Epuration Extrarénale Continue:

L'exemple du Meropenem

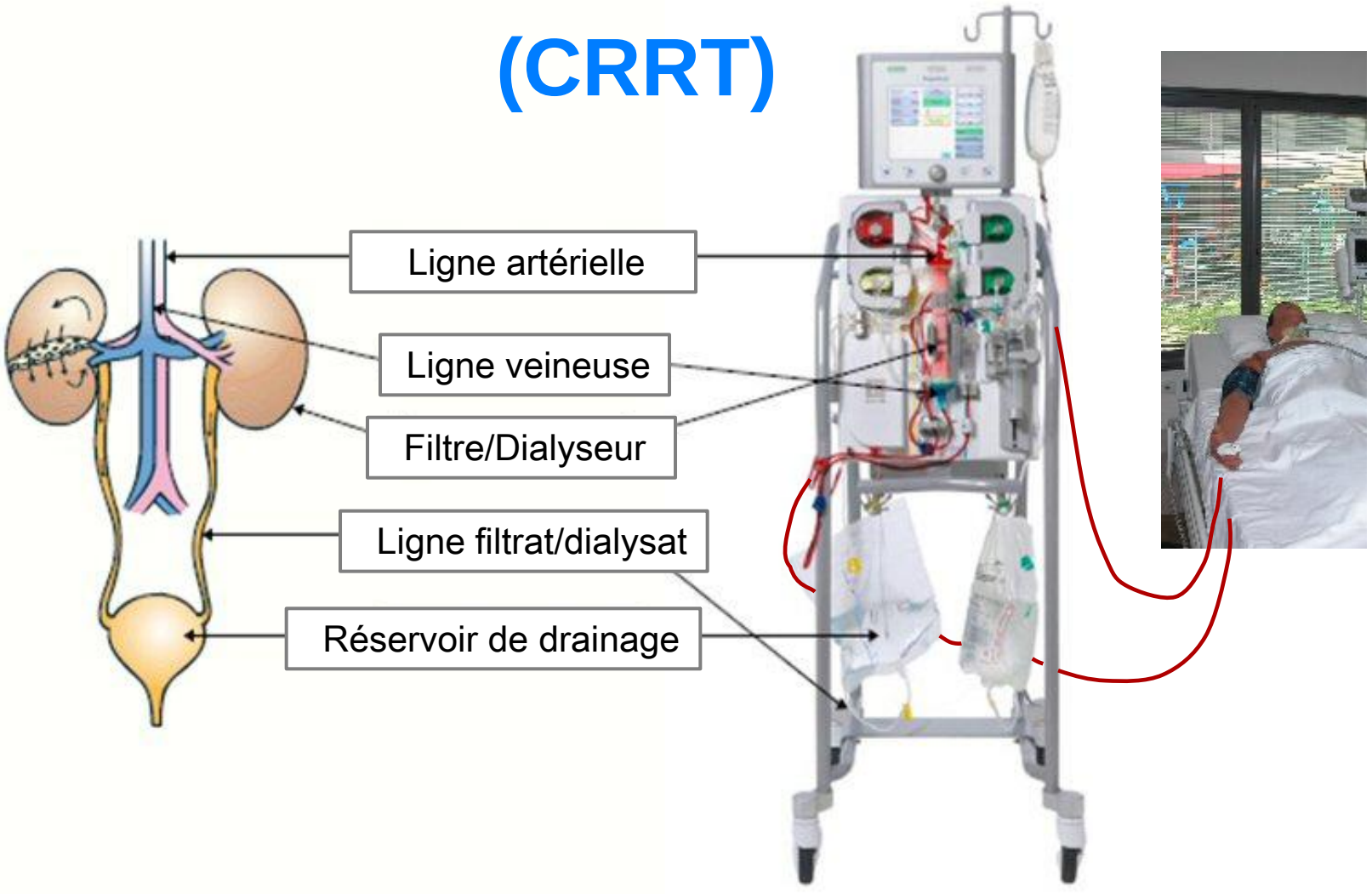
Thierry Buclin

Division de Pharmacologie clinique

CHUV – Lausanne

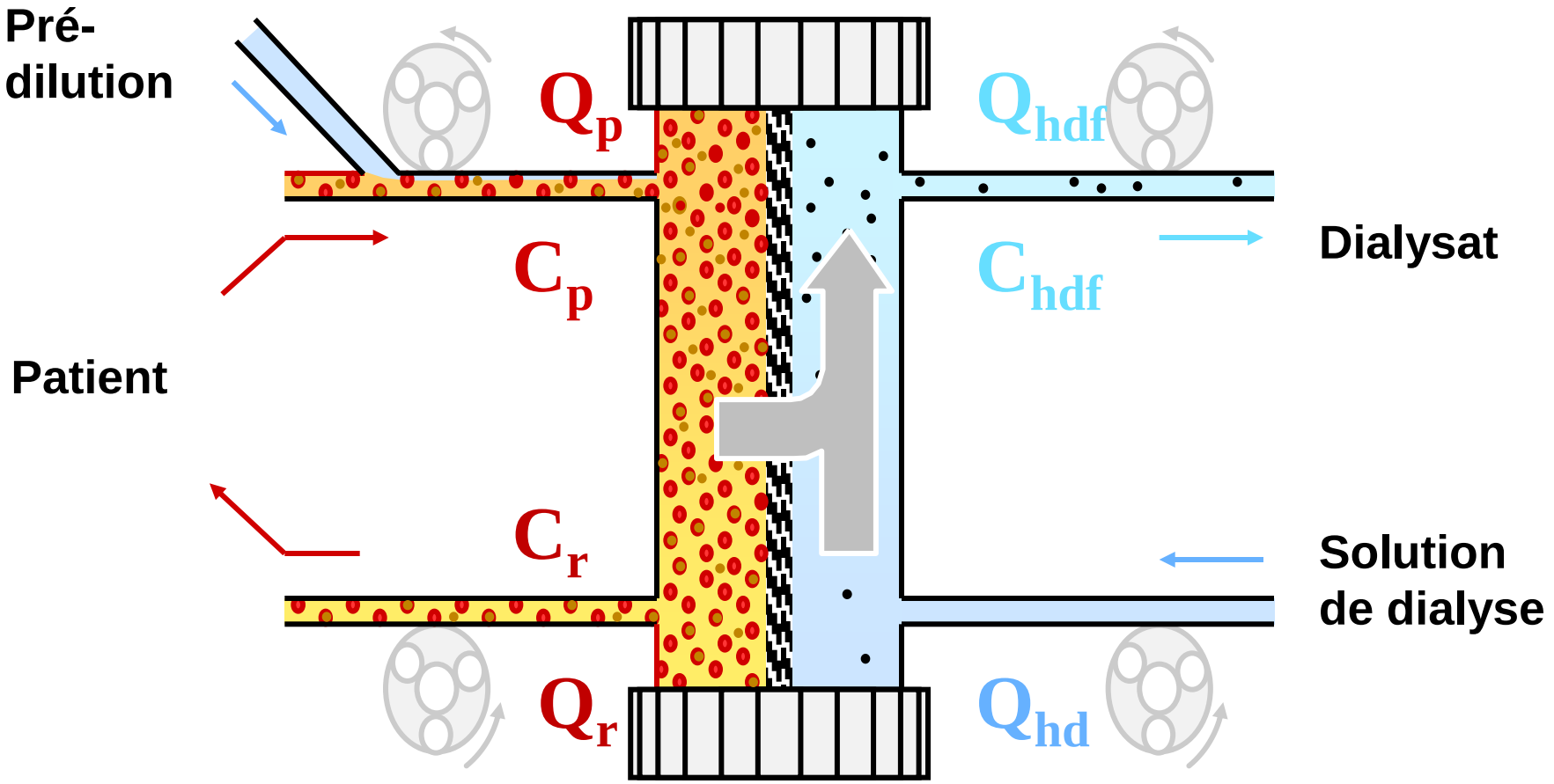
Université de Lausanne

Continuous Replacement Therapy (CRRT)



http://www.baxterhealthcare.co.uk

Hémodiafiltration



Gradient de pression ⇒ *Transport convectif (filtration)*

Gradient de concentration ⇒ *Transport diffusif (dialyse)*

Principes de base

- **PK générale**

$$\Rightarrow \text{Concentration moyenne} = \text{Dose} \times \text{Intervalle} \; / \; CL_{systémique}$$

- **Conservation de la masse**

$$\Rightarrow \text{Quantité éliminée} = \Delta C_{plasma} \times Q_{plasma} = C_{hdf} \times Q_{hdf}$$

- **Transfert transmembranaire passif**

$$\Rightarrow \text{Vitesse d'élimination} = C_{plasma} \times CL_{hdf} = C_{plasma} \times S_{hdf} \times Q_{hdf}$$

Hémodiafiltration

Clairance d'hémodiafiltration:

$$S_{hdf} = \frac{C_{hdf}}{C_p} \Rightarrow CL_{hdf} = S_{hdf} \times Q_{hdf}$$

Approximation : $S_{hdf} \cong f_u$

Mais:

- Caractéristiques chimiques (poids mol., charges)
- Filtre (matériel, adsorption, âge)
- Facteurs patient (protéines sériques, coagulation)
- Débit dialyse/filtration (compétition f/d, gradient, temps d'équilibtation)

Approche générale

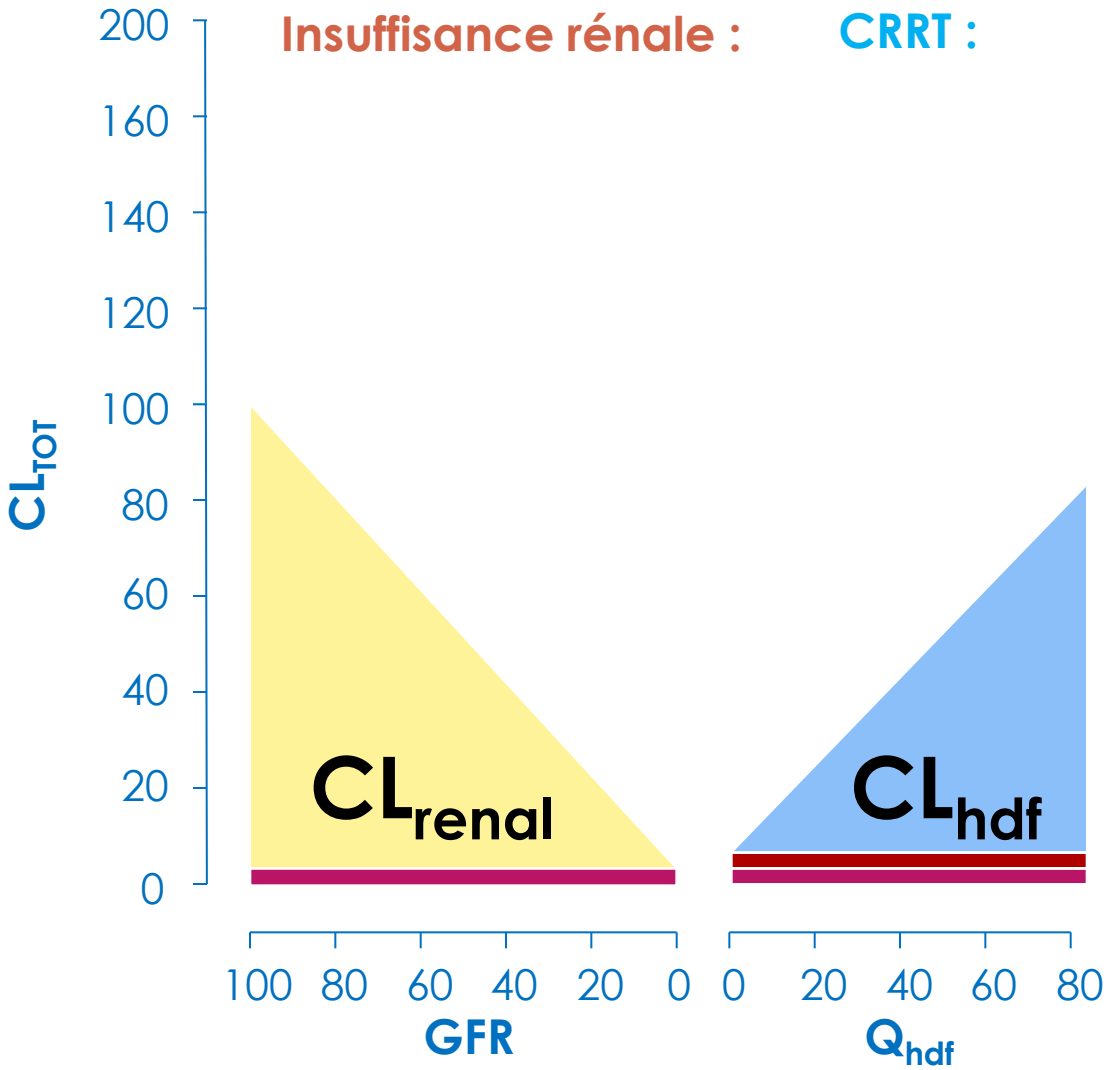
- **Sieving :** $S_{hdf} \approx f_u$
- **CL_{hdf} :** $CL_{hdf} \approx S_{hdf} \times Q_{hdf}$
- **CL_{totale}:** $CL_{patient} \approx CL_{hdf} + Q_0 \times CL_{normal}$

⇒ Prédictions de la PK du patient à partir des paramètres de référence (f_u, Q_0 , CL_{normal}) et du Q_{hdf} du patient. Applicable à **hd**, **hf** et **hdf**.

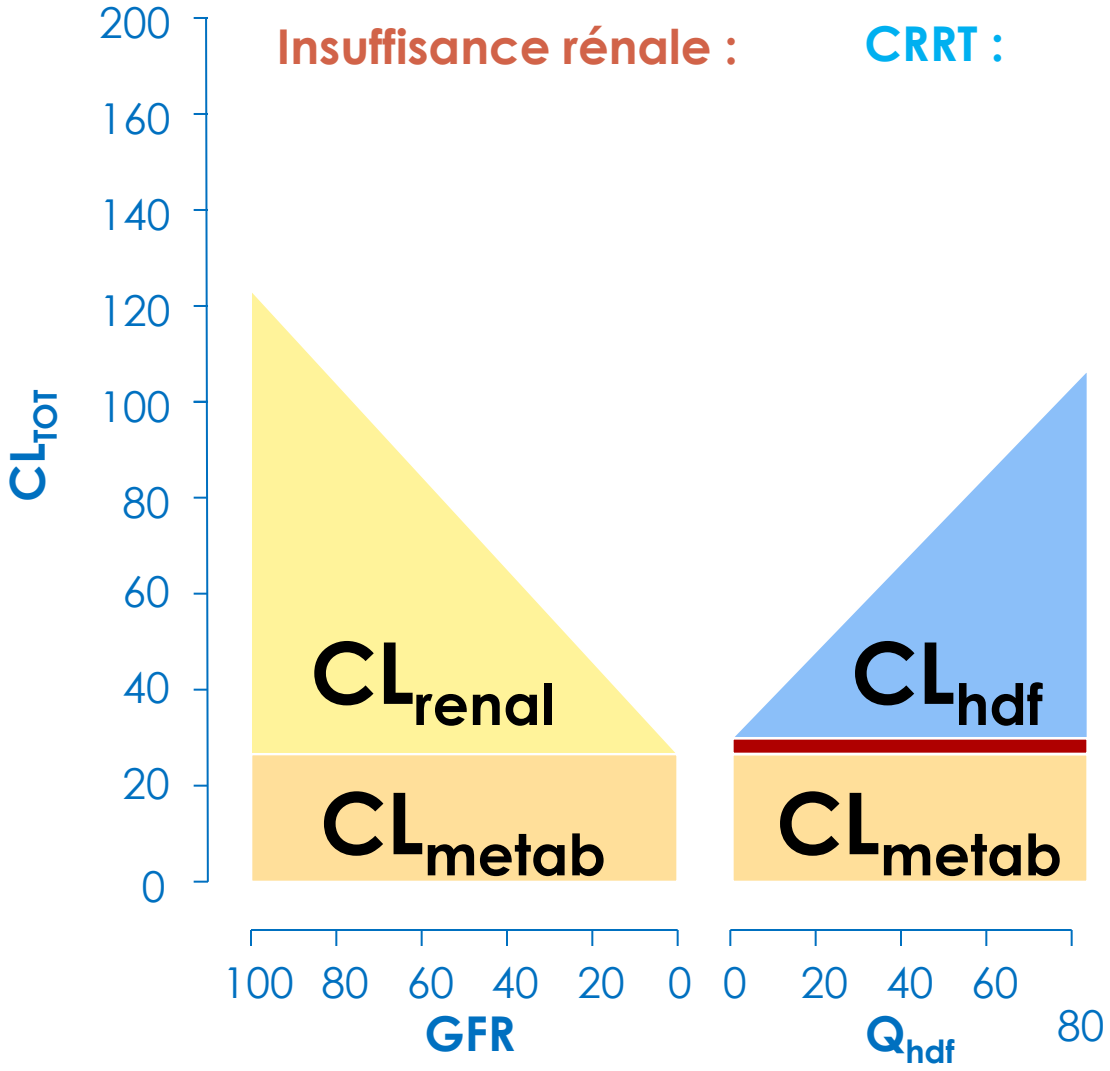
Attention

- f_u altéré par insuf. rénale, pH, dysprotéinemie, déplacements
- S_{hdf} « « MW, charges, filtre, protéines sériques, conditions hdf
- CL_{hdf} « « *drug trapping* dans le filtre
- P_0 « « insuf. rénale, comorbidités, polymorphismes, interactions
- CL_{normal} « « comorbidités, GFR résiduelle

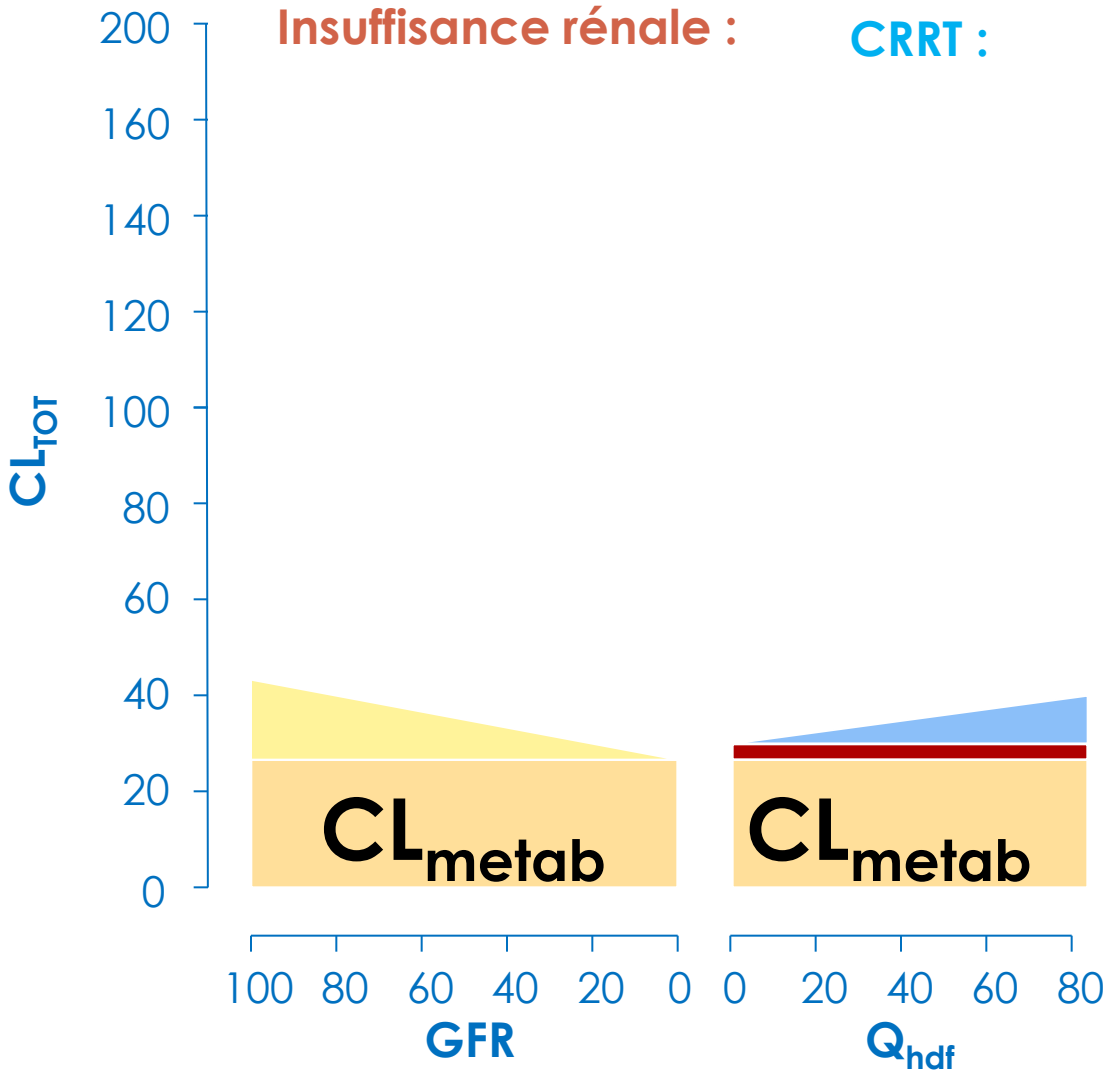
Amikacine


Insuffisance rénale :
CRRT :
200
160
140
120
100
80
60
40
20
0
CLTOT
CLrenal
CLhdf
100 80 60 40 20 0
0 20 40 60 80
GFR
Qhdf

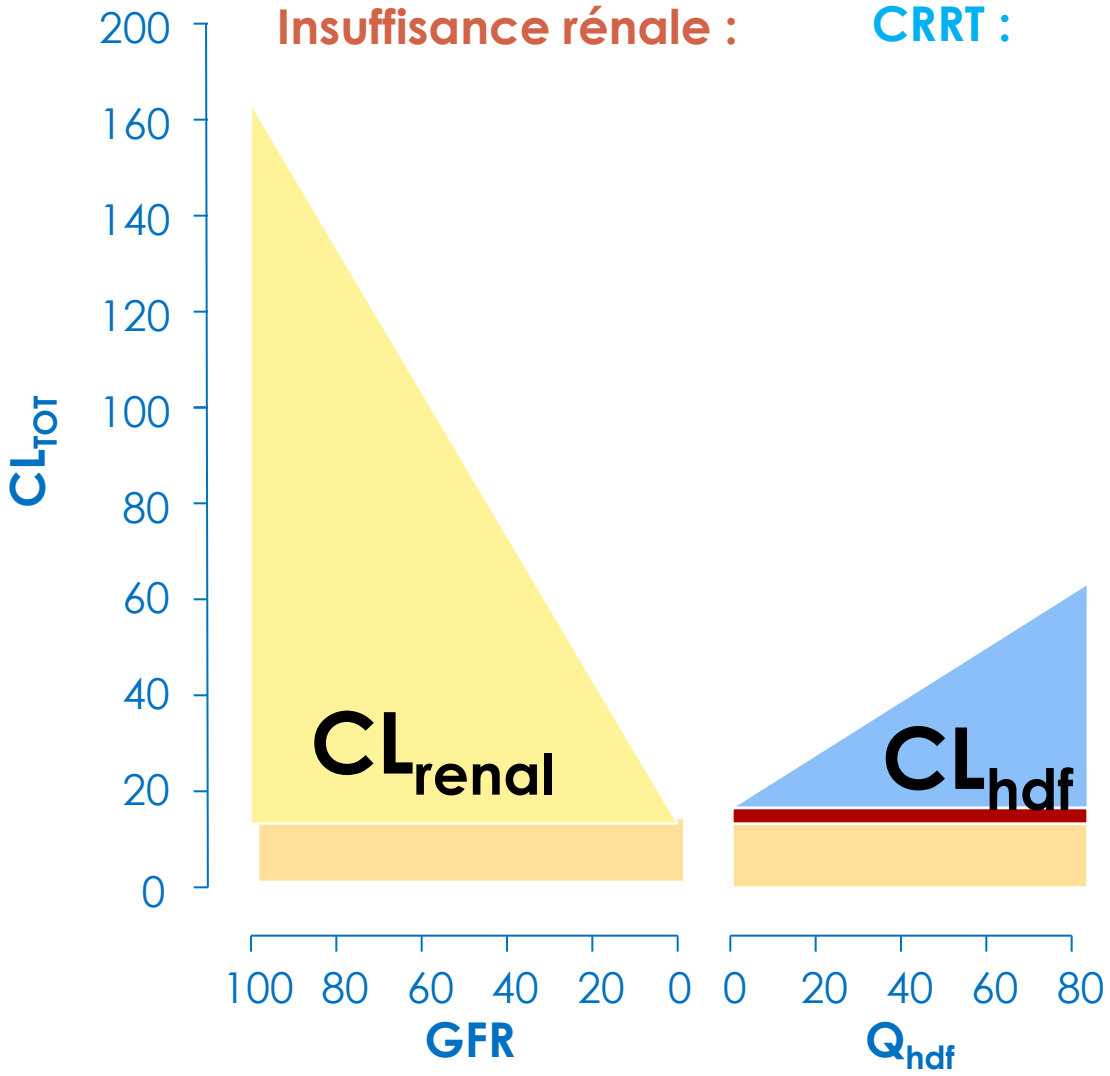
Pipéracilline



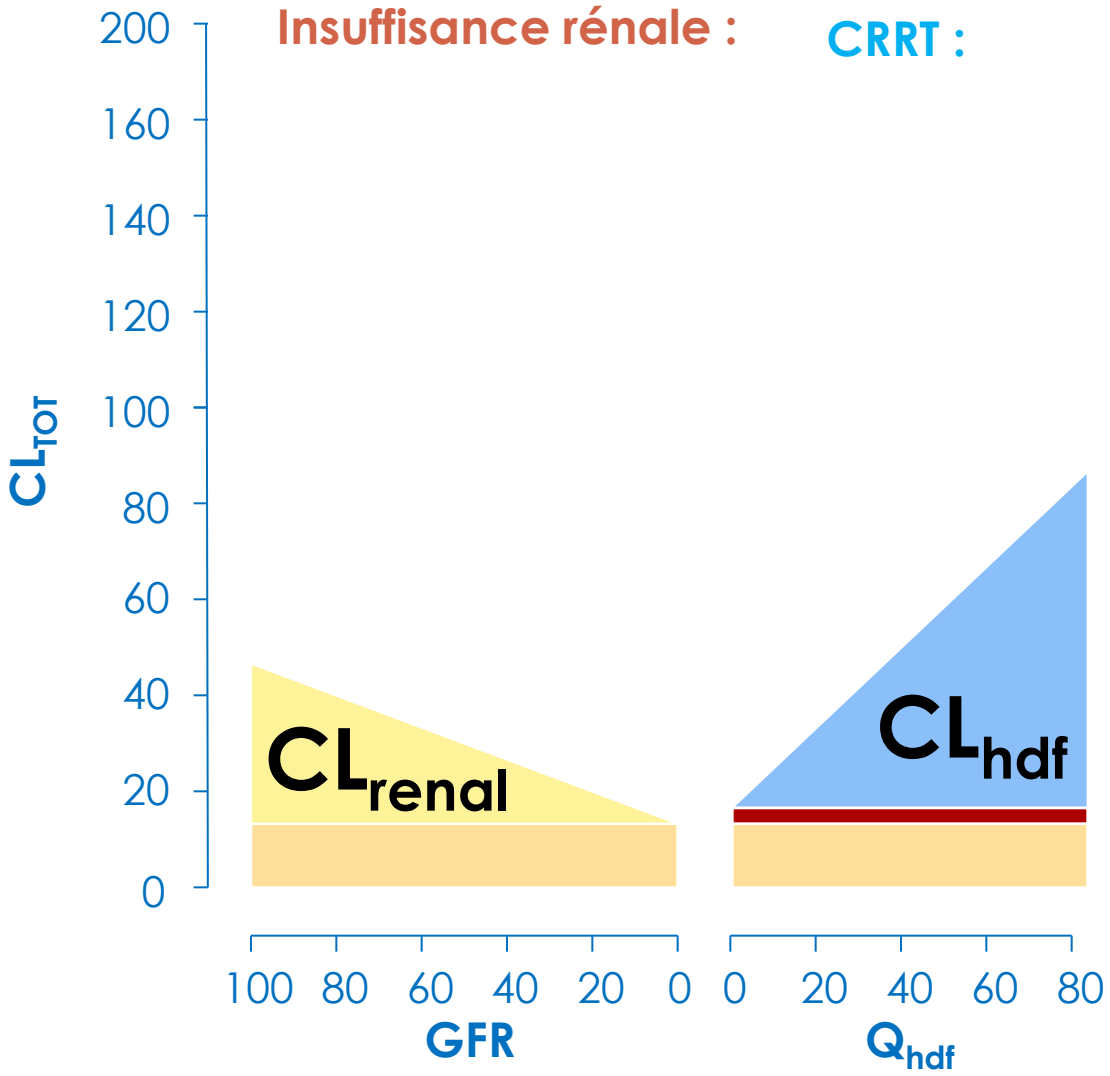
Doxycycline



Pénicilline



Fluconazole



Dosage Adaptation of Anti-infective Drugs in Continuous Renal Replacement Therapy

Ganciclovir

→ Enter usual dosage

Dose (mg)	Interval (h)	i.e. daily dose (mg/day)	MIC (mg/L)
350	12	700.0	0.4

→ Enter patient GFR and epuration settings

GFR (ml/min)	Q_{dial} (L/h)	Q_{filtr} (L/h)
0	1.5	0.5

→ Total clearance / Half life / Recommended dosage predicted by the model

CL_{tot} (L/h)	$t_{1/2}$ (h)	Daily dose (mg/day)
4.21	12.68	196

In this situation the treatment should be adapted on both the unit dose and the dosing interval

→ Enter practical dosage for simulation :

Dose (mg)	Interval (h)	Infusion duration (min)
185	23	30

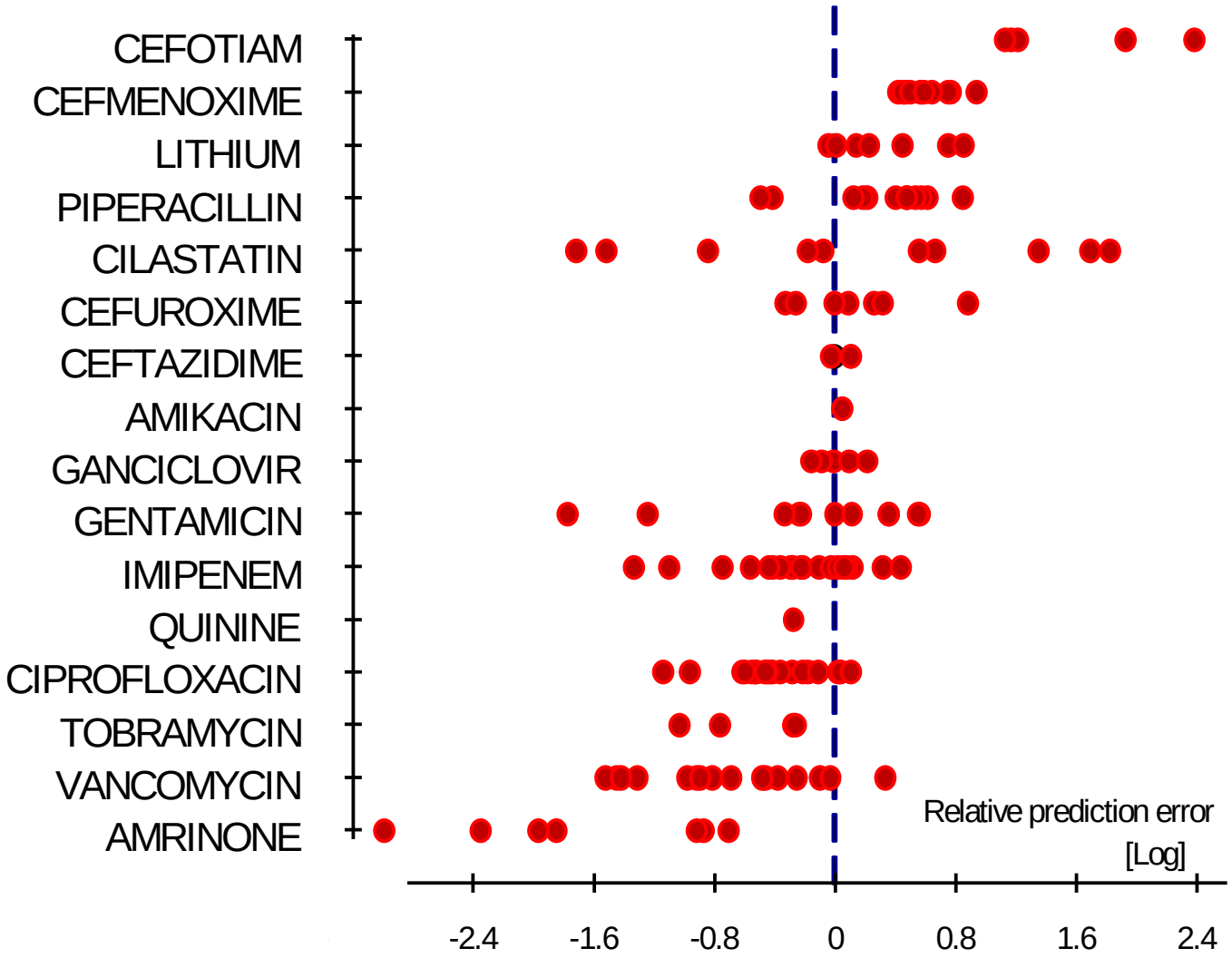
→ Prediction of exposure

C_{min} (mg/L)	C_{max} (mg/L)	$AUC_{interval}$ (h.mg/L)	T > MIC (h)	AUC > MIC (h)
1	3.34	44	22.7	110.1

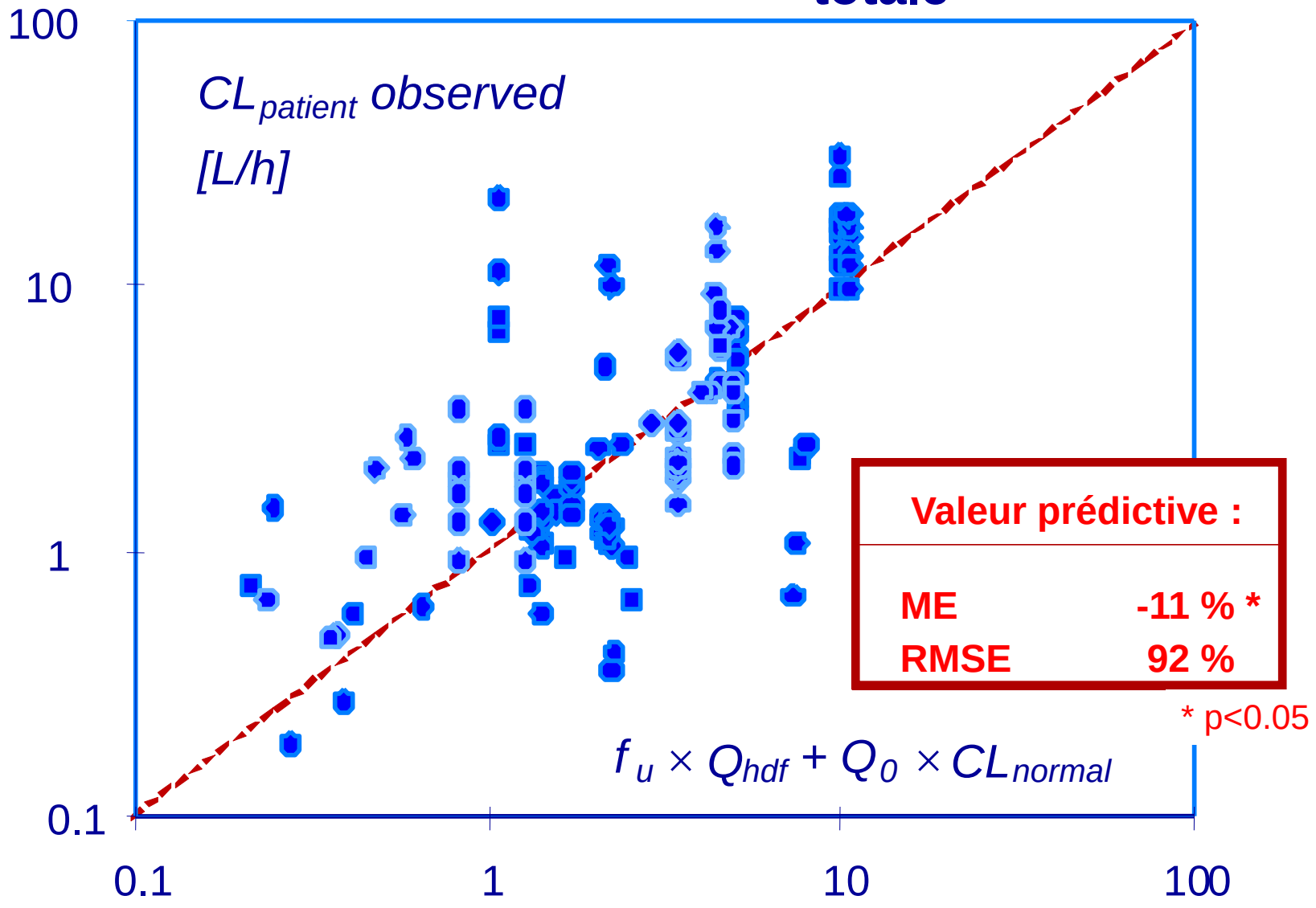
At steady-state, the circulating concentrations are expected to remain

→ over the MIC for 100% of dosing interval

Erreur de prédiction CL_{totale}



Pédiction CL_{totale}



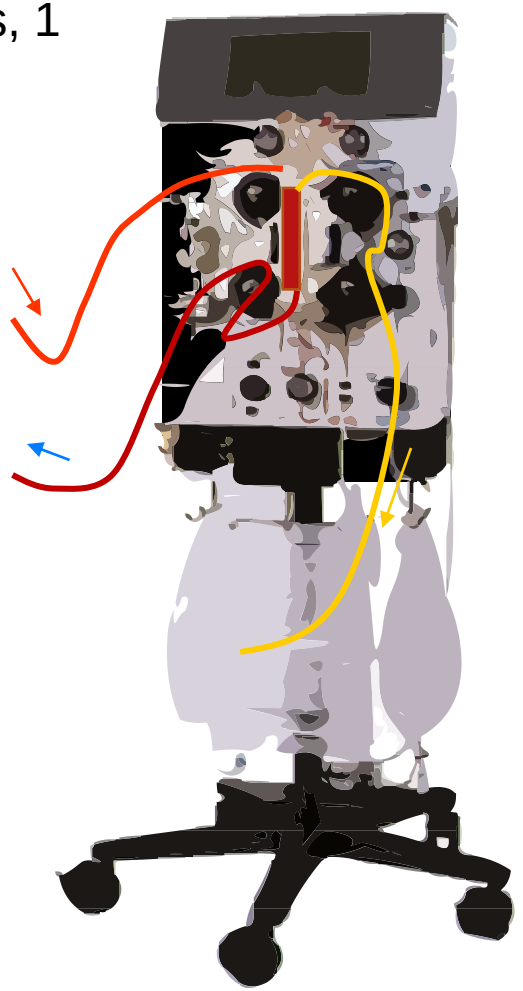
Meropenem study

15 ICU patients (10 septic, 4 cardiogenic shocks, 1 ARF), 6 F, 61± 8 yr, 71± 15 kg

Meropenem 1 g/12h (8 patients),
0.5 g/12h (5), 1 g/8h (1), 0.5 g/8h (1)

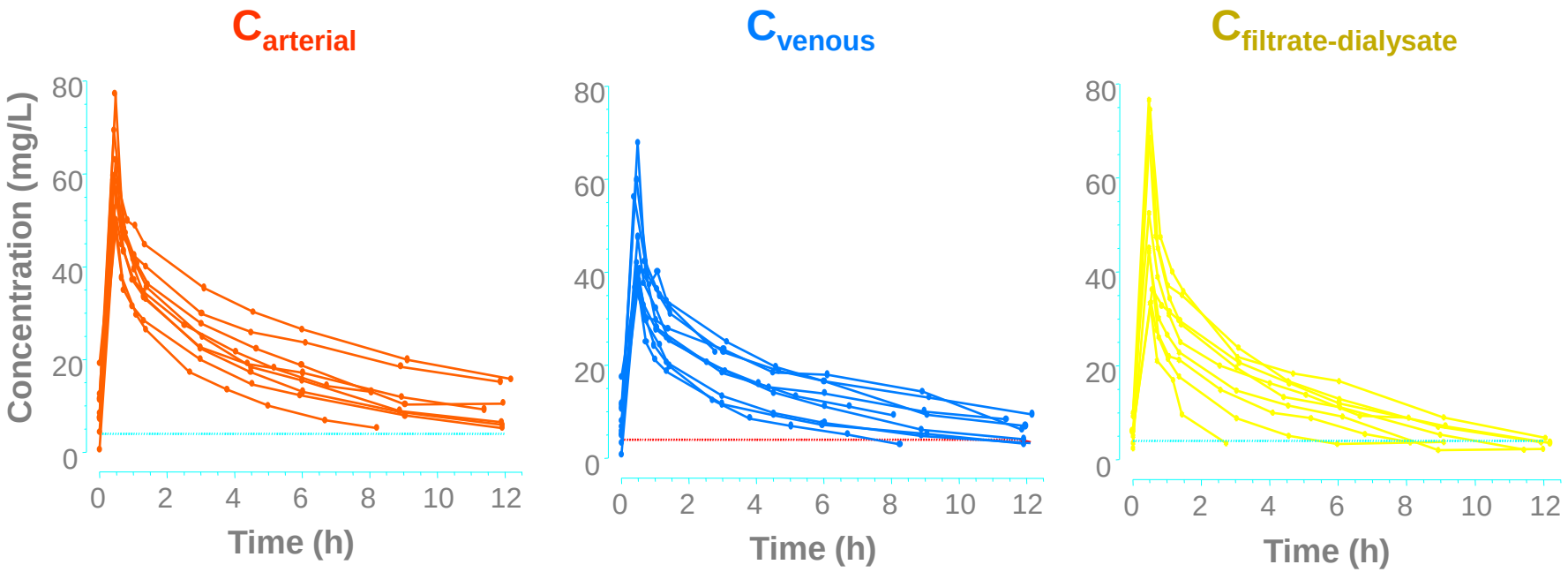
CVVHDF Prisma (13 patients) with
Q_{blood} 7.1 ± 0.9 L/h, predil 0.5 ± 0.3 L/h,
substr 0.13 ± 0.07 L/h, dialysis 1.2 ± 0.3 L/h
$\Rightarrow Q_{hdf}$ **1.8 ± 0.4 L/h**

10 samplings from arterial, venous and filtrate-dialysate lines, over 1 dosing interval. HPLC.



Observations

Meropenem dosage : 1 g / 12 h



Compartmental analysis

	Mean	CV
• **Sieving / transfert coefficient**		
Model parameter	**0.91**	33%
• **Epuration clearance** [L/h] **:**		
$CL_{EPUR} = S_C \cdot Q_{FD}$	**1.7**	39%
• **CVVHDF clearance** [L/h] **:**		
$CL_{CVVHDF} = \frac{V \cdot k_{13}}{k_{31} + k_{34} + k_{10}} \cdot (k_{30} + k_{34})$	**1.8**	26%
• **Total patient clearance** [L/h] **:**		
$CL_{TOT} = CL_{CVVHDF} + CL_{NR}$	**5.1**	46%
• **« Catalyzer » clearance** [h] **:**		
$CL_{catalyzer} = k_{30} \cdot V_f$	**0.7**	85%

Recommendations

	F. Rénale normale	Approche générale *	Littérature **	Etude
Q_{FD} (L/h) :	-	**1.8**	**1.7** (0.4-2.8)	**1.8** (0.8-2.5)
CL_{TOT} (L/h) :	**15**	**7**	**5.1** (3.1-8.6)	**5.1** (3.0-9.4)
Adaptation :	**100%**	**45%**	**15-42 %**	**38-50 %**
Dose/ intervalle :	**2000/8 h**	**900/8 h – 1800/16 h**	**500/12 h – 1000/8 h**	**750/8 h – 1500/12 h**

* Fu = 0.98 $\Rightarrow$ CL_{fd} = 1.8 L/h; P_0 = 0.35 $\Rightarrow$ $CL_{patient}$ = 0.35 x 15 + 1.8 = 7 L/h

** 7 articles sur meropenem et CVVHD

Caractérisation du profil pharmacocinétique du méropénème chez des patients de soins intensifs avec ou sans épuration extrarénale