Médicaments et EER

CHU Bordeaux

JOURNÉES STAR 2011

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Cas Clinique

- Mr D., 59 ans, post-op de DPC pour ADK
- J+5 : Cytolyse importante avec extériorisation de liquide brunâtre par la lame.
- TDM : pas de collection, doute sur nécrose hépatique isolée.
- J+7 : Changement d'aspect du liquide + déglobulisation modérée + syndrome septique
  - Fistule biliaire drainée, transfert réa, pas de reprise

Cas Clinique

- J+9 : Altération de la fonction rénale, aggravation du syndrome septique = REPRISE
  - Nécrose hépatique localisée
  - Fistule voie biliaire
  - Désunion anastomotique
    - Suture, réparation et drainage.
- Choc septique en post-op immédiat
  - Remplissage, Noradrénaline, SDRA…

Cas Clinique

- Biologie :
  - Lactates 3,71; Créat 130 µmol/l; Urée 12,5 mmol/l
  - K^+ 5,5; Na^+ 144; GB 15,6; CRP 210
  - Diurèse 12 dernières heures = 0,4 ml/kg/h
- Hemocs et prélèvements abdo en cours
- ATB: Tazocilline + Amikacine
- Epuration extra-rénale ?

OUI

Noradrénaline ?

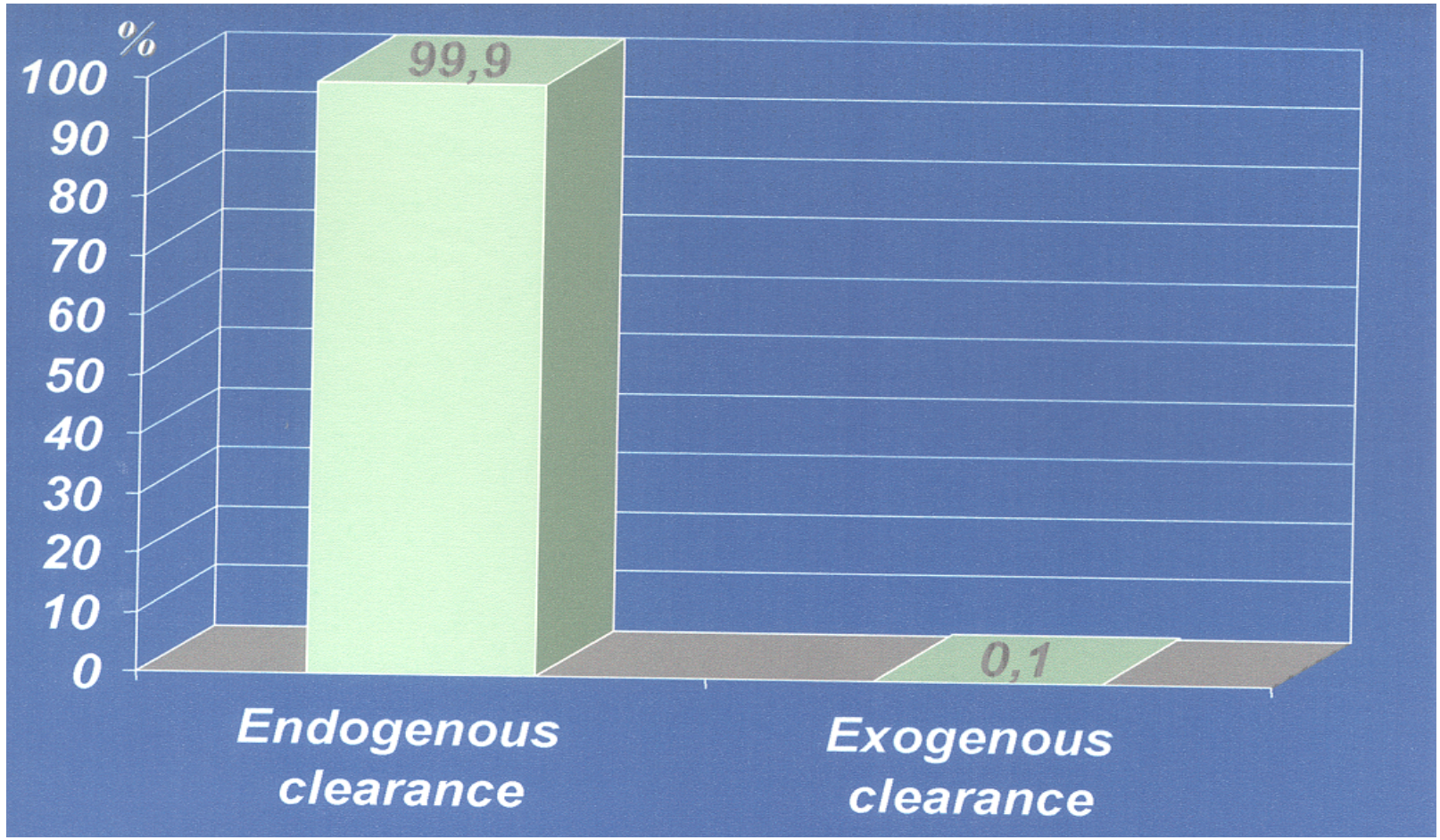
- L'hémofiltration augmente t'elle la clairance de la noradrénaline?
- OUI
- NON

Antibiotique ?

- Tazocilline selon quelle modalité ?
  (une seule réponse)

- 4 g toutes les 8h
- 3 g Toutes les 6h
- 4 g toutes les 6h
- 12 g au PSE
- 16 g au PSE

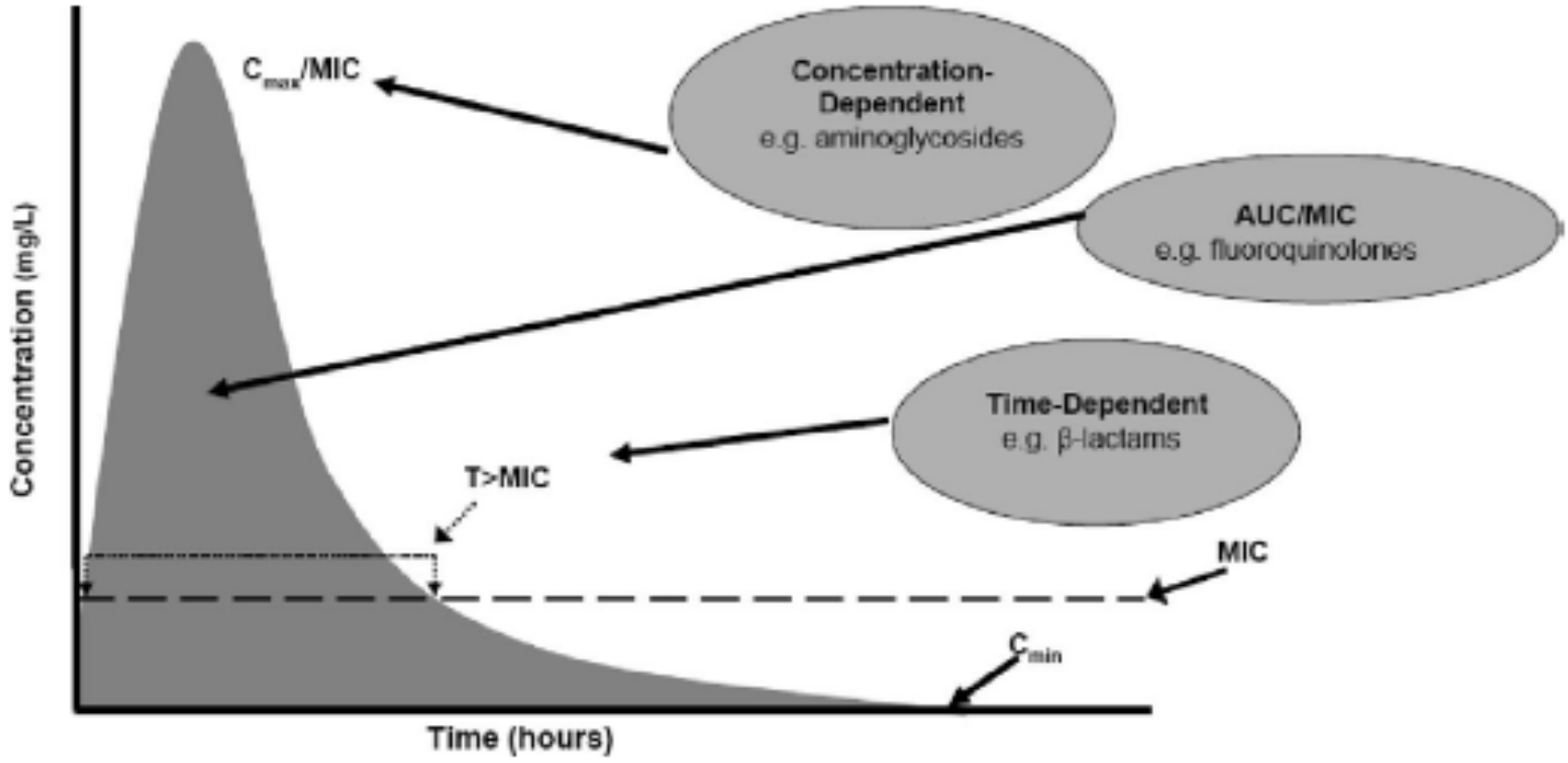
Noradrénaline ?



Bellomo R et al. Crit Care Med 1994;22:833-7

Pharmacokinetic issues for antibiotics in the critically ill patient

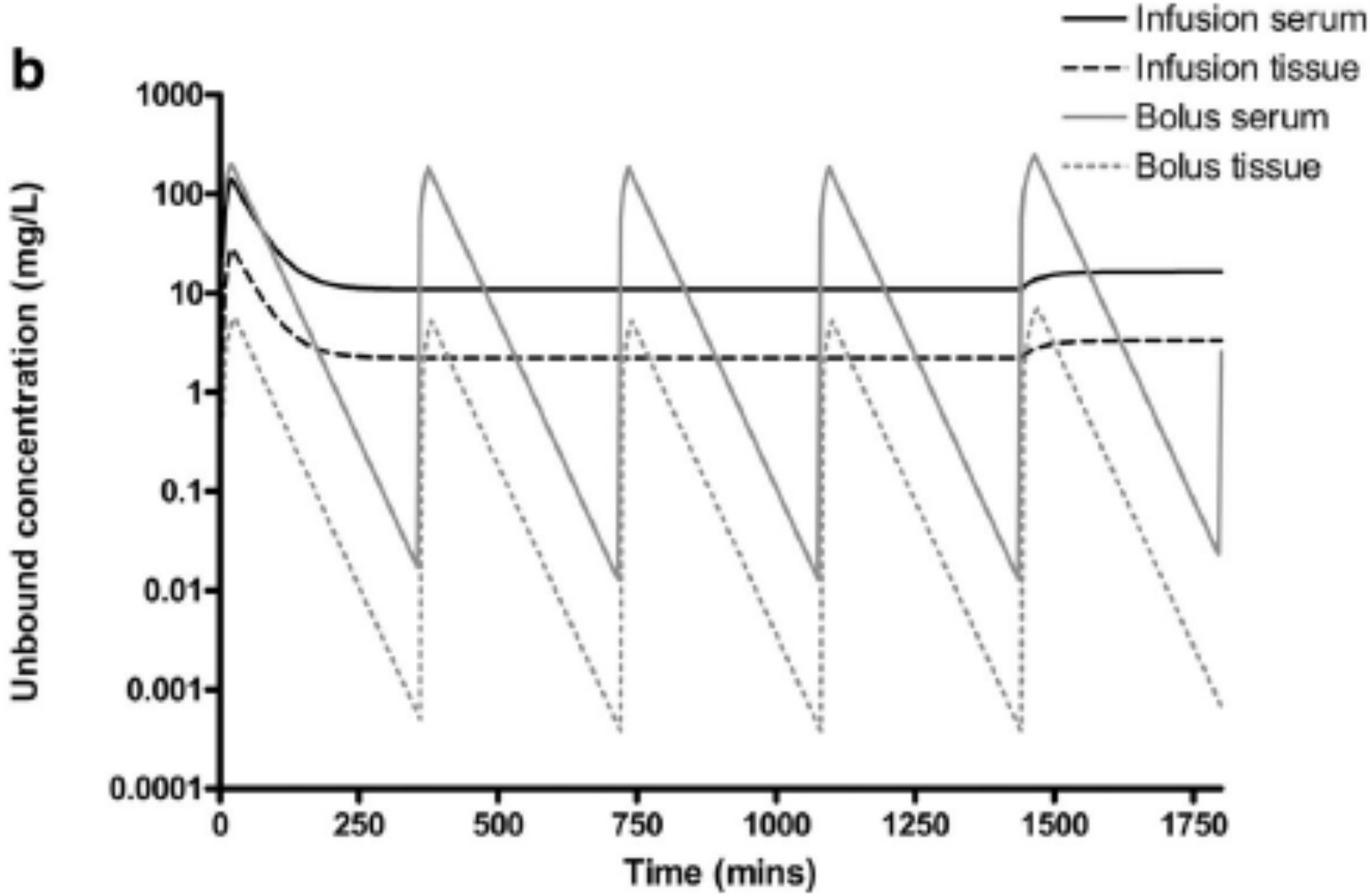
Jason A. Roberts, B Pharm (Hons); Jeffrey Lipman, FJFICM, MD

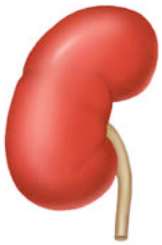


Piperacillin penetration into tissue of critically ill patients with sepsis—Bolus versus continuous administration?

Jason A. Roberts, BPharm (Hons); Michael S. Roberts, DSc; Thomas A. Robertson, PhD; Andrew J. Dalley, PhD; Jeffrey Lipman, FJFICM, MD

Crit Care Med 2009 Vol. 37, No. 3





Piperacillin penetration into tissue of critically ill patients with sepsis—Bolus versus continuous administration?

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Conclusions: Patients with sepsis do not seem to have the same level of impairment of tissue distribution as described for patients with septic shock. A 25% lower dose of piperacillin administered by continuous infusion seems to maintain higher trough concentrations compared with standard bolus dosing. It is likely that the clinical advantages of continuous infusion are most likely to be evident when treating pathogens with high minimum inhibitory concentration, although without therapeutic drug monitoring and subsequent dose adjustment, infusions may never achieve target concentrations of organisms with very high minimum inhibitory concentrations in a small number of patients. (Crit

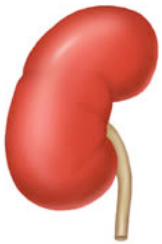
Cas Clinique

- Hemocs :
  - Klebsiella Oxytoca BLSE
- Prélèvements abdo :
  - Klebsiella Oxytoca BLSE
  - Enterococcus Faecalis
  - Proteus Mirabilis
- ANTIBIOTHERAPIE ?

Antibiotique ?

- Quelle nouvelle stratégie antibiotique ?
  - (plusieurs réponses)

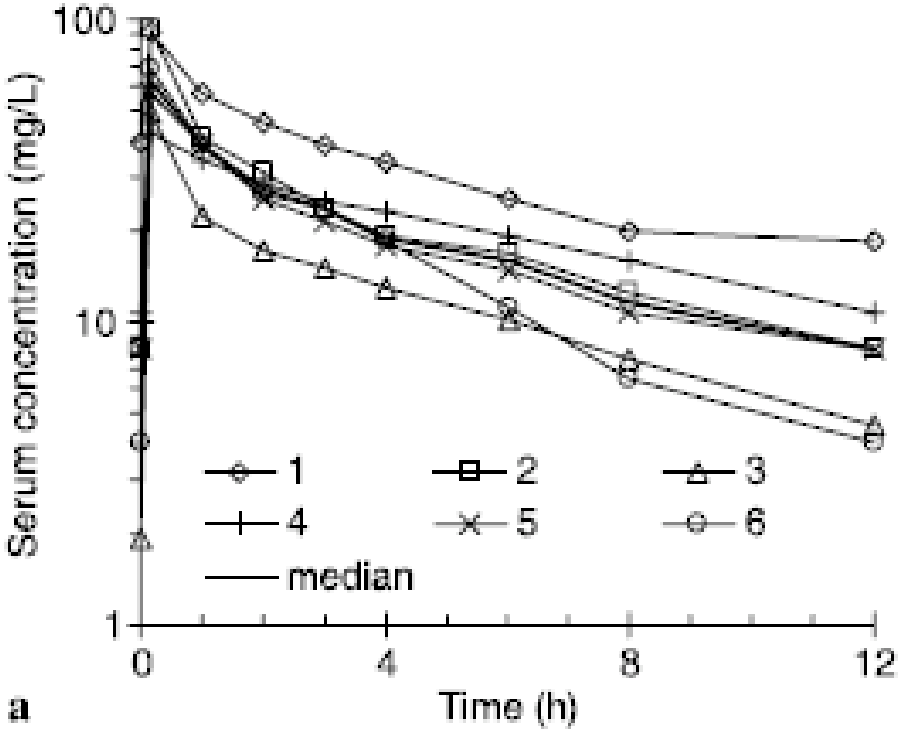
- Imipenem 500 mg en 1h 3 X par jour
- Imipenem 1,5 g au PSE sur 24h
- Doripenem 500 mg en 1h 3 X par jour
- Doripenem 500 mg en 8h 3 X par jour
- Ceftazidime 4 g au PSE
- Meropenem 2 g au PSE sur 24h

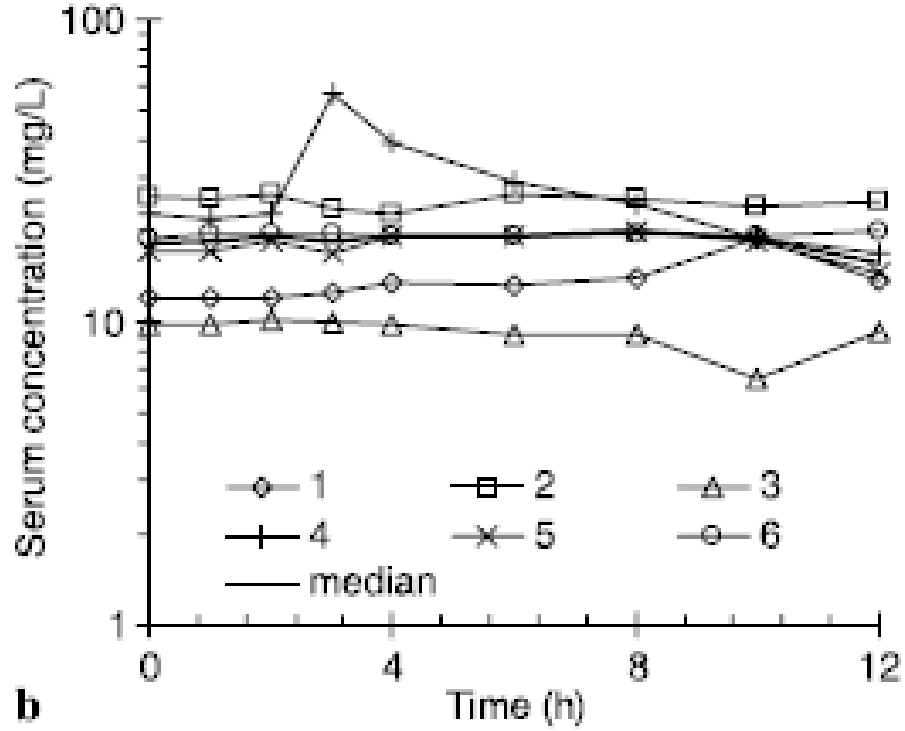


Pharmacokinetics of meropenem during intermittent and continuous intravenous application in patients treated by continuous renal replacement therapy

Julia Langgartner
Antje Vasold
Thomas Glück
Michel Reng
Frieder Kees

Intensive Care Med (2008) 34:1091–1096





Clairance ?

- Eléments augmentant la « clairance » d'un médicament ? (plusieurs réponses)

- Haut poids moléculaire
- Convection
- Faible fixation protéique
- Haut volume de distribution
- Débit de filtration
- Filtre en polyacrylonitrile

Facteurs de variation de l'élimination

FACTEURS liés aux médicaments

. Poids moléculaire
. Volume de distribution
. Fixation protéique
. Coefficient de partage (hydrophile/Lipophile)
. % de métabolisme rénal
. Charges moléculaire

FACTEURS liés à la techniques

. Continue / Intermittent
. Convectif et/ou Diffusif
. Pré et/ou Post dilution
. Qs / Qd / Quf
. Type de membrane :
    . Taille des pores
    . Perméabilité hydrique
    . Capacité Adsorption
    . Surface d'échange
    . Age du filtre
    . Charges membranaire

FACTEURS liés aux patients

. Augmentation du volume de distribution
. pH
. Héparinothérapie / AG nutrition
. Albuminémie
. Clairances résiduelles

Volume de distribution

Lipophiles		Hydrophiles	
1 l/kg	Rifampicine	Pénicillines	0,2-0,3 l/kg
0,8 l/kg	Métronidazole	C3G	0,1-0,3 l/kg
1,8-3 l/kg	Fluoroquinolones	Glycopeptides	0,3-0,6 l/kg
1 l/kg	Phénicolés	Aminosides	0,1-0,3 l/kg

Vd élevé

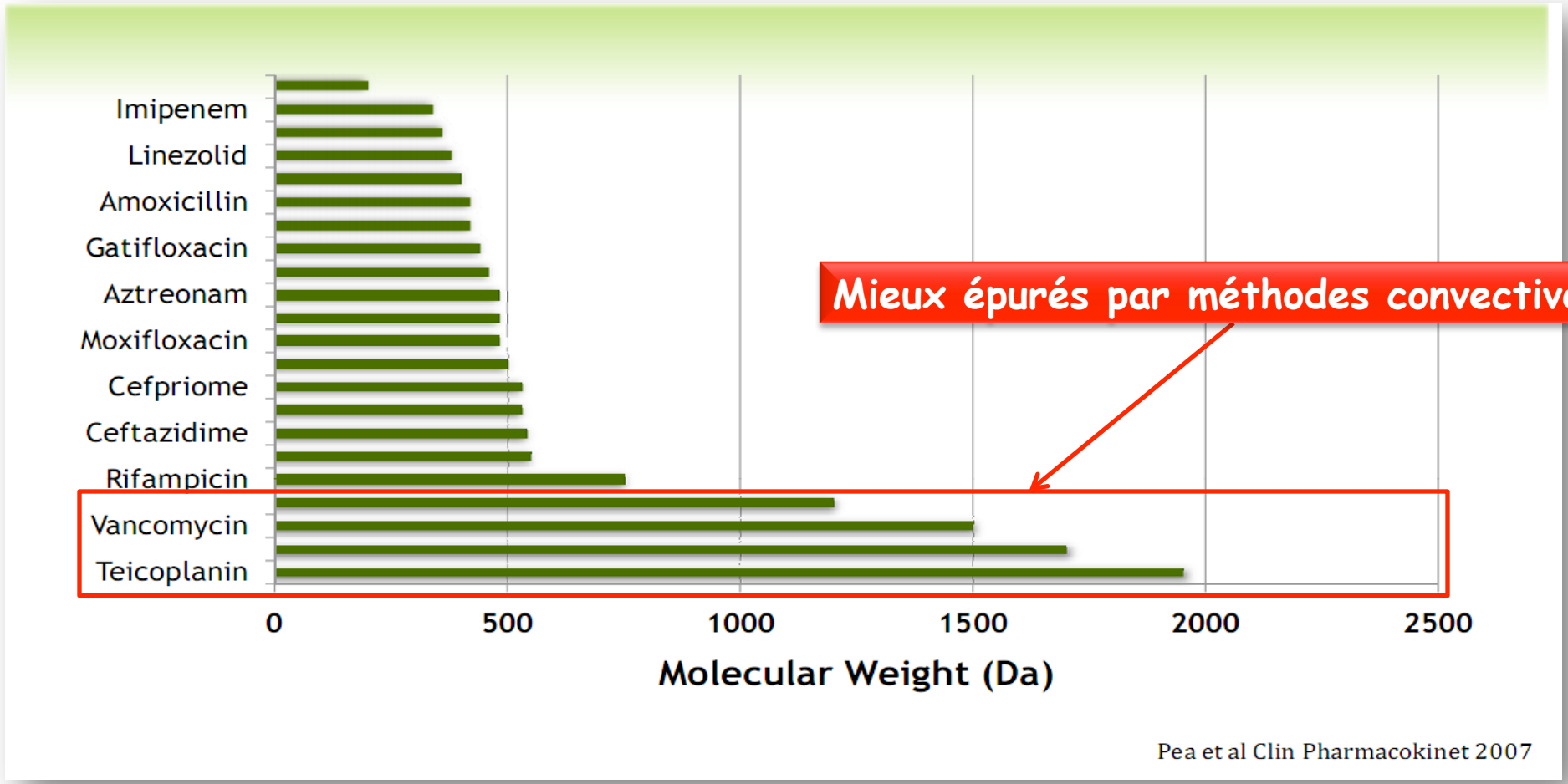
Vd réduit

Linezolid

0,6-0,8 l/kg

Si Vd >1l/kg pas d'adaptation en EER même si élimination rénale

Poids Moléculaire



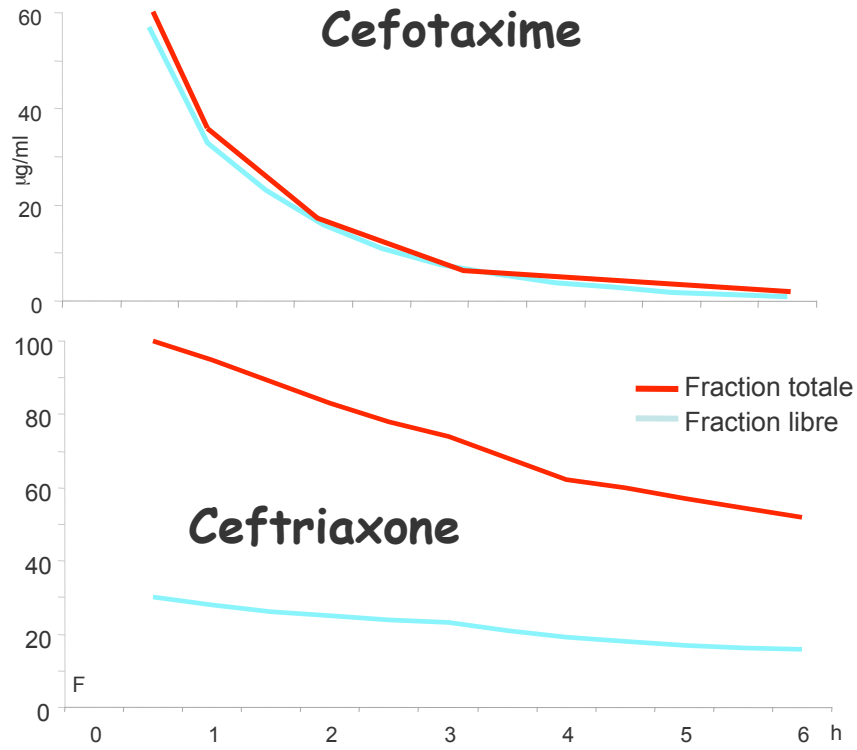
Pea et al Clin Pharmacokinet 2007

Taux de Fixation Protidique

Forme libre plasmatique

35%

95%



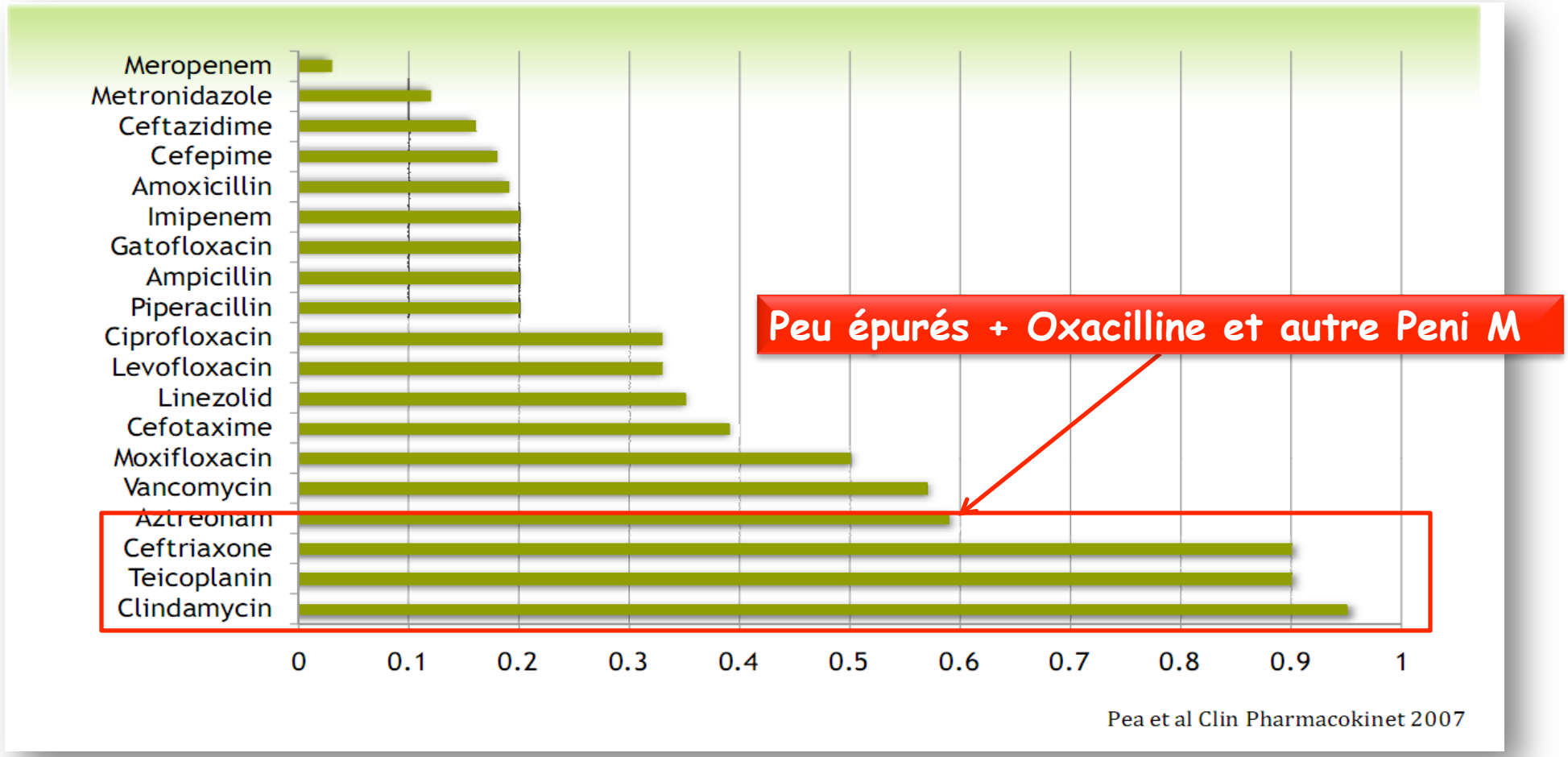
65%

5%

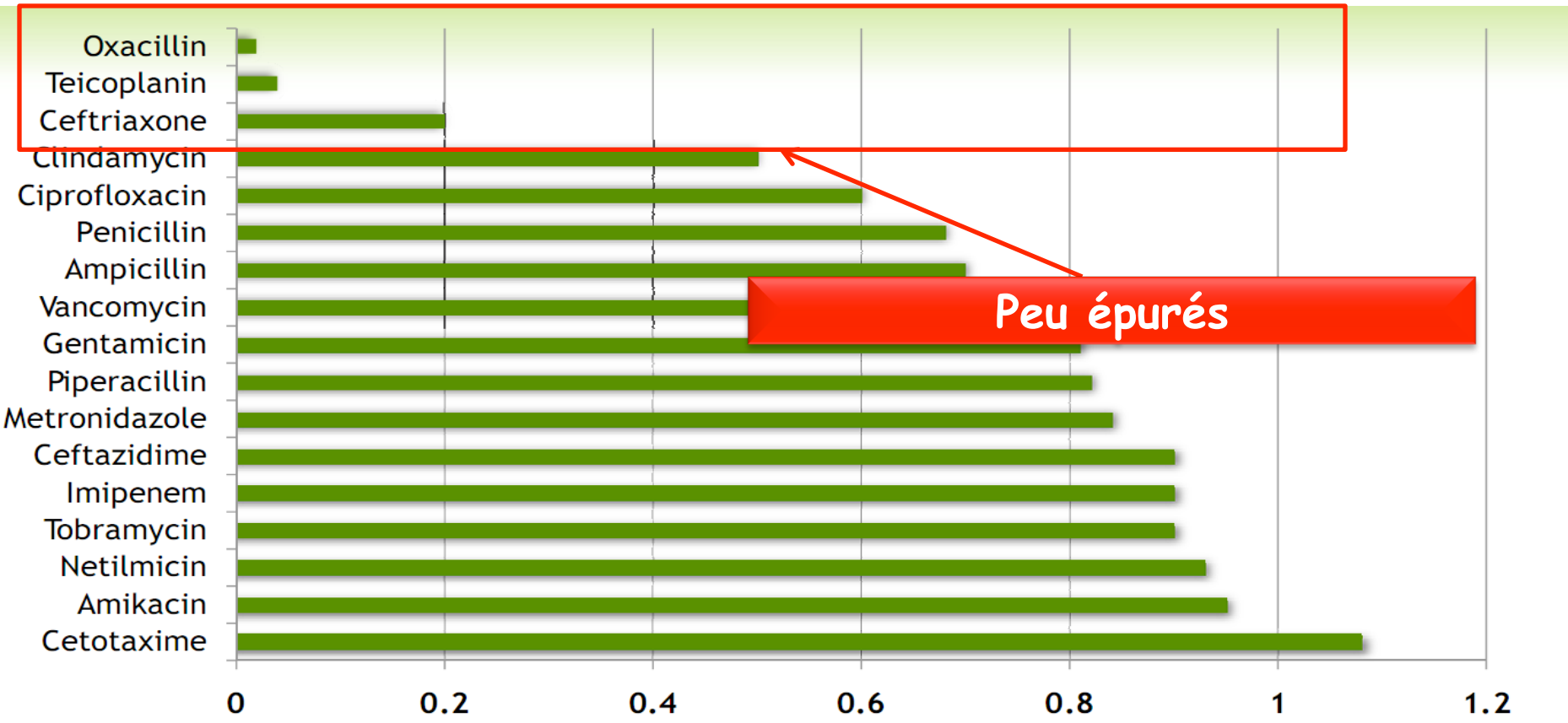
Fixation Protéique

Scaglione et al. JAC 1990

Taux de Fixation Protidique

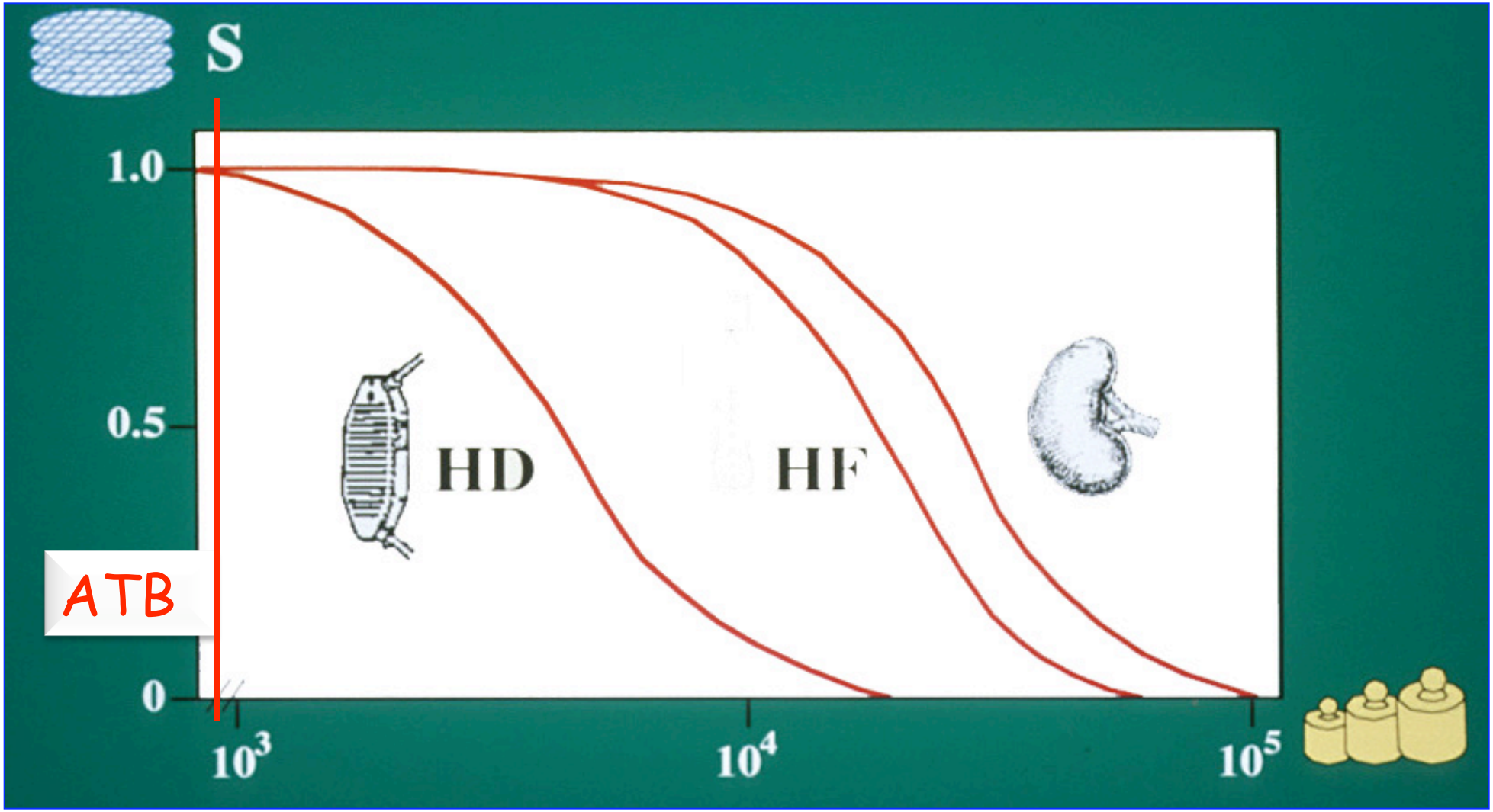


Sieving Coefficients



Pea et al Clin Pharmacokinet 2007

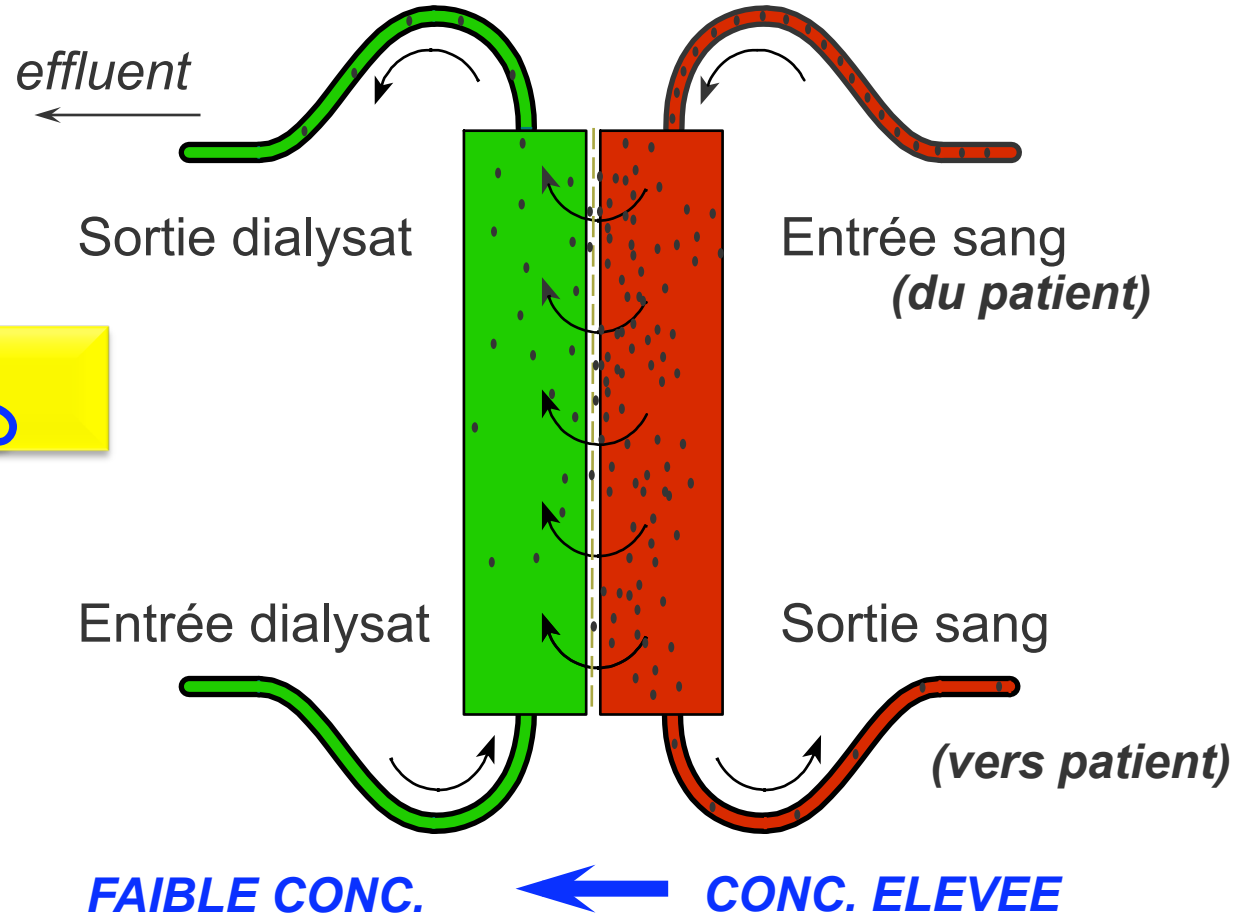
Sieving coef / Poids moléculaire



Hémodialyse

DIFFUSION

$$CL_{UF} = SC_D * Q_D$$



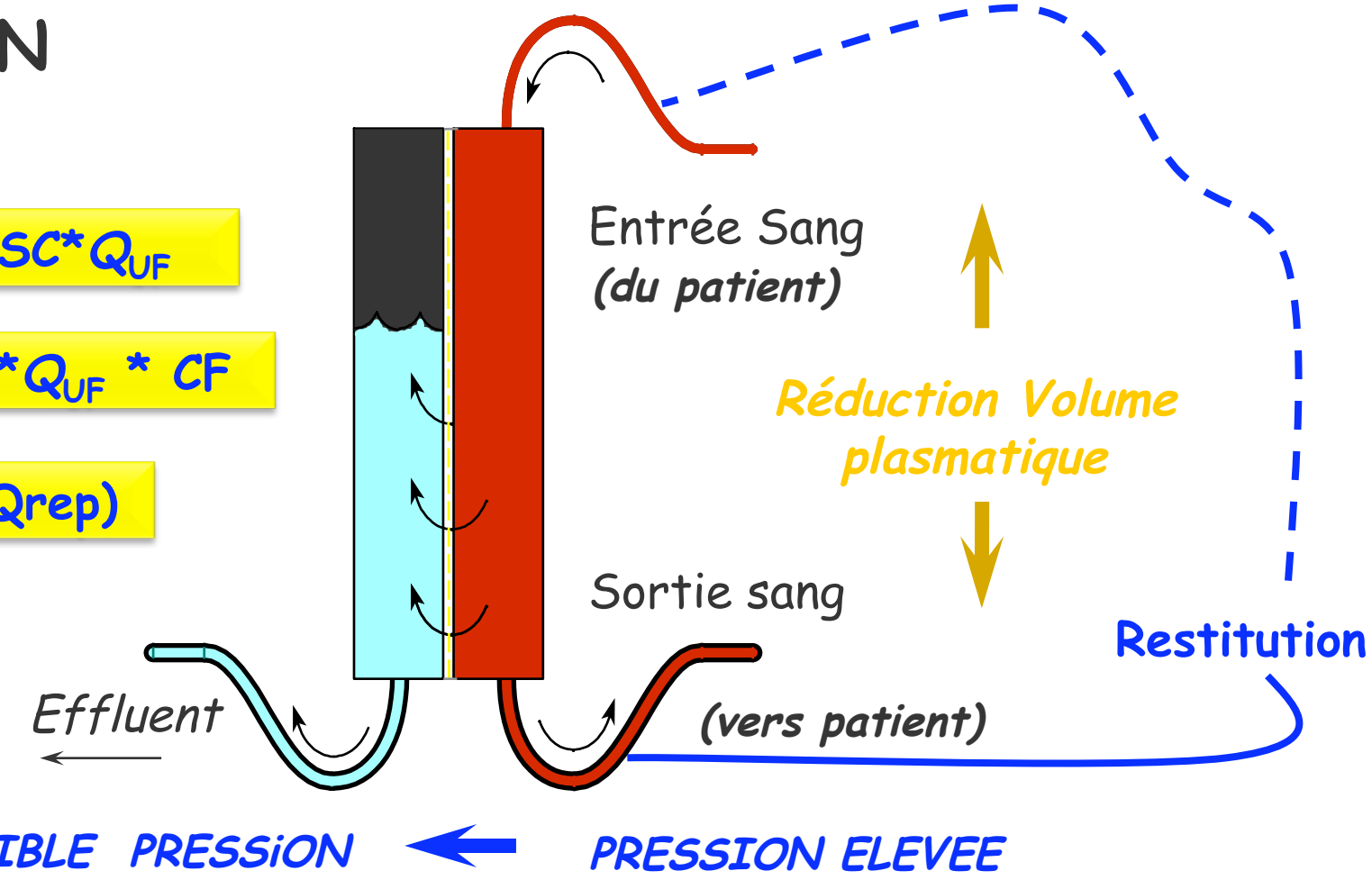
Hémofiltration

CONVECTION

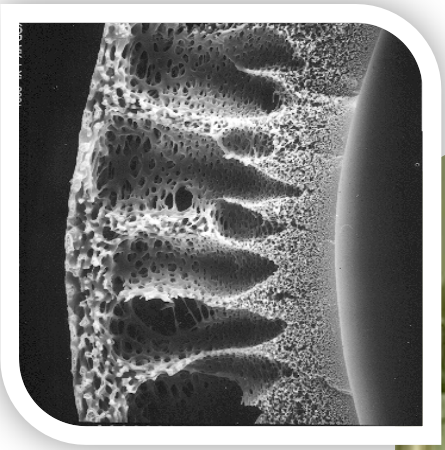
Postdilution $CL_{UF} = SC * Q_{UF}$

Predilution $CL_{UF} = SC * Q_{UF} * CF$

$CF = Qb / (Qb + Qrep)$

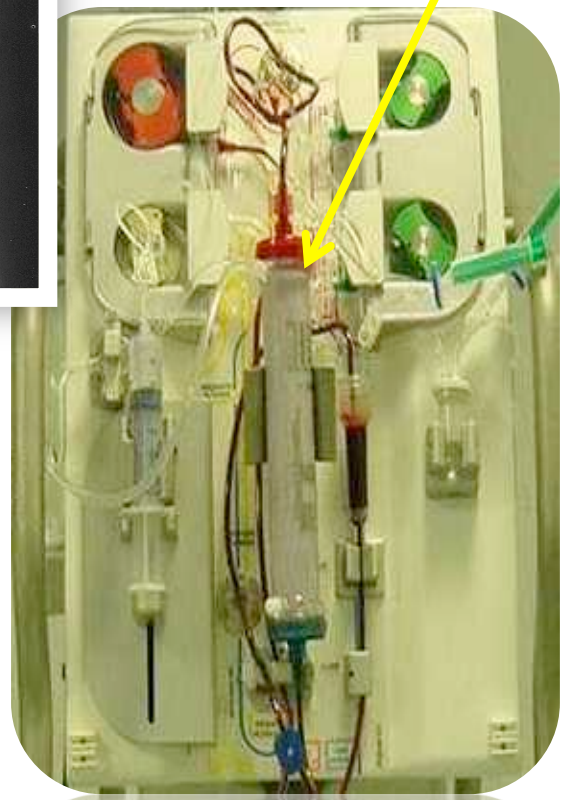


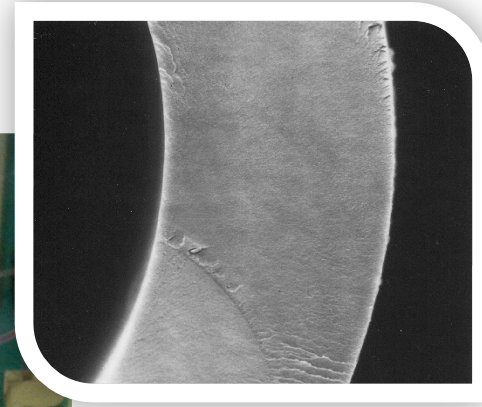
Adsorption



PES

Membrane





AN69

Clairance et élimination

Clairance Totale

$$Cl_{tot} = Cl_{rein} + Cl_{foie} + Cl_{...} + Cl_{CRRT}$$

Elimination

$$\text{Elimination (ml/min)} = Cl_{tot}\text{(ml/min)} \times \text{Concentration (mg/ml)}$$

Demie-vie

$$T_{1/2} = 0{,}693 \times Vd / Cl_{tot}$$

Adaptation posologique

Dose de charge = [plasmatique souhaitée] (mg/l) x Vd (L)

- **Calcul de la clairance de CRRT**
- CVVHpost= $Sc*Q_{UF}$
- CVVHpré= $Sc*Q_{UF}*(Qs/(Qs+Q_{UFpré}))$
- CVVHD= $Sd*Q_D$
- CVVHDF(post)= $Sd*(Q_{uf}+Q_D)$

Calcul de la clairance Totale
$Cl_{CRRT}+Cl_{non\ CRRT}$

Cible Pharmacocinétique ?

Temps Dépendant T>CMI

Elimination
=Concentration x Cl_{tot}

Posologie IVSE
=élimination

Concentration Dépendant Cmax/CMI

Demi-vie
=0,693 x Vd / Cl_{tot}

Intervalle
=$5xT_{1/2}$

Concentration Dépendant AUC_{24}/CMI

Concentration Moyenne cible
=$AUC_{24}/24$

Intervalle
=Dose/([plasmatique]xCl_{tot}

Antibiotic Dosing in Critically Ill Adult Patients Receiving Continuous Renal Replacement Therapy

Robin L. Trotman,[1] John C. Williamson,[1] D. Matthew Shoemaker,[2] and William L. Salzer[2]

Clinical Infectious Diseases 2005; 41:1159–66

Table 1. Pharmacokinetic and pharmacodynamic parameters of drugs used for treatment of critically ill adult patients receiving continuous renal replacement therapy.

Drug	PBC, %	Primary route of elimination[a]	Volume of distribution, L/kg	Half-life for normal renal function, h	Time-dependent or concentration-dependent killing	Target trough level, mg/L[b]
Acyclovir	15	Renal	0.6	2–4	Time	NA[c]
Ampicillin	28	Renal	0.29	1.2	Time	8
Aztreonam	56	Renal	0.2	1.7–2.9	Time	8
Cefepime	16	Renal	0.25	2.1	Time	8
Cefotaxime	27–38	Renal	0.15–0.55	1	Time	8
Ceftazidime	21	Renal	0.23	1.6	Time	8
Ceftriaxone	90	Hepatic	0.15	8	Time	8
Cilastatin	40	Renal	0.20	1	NA	NA
Ciprofloxacin	40	Renal	1.8	4.1	Concentration	1
Clavulanate	30	Hepatic	0.3	1	NA	NA
Clindamycin	60–95	Hepatic	0.6–1.2	3	Time	2
Colistin	55	Renal	0.34	2	Concentration	4
Daptomycin	92	Renal	0.13	8	Concentration	4
Fluconazole	12	Renal	0.65	30	Time	8–16[d]
Imipenem	20	Renal	0.23	1	Time	4

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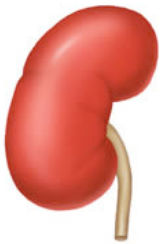
Table 2. Antibiotic dosing in critically ill adult patients receiving continuous renal replacement therapy.

Drug	Dosage, by type of renal replacement therapy	
	CVVH	CVVHD or CVVHDF
Amphotericin B formulation		
Deoxycholate	0.4–1.0 mg/kg q24h	0.4–1 mg/kg q24h
Lipid complex	3–5 mg/kg q24h	3–5 mg/kg q24h
Liposomal	3–5 mg/kg q24h	3–5 mg/kg q24h
Acyclovir	5–7.5 mg/kg q24h	5–7.5 mg/kg q24h
Ampicillin-sulbactam[a]	3 g q12h	3 g q8h
Aztreonam	1–2 g q12h	2 g q12h
Cefazolin	1–2 g q12h	2 g q12h
Cefepime	1–2 g q12h	2 g q12h
Cefotaxime	1–2 g q12h	2 g q12h
Ceftazidime	1–2 g q12h	2 g q12h
Ceftriaxone	2 g q12–24h	2 g q12–24h

Antibiotic Dosing in Critically Ill Adult Patients Receiving Continuous Renal Replacement Therapy

Robin L. Trotman,[1] John C. Williamson,[1] D. Matthew Shoemaker,[2] and William L. Salzer[2]

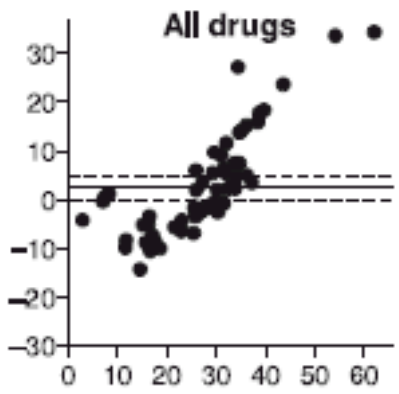
Drug	Dosage, by type of renal replacement therapy	
	CVVH	CVVHD or CVVHDF
Daptomycin	4 or 6 mg/kg q48h	4 or 6 mg/kg q48h
Fluconazole[b]	200–400 mg q24h	400–800 mg q24h[c]
Imipenem-cilastatin[d]	250 mg q6h or 500 mg q8h	250 mg q6h, 500 mg q8h, or 500 mg q6h
Levofloxacin[b]	250 mg q24h[e]	250 mg q24h[e]
Linezolid[b]	600 mg q12h	600 mg q12h
Meropenem	1 g q12h	1 g q12h
Moxifloxacin	400 mg q24h	400 mg q24h
Nafcillin or oxacillin	2 g q4–6h	2 g q4–6h
Piperacillin-tazobactam[f]	2.25 g q6h	2.25–3.375 g q6h
Ticarcillin-clavulanate[g]	2 g q6–8h	3.1 g q6h
Vancomycin	1 g q48h[e]	1 g q24h[e]
Voriconazole[h]	4 mg/kg po q12h	4 mg/kg po q12h

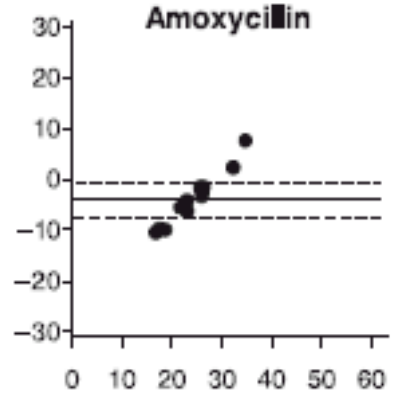


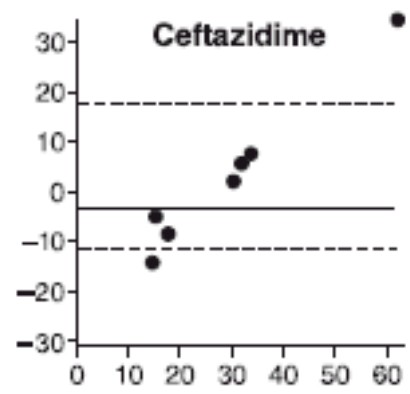
Discrepancies between observed and predicted continuous venovenous hemofiltration removal of antimicrobial agents in critically ill patients and the effects on dosing

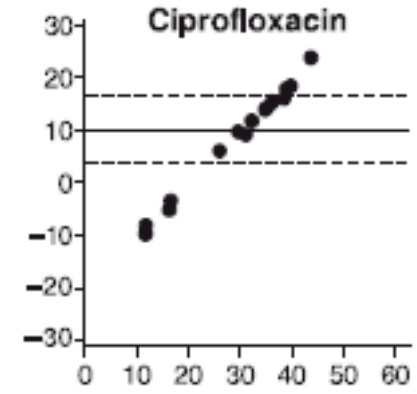
Catherine S. C. Bouman
Hendrikus J. M. van Kan
Richard P. Koopmans
Johanna C. Korevaar
Marcus J. Schultz
Margreeth B. Vroom

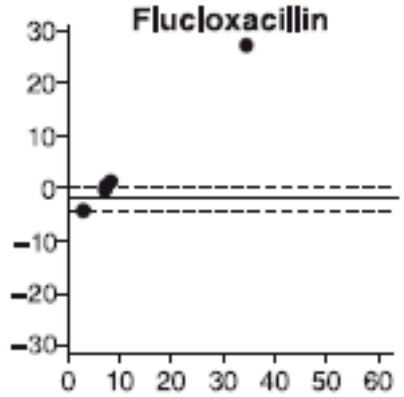
Intensive Care Med (2006) 32:2013–2019

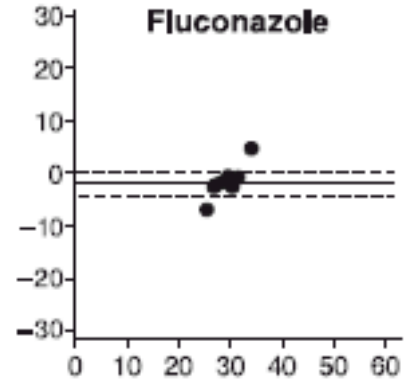


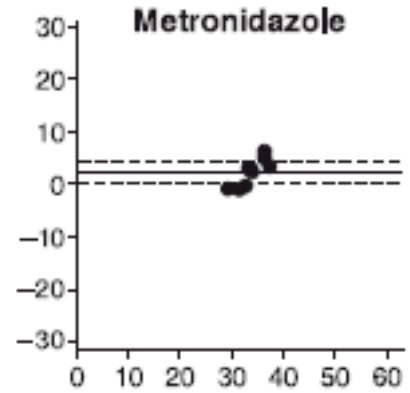


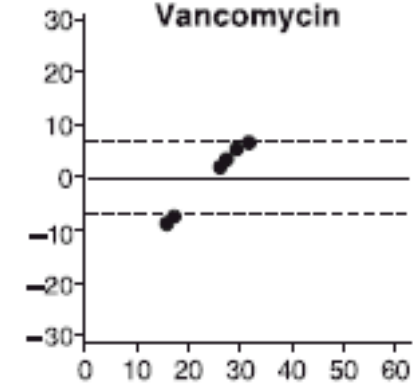












Conclusion

- ANTIBIOTHERAPIE / CRRT
- Dose identique à un patient sans IRA
- Bolus
- Infusion continue pour les temps dépendant
- Augmenter la dose si augmentation épuration
- Schéma à adapter en fonction de la durée

DOSER

Conclusion

- Ne pas oublier les autres médicaments
- La morphine ≠ Sufenta ou Fenta
- Attention aux médicaments cardio
- Ne pas oublier les vitamines