## KEY POINTS

- **Poor model performance in ECMO patients was observed following the external evaluation of 20 popPK models. No model had satisfactory bias/imprecision values**
  - **The best performing models were the ones by Fillâtre et al. (ECMO and non-ECMO data) and by Sukarnjanaset et al. (non-ECMO data).**
  - **Stratification showed that three ICU models and one ECMO model had an improved bias/imprecision for certain categories such as augmented renal clearance or renal replacement therapy, but the majority of model performances remained inadequate.**
- **The results of this evaluation differ from those of previous evaluations in non-ECMO critically ill patients in terms of model performance[4,5,6].**
  - **This may indicate that some models are better suited for ECMO patients and that some differences between non-ECMO and ECMO patients exist that may not be properly identified in existing models.**
- **Re-estimation of the model by Kim et al. offered good estimation precision and a notable improvement in bias, whereas the one by Fillâtre et al. had extreme estimate with poor precision for the IIV of peripheral volume. The model by Kim et al. could thus be used as a reference model for the development of a new model using the $PRIOR approach to guide structure choice and further explore covariates that can better describe ECMO data.**

## REFERENCES

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RQRM Réseau québécois de recherche sur les médicaments
inven_T
IRSC CIHR Instituts de recherche en santé du Canada Canadian Institutes of Health Research