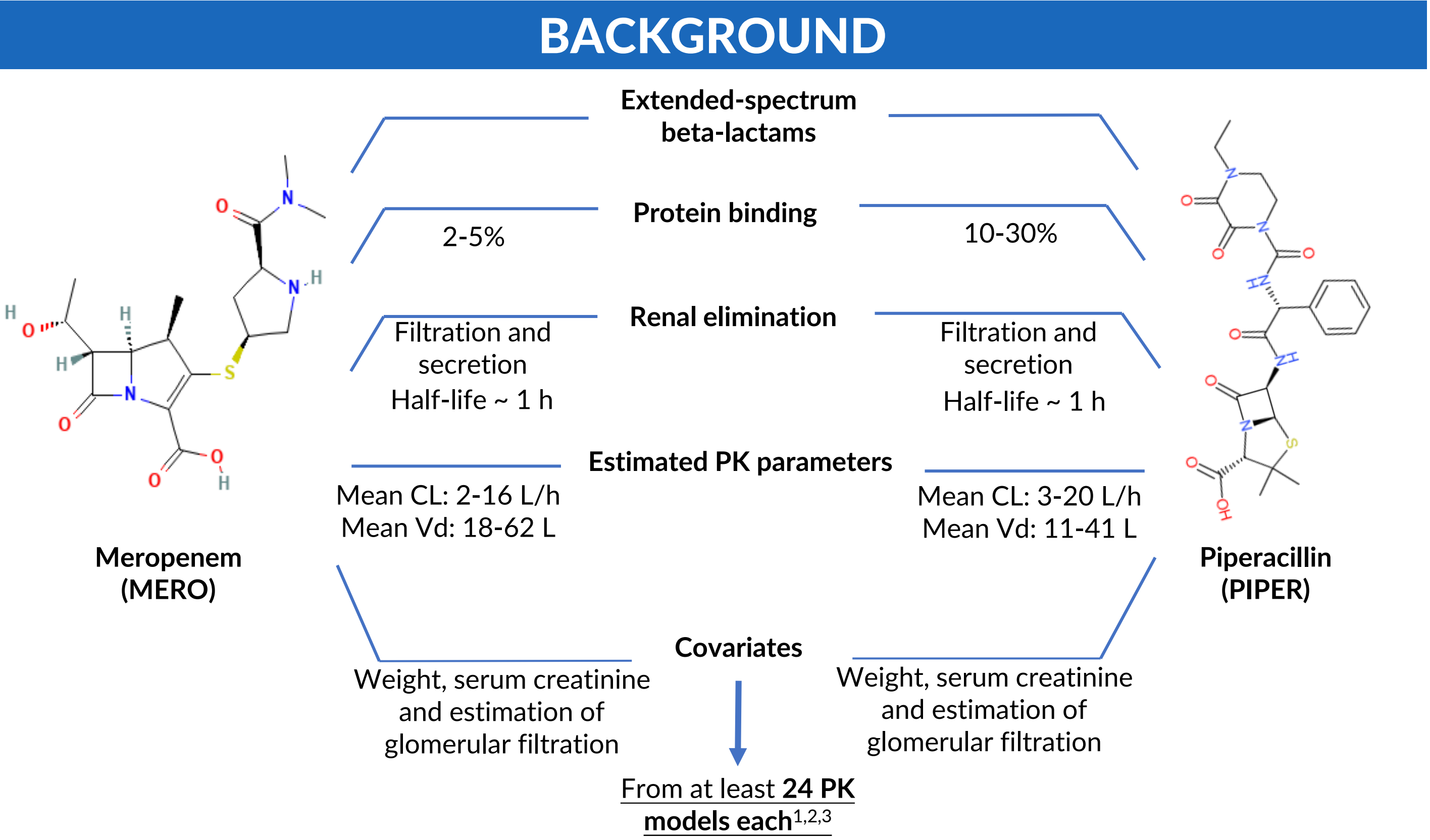


Joint model for piperacillin and meropenem: Assessing the impact of a joint pharmacokinetic modeling approach on covariate inclusion and probability of target attainment

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Piperacillin and meropenem share similar properties

A joint PK model may be feasible for these antibiotics to simplify model-informed precision dosing

- OBJECTIVES**
- Develop independent models for PIPER and MERO and a joint model with a pooled dataset.
 - Assess the impact on covariate selection and on probability of target attainment (PTA) when using a joint model vs an independent model.

METHODS

Population

Prospective observational study

Critically ill patients in Canada

Hôpital du Sacré-Cœur de Montréal (HSCM)

Centre hospitalier de l'Université de Montréal (CHUM)

Centre hospitalier universitaire de Sherbrooke (CHUS)

Patients receiving MERO or PIPER by intravenous injection

Sampling schedule:

- Peak (30 min post-infusion)
- Middle (3-8 h post-infusion)
- Trough (6-12 h post-infusion)

On days 1, 4 and 7

Table 1. Dosing regimens for each molecule

MERO	PIPER
0.5 to 2 g every 8-12 h over 30 min OR over 3 h	2 to 4 g every 6 h over 30 min OR over 3 h

Model development and evaluations

Model development

Structural model

Separate, independent models

Total PIPER Total MERO

Combined, joint model

Total PIPER + MERO

Estimation of parameters with the Laplacian method with interaction.

Handling of below limit of quantification data was done with the M3 method⁴.

Joint model: separation of PK parameters by drug was explored to assess drug differences

Covariate model

Tested covariates

Age

Weight

Serum creatinine (SCR)

Creatinine clearance (CLCR)

Drop in objective function value (OFV) by at least 6.61 points

Visual improvement of goodness-of-fit plots

Improvement in estimated inter-individual variability (IIV)

Monte Carlo simulations (N=1000) were performed for each model to evaluate PTA for three patients with difference renal functions:

Renal insufficiency: 30 mL/min

Normal: 80 mL/min

Augmented renal clearance (ARC): 130 mL/min

Table 2. Simulated dosing regimens

Mode	MERO	PIPER
II	0.5 to 2 g every 6, 8 or 12 h over 30 min	2 to 4 g every 6 or 8 h over 30 min
PI	0.5 to 2 g every 6 or 8 h over 3 or 4 h	2 to 4 g every 6 or 8 h over 3 or 4 h
CI	2 g over 30 min + 0.5 to 6 g over 24 h	4 g over 30 min + 2 to 12 g over 24 h

CI/II/PI: continuous/intermittent/prolonged infusions

Dosing regimen was retained when PTA was at least 90% for the following targets:

MERO	PIPER
100% of time above 8 mg/L	100% of time above 16 mg/L

Targets correspond to respective breakpoints against *Pseudomonas aeruginosa*⁵

Model comparison

The final models were compared based on **three criteria**

- Covariates retained
- Parameter estimates
- Dosing simulations

Differences in CL and Vd were calculated

Similar recommendations if PTA differences of less than 5% between models

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HSCM Hôpital du Sacré-Cœur de Montréal

CHUS Centre hospitalier universitaire de Sherbrooke

CHUM Centre hospitalier de l'Université de Montréal

IRSC CIHR Institut de recherche en santé de Québec

Fonds de recherche Santé Québec

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RESULTS

Table 3. Patient characteristics

Characteristics	Full dataset (n=97)	Piperacillin (n=70)	Meropenem (n=27)
N (Male/Female)	67/30	49/21	18/9
Age (years)	64 (49-74)	67 (50-75)	58 (46-66)
Weight (kg)	86 (69-97)	83 (72-95)	89 (67-100)
Albumin (g/L)	26 (21-30)	24 (20-27)	28 (26-31)
Serum creatinine (μmol/L)	85 (59-141)	97 (71-155)	55 (43-82)
Creatinine clearance (mL/min)*	80 (45-153)	63 (42-110)	166 (97-204)
N samples	400	233	167

Data presented as median (interquartile range)

* Calculated with the Cockcroft-Gault equation

Table 4. Model characteristics

Piperacillin	Meropenem
For male, CL (L/h) = 6.81 * (CLCR/62)	For CLCR < 200: CL (L/h) = 12.6 * (CLCR/166)
IIV (CV%): 34.9%	IIV (CV%): 35.2%
V (L) = 26.4	V (L) = 27.0
Proportional residual error: 32.2%	Proportional residual error: 43.0%
Joint model	Joint model
CL (L/h) = 7.2 * (CLCR/80) ^{0.73}	CL (L/h) = 7.2 * (CLCR/80) ^{0.73}
IIV (CV%): 43.2%	IIV (CV%): 43.2%
V (L) = 25.7	V (L) = 25.7
Proportional residual error: 36.7%	Proportional residual error: 36.7%

CV: coefficient of variation

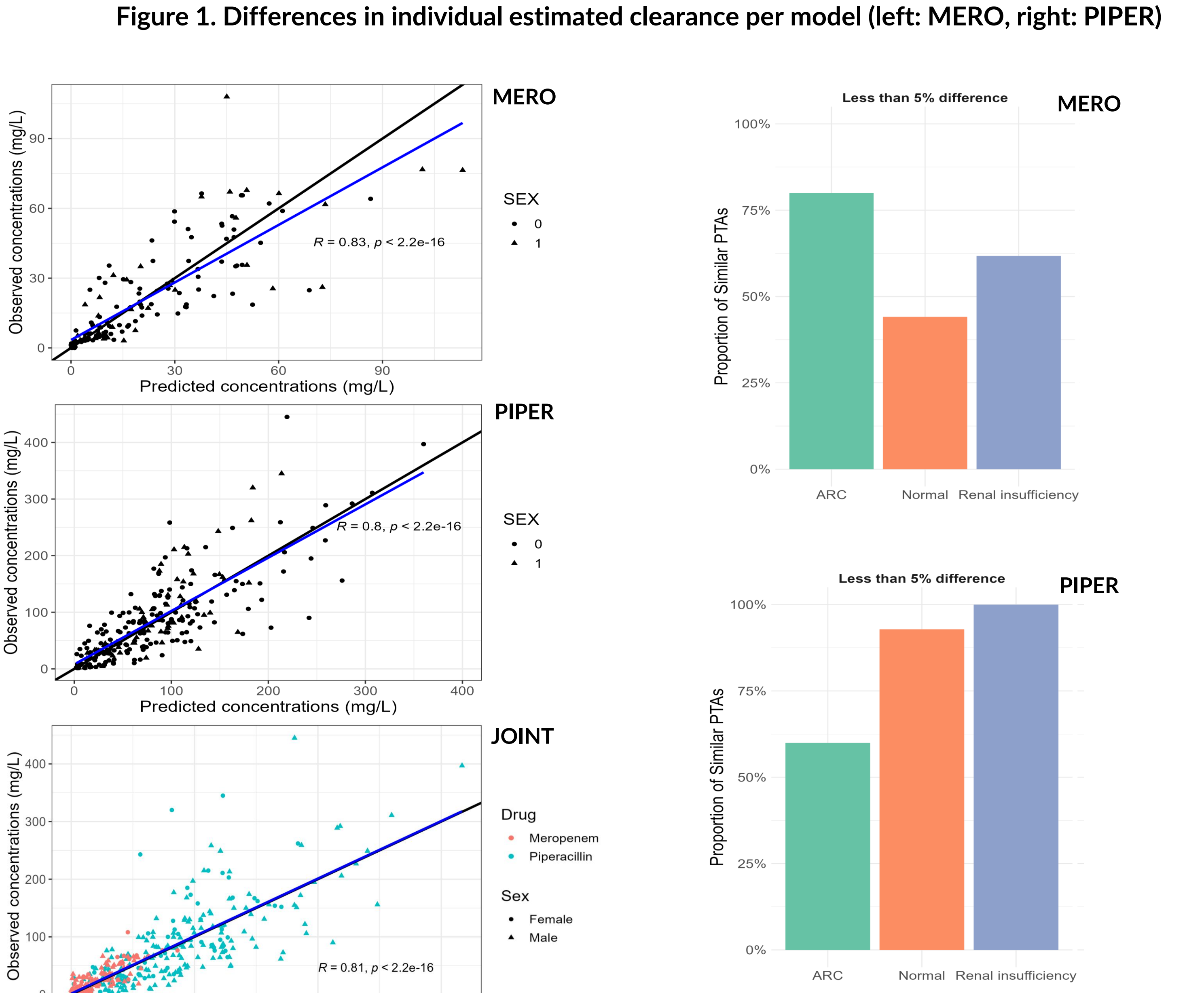
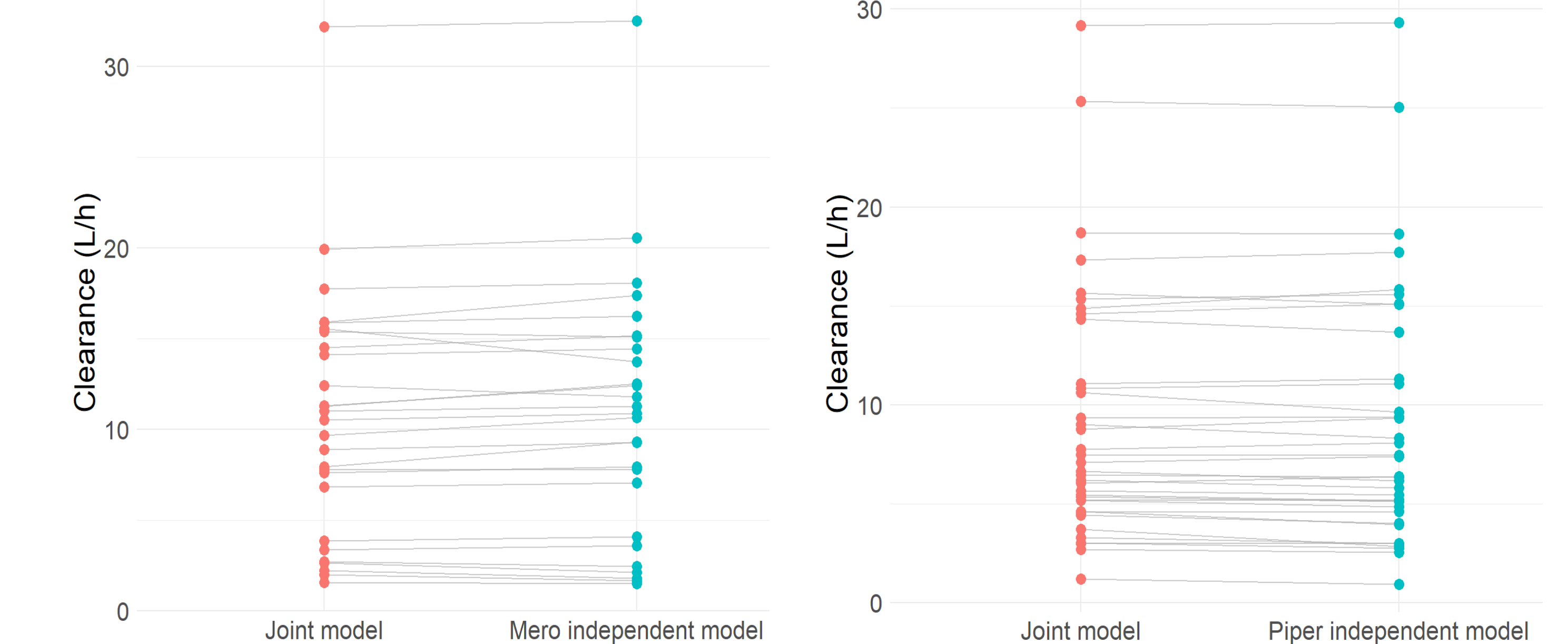


Table 5. Comparison of recommended dosing regimens from independent and joint models

Renal group	MERO model	Joint model	PIPER model	Joint model
Normal	2 g every 8 h over 30 min	2 g every 8 h over 4 h	Male: 4 g every 6 h over 3 h Female: 4 g every 6 h over 3 h	3 g every 6 h over 3 h
Renal insufficiency	0.5 g every 6 h over 30 min	1 g every 6 h over 30 min	Male: 2 g every 6 h over 30 min Female: 2 g every 6 h over 3 h	2 g every 6 h over 3 h
Augmented renal clearance	2 g + 6 g over 24 h	2 g + 6 g over 24 h	Male: 4 g + 12 g over 24 h Female: 4 g + 12 g over 24 h	4 g + 10 g over 24 h

Recommended dosing regimens where PTA was ≥ 90% for targets of 100% above 8 mg/L (MERO) or above 16 mg/L (PIPER)

KEY FINDINGS

- Individual parameter estimates did not differ greatly between the independent and joint models for both MERO and PIPER.
- Covariates between independent and joint models differed but were all related to renal function as with most PIPER/MERO models.
- Discrepancies in PTAs were observed mostly in groups that were underrepresented in the respective independent datasets.
- Recommended doses to achieve a minimal PTA of 90% differed between independent and joint models.

1. El-Haffaf et al. Clin Pharmacokinet. 2021
2. Yang et al. Front Pharmacol. 2022
3. Greppmair et al. Intensive Care Med. 2023

4. Ahn et al. J Pharmacokinet Pharmacodyn. 2008
5. EUCAST. Clinical breakpoint. 2025