Clairance rénale augmentée et antibiotiques

Pr Keyvan Razazi

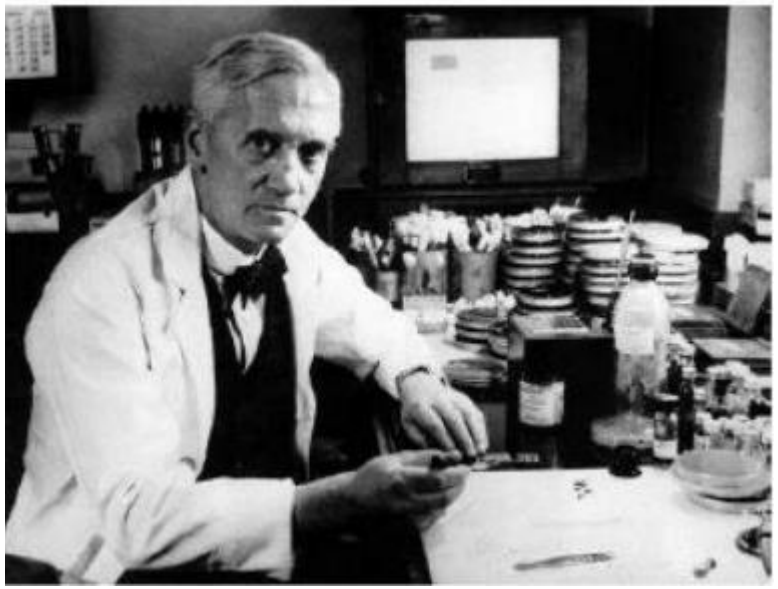
3ème journée G2I

22 Mars 2024

MEDECINE INTENSIVE REANIMATION
HOPITAL HENRI MONDOR

Liens d’intérêt

- Shionogi
- MSD
- Pfizer



"There may be a danger, though, in underdosage,. The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant."

Alexander Fleming -1945.

Connu depuis longtemps

INCREASED GLOMERULAR FILTRATION RATE IN PATIENTS WITH MAJOR BURNS AND ITS EFFECT ON THE PHARMACOKINETICS OF TOBRAMYCIN

PHILIPPE LOIRAT, M.D., JEAN ROHAN, M.D., ALICE BAILLET, M.Sc., FRANCOIS BEAUFILS, M.D., RENE DAVID, M.D., AND ANTOINE CHAPMAN, M.D.

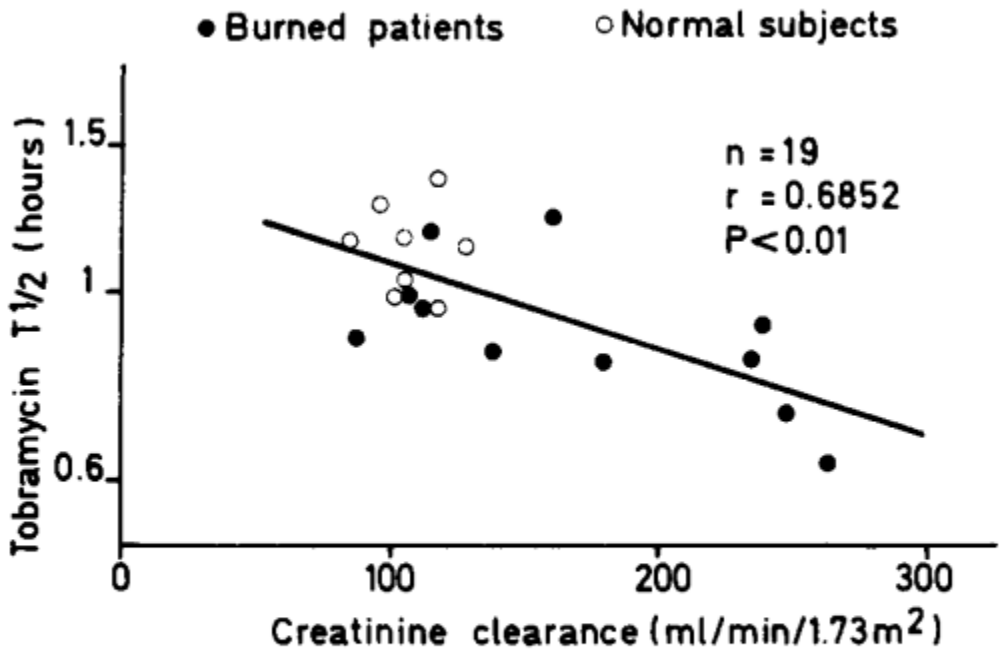


Figure 2. Tobramycin Plasma Half-Life (T½) versus Creatinine Clearance in 11 Burned Patients (Group 1) and Eight Normal Subjects.

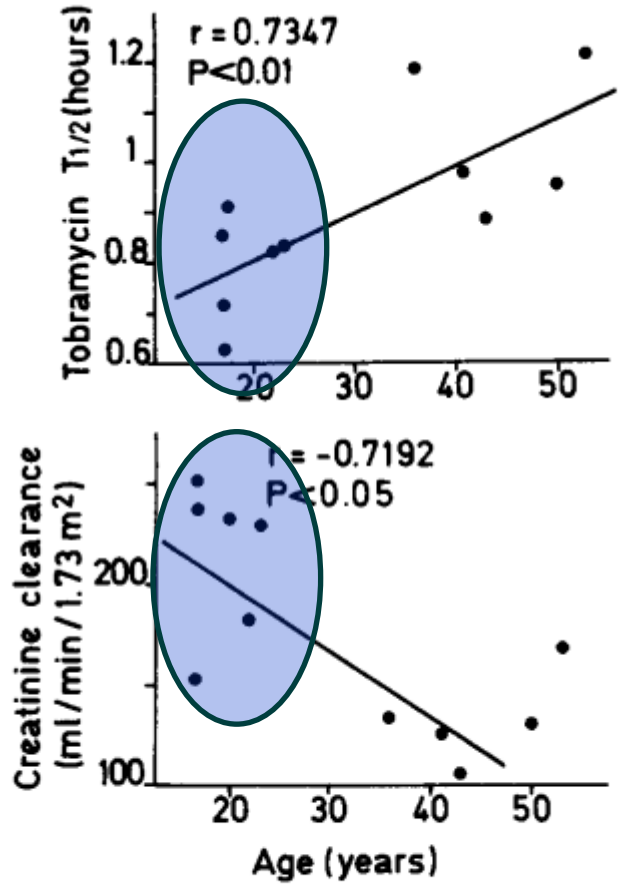


Figure 3. Tobramycin Plasma Half-Life (T½) and Creatinine Clearance versus Age in 11 Burned Patients (Group 1).

MAJOR ARTICLE

DALI: Defining Antibiotic Levels in Intensive Care Unit Patients: Are Current β-Lactam Antibiotic Doses Sufficient for Critically Ill Patients?

Jason A. Roberts,[1,2] Sanjoy K. Paul,[3,4] Murat Akova,[5] Matteo Bassetti,[6] Jan J. De Waele,[7] George Dimopoulos,[8] Kirsi-Maija Kaukonen,[9] Despoina Koulenti,[1,8] Claude Martin,[10,11] Philippe Montravers,[12] Jordi Rello,[13] Andrew Rhodes,[14] Therese Starr,[2] Steven C. Wallis,[1] and Jeffrey Lipman[1,2]; for the DALI Study[a]

Table 3. Antibiotic Data for Achievement of Pharmacokinetic/Pharmacodynamic Targets[a] in Critically Ill Patients

	Antibiotic (No. of Patients)								
Dosing and PK/PD Data	Amoxicillin (n = 71)	Ampicillin (n = 18)	Cefazolin (n = 14)	Cefepime (n = 14)	Ceftriaxone (n = 33)	Doripenem (n = 13)	Piperacillin (n = 109)	Meropenem (n = 89)	Total (N = 361)
Dosage per 24 h[b], g	6.0 (3.5–6.0)	12.0 (8.3–12.0)	3.0 (3.0–4.0)	6.0 (5.0–6.0)	2.0 (2.0–4.0)	1.75 (1.50–3.0)	12.0 (12.0–16.0)	3.0 (3.0–4.0)	
50% $fT_{>MIC}$ achieved	52.1%	55.6%	100.0%	78.6%	97.0%	100.0%	80.6%	95.0%	78.9%
50% $fT_{>4\times MIC}$ achieved	16.9%	27.8%	50.0%	50.0%	93.9%	69.2%	48.9%	68.8%	48.9%
100% $fT_{>MIC}$ achieved	18.3%	33.3%	78.6%	78.6%	93.9%	76.9%	67.0%	69.7%	60.4%
100% $fT_{>4\times MIC}$ achieved	11.3%	22.2%	14.3%	71.4%	87.9%	30.8%	30.3%	41.6%	35.0%

Abbreviation: PK/PD, pharmacokinetic/pharmacodynamic.

Table 3 Multivariate analysis, with PK/PD target non-attainment as the dependent variable

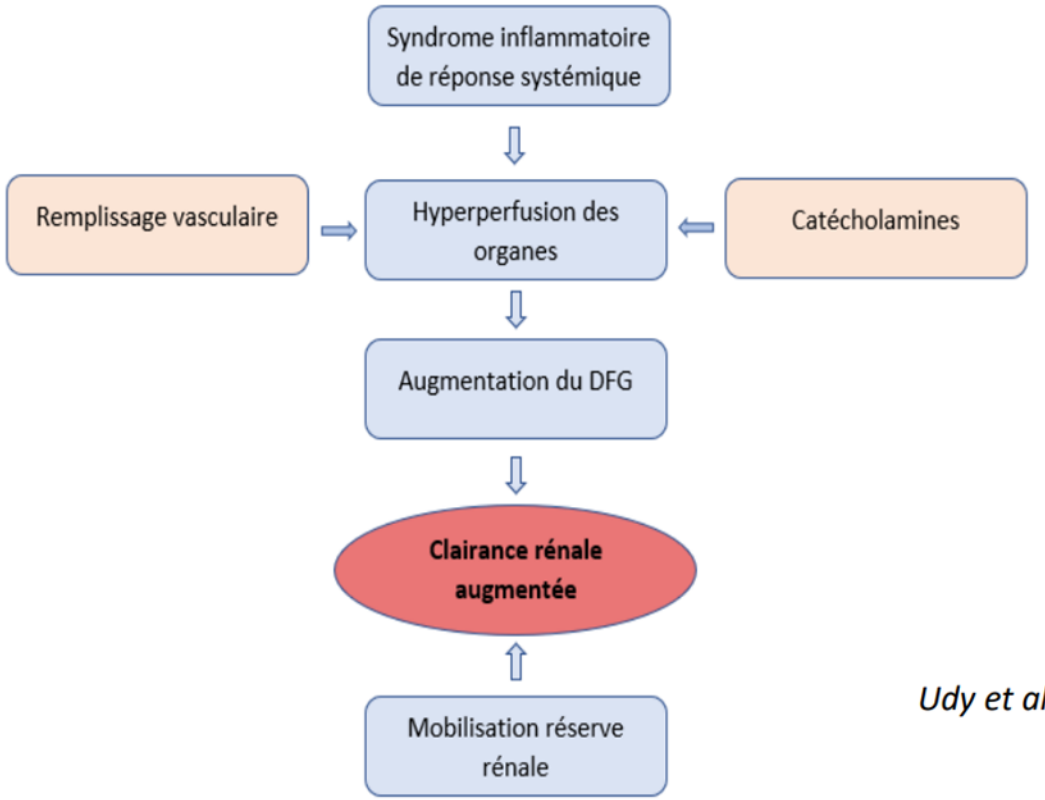
	p value	Odds ratio	95 % CI	
			Lower	Upper
Factors associated with not reaching concentrations above the MIC during at least 50 % of the dosing interval				
Age (per year)	0.151	0.983	0.960	1.006
Interval between start AB and sampling (per day)	0.086	0.905	0.807	1.014
APACHE II score on admission (per point)	0.879	0.996	0.952	1.043
SOFA on the day of AB sampling (per point)	0.069	0.908	0.818	1.008
Cockroft-Gault CL_{CR} (per mL/min)	0.173	1.004	0.998	1.010
Trauma as an admission diagnosis	0.947	0.968	0.368	2.543
Surgery in the previous 24 h	0.681	0.828	0.337	2.034
Extended/continuous infusion (vs. intermittent)	0.027	0.340	0.131	0.882
Prophylaxis indication	0.067	2.088	0.949	4.595
Hosmer–Lemeshow goodness of fit, $p = 0.928$				
Factors associated with not reaching concentrations above the MIC during 100 % of the dosing interval				
Age (per year)	0.656	0.995	0.975	1.016
Interval between start AB and sampling (per day)	0.101	0.932	0.856	1.014
APACHE II score on admission (per point)	0.425	1.015	0.978	1.054
SOFA on the day of AB sampling (per point)	0.733	0.986	0.909	1.069
Cockroft-Gault CL_{CR} (per mL/min)	0.000	1.012	1.006	1.019
Ratio antibiotic dose to DD_{ICU}	0.338	0.977	0.991	1.003
Trauma as an admission diagnosis	0.056	2.596	0.977	6.899
Surgery in the previous 24 h	0.068	2.105	0.946	4.682
Extended/continuous infusion (vs. intermittent)	0.000	0.252	0.118	0.538
Prophylaxis indication	0.834	0.926	0.452	1.898
Hosmer–Lemeshow goodness of fit, $p = 0.225$				

AB antibiotic, *APACHE* acute physiology and chronic health evaluation, CL_{CR} creatinine clearance, *SOFA* sequential organ failure assessment

Clairance rénale augmentée: définition

- Augmentation de la capacité rénale à éliminer une substance donnée du sang
- DFG > 130 ml/min/1,73 m²
- Fréquence: 14 à 80%

Mécanisme



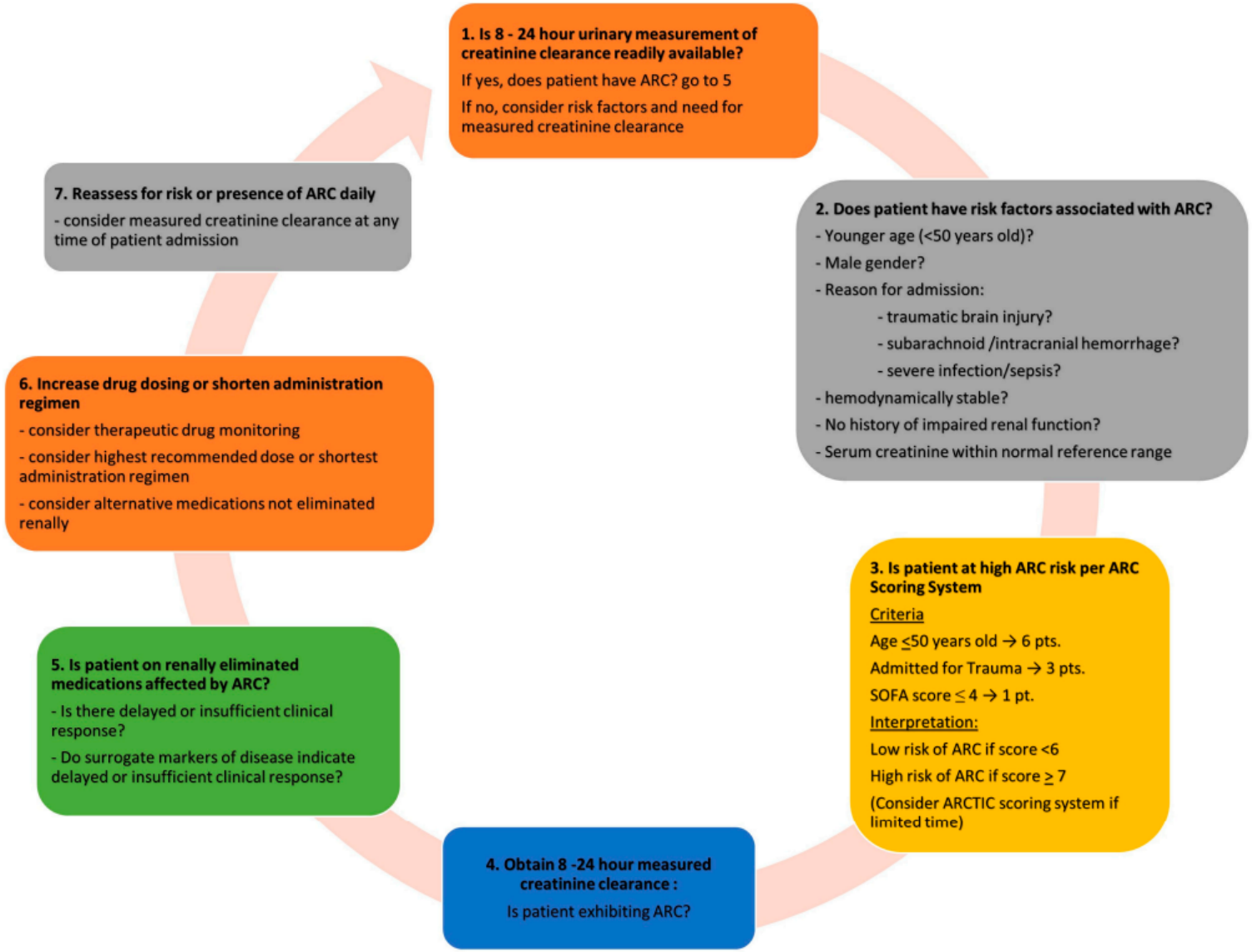
Udy et al, Nat.Rev.Nephrol, 2011

- Diminution des résistances vasculaires périphériques
- Augmentation du débit cardiaque et du débit rénal
- Hypothermie
- Perte de l'autorégulation

Facteurs de risque

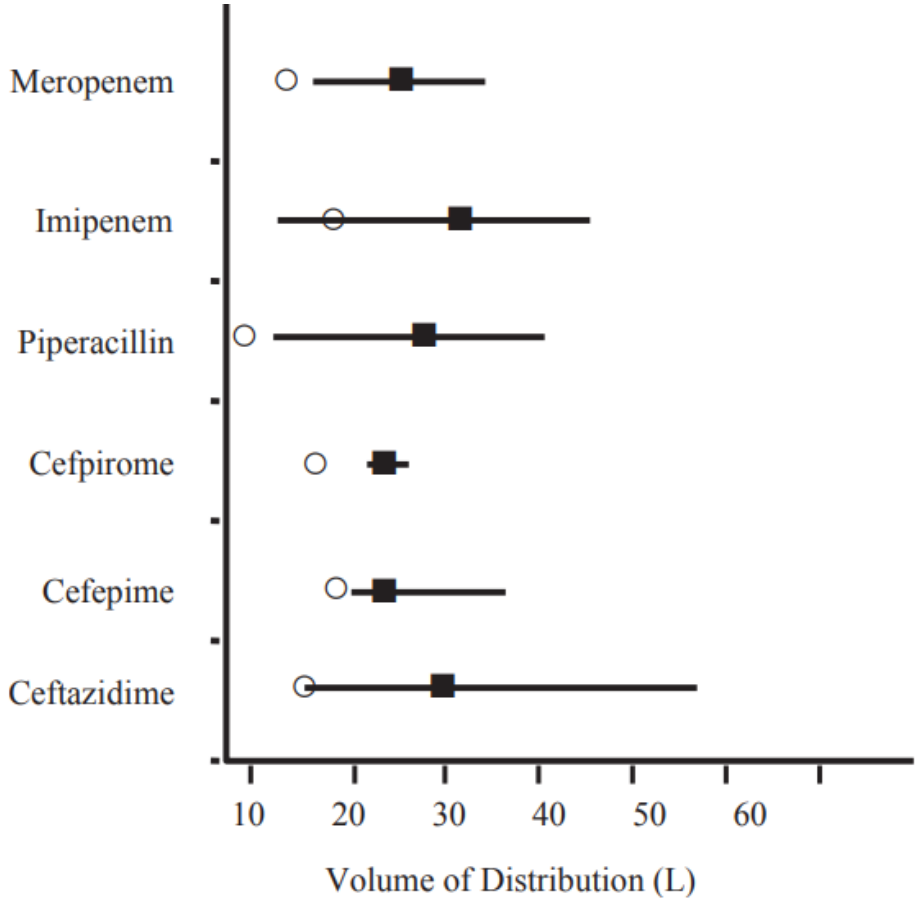
The ARC risk scoring systems.

	ARC Scoring System [23,35]	ARCTIC Scoring System [4]
Criteria	Age 50 or younger = 6 pts Trauma = 3 pts SOFA score ≤ 4 = 1 pt	SCr < 62 µmol/L = 3 pts Male sex = 2 pts Age <56 years = 4 pts Age: 56–75 years = 3 pts
Interpretation	0–6 points→low ARC risk 7–10 points→high ARC risk	>6 points→high ARC risk <6 points→low ARC risk
Sensitivity	100%	84%
Specificity	71%	68%


1. Is 8 - 24 hour urinary measurement of creatinine clearance readily available?
If yes, does patient have ARC? go to 5
If no, consider risk factors and need for measured creatinine clearance
2. Does patient have risk factors associated with ARC?
- Younger age (<50 years old)?
- Male gender?
- Reason for admission:
- traumatic brain injury?
- subarachnoid /intracranial hemorrhage?
- severe infection/sepsis?
- hemodynamically stable?
- No history of impaired renal function?
- Serum creatinine within normal reference range
3. Is patient at high ARC risk per ARC Scoring System
Criteria
Age ≤50 years old → 6 pts.
Admitted for Trauma → 3 pts.
SOFA score ≤ 4 → 1 pt.
Interpretation:
Low risk of ARC if score <6
High risk of ARC if score ≥ 7
(Consider ARCTIC scoring system if limited time)
4. Obtain 8 -24 hour measured creatinine clearance :
Is patient exhibiting ARC?
5. Is patient on renally eliminated medications affected by ARC?
- Is there delayed or insufficient clinical response?
- Do surrogate markers of disease indicate delayed or insufficient clinical response?
6. Increase drug dosing or shorten administration regimen
- consider therapeutic drug monitoring
- consider highest recommended dose or shortest administration regimen
- consider alternative medications not eliminated renally
7. Reassess for risk or presence of ARC daily
- consider measured creatinine clearance at any time of patient admission

Autres facteurs en réanimation

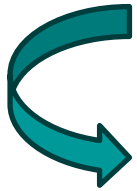
Augmentation du volume de distribution en réanimation



Gonçalves Pereira Crit car 2013

Hypoalbuminémie

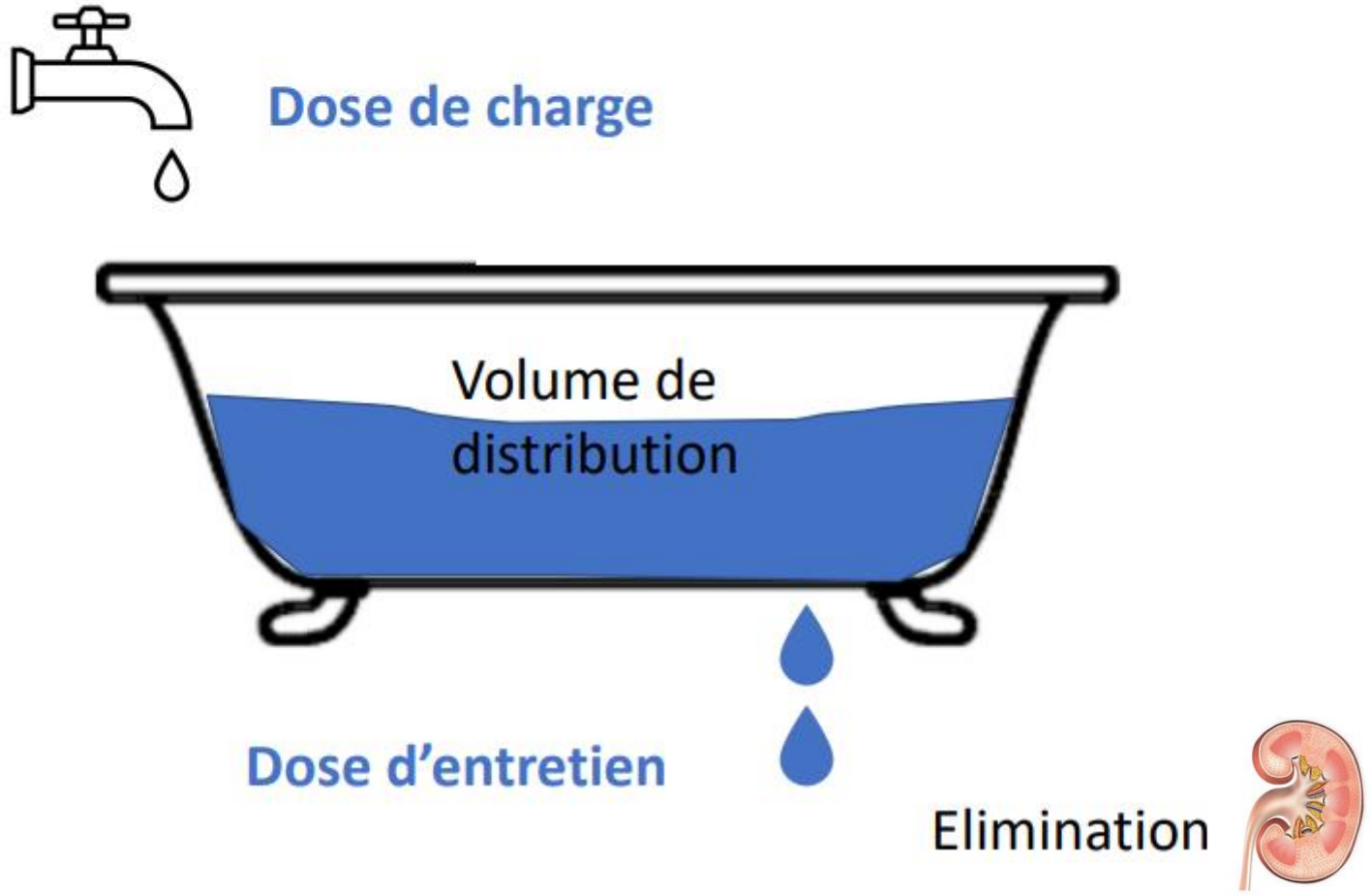
- Fréquente: 50% Alb<25g/L

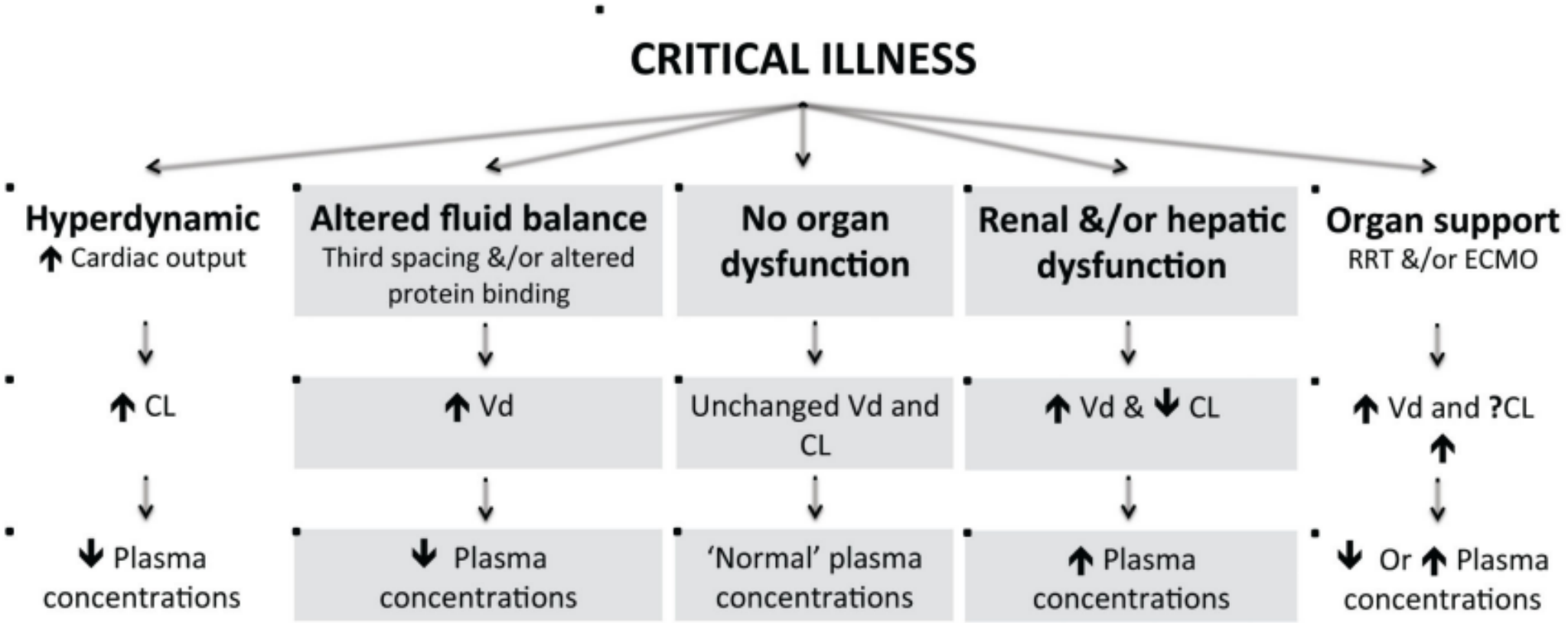


Augmentation du volume de distribution x2

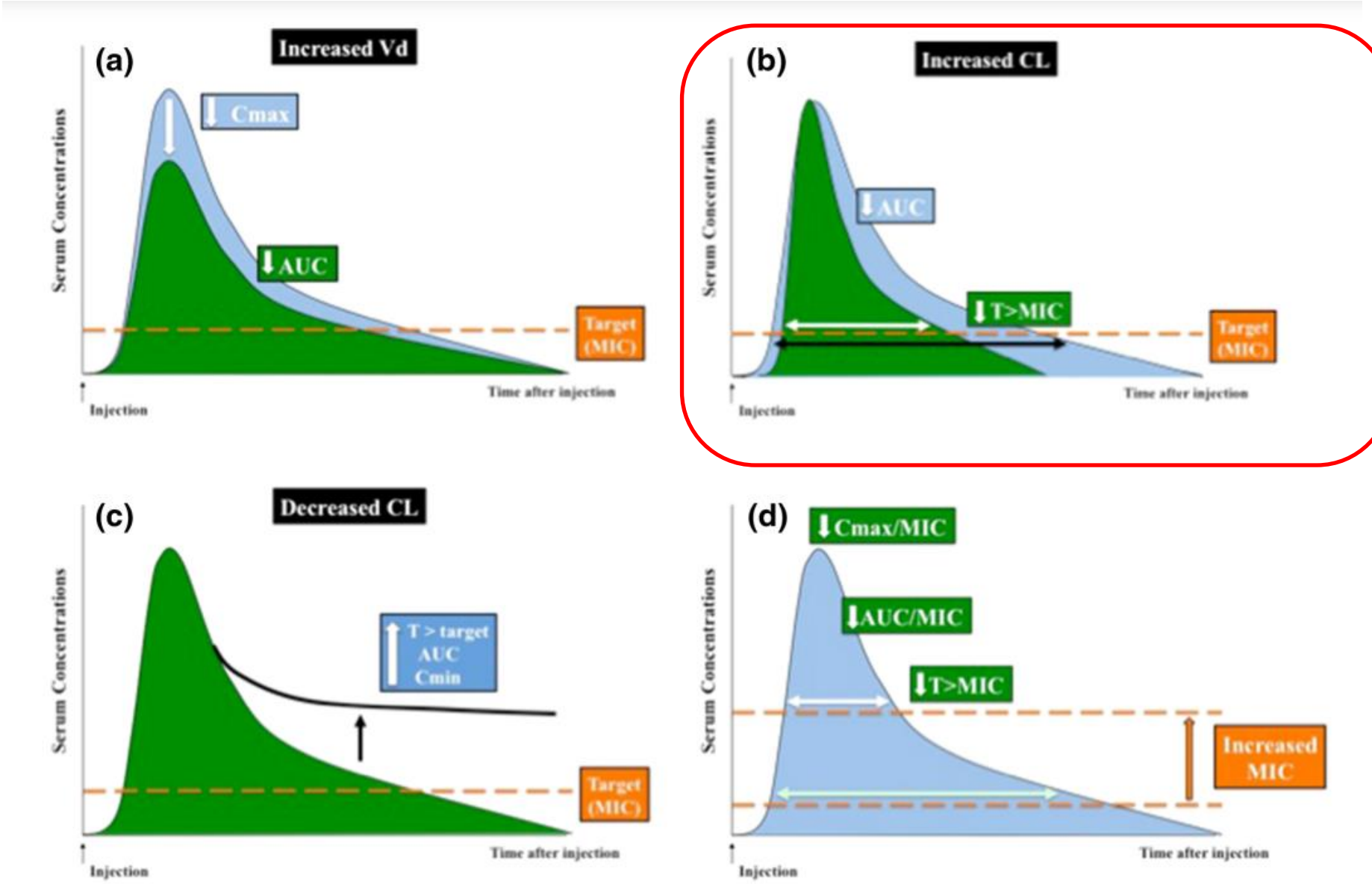
Antibiotic	MW (Da)	Free Fraction (%)	$t_{1/2}$ (Hours)	V_d (L/kg)	Initial Dose for Critically Ill Adults	Toxicity Threshold
ampicillin/sulbactam	581/255	85/62	1.2/1	0.29/0.25	3 g	>8 × MIC
amoxicillin/clavulanate	365/199	82/75	1–1.4/1	0.36/0.21	1.2 g	c_{min} > 40 mg/L
oxacillin	401	6–10	0.5–0.7	0.4	2 g	>8 × MIC
flucloxacillin	454	4–5	0.5–1	2.18	2 g	c_{min} > 125 mg/L
piperacillin	518	70	1	0.24	4 g	c_{min} > 361 mg/L
piperacillin/tazobactam	518/300	70/78	1/1	0.24/0.40	4.5 g	c_{min} > 64 mg/L c_{ss} > 157 mg/L
cefazolin	454	20	2	0.19	2 g	>8 × MIC
cefoxitin	427	21–35	1	0.23	2 g	>8 × MIC
cefuroxime	424	50–67	1.5	0.19	1.5 g	>8 × MIC
ceftazidime	547	90	2.8	0.28–0.40	2 g	>8 × MIC
ceftriaxone	554	10	5–9	0.1–0.2	2 g	>8 × MIC
cefotaxime	455	50–70	1.5	0.28	2 g	>8 × MIC
ceftaroline	684	80	2.7	0.29	600 mg	>8 × MIC
ceftolozane/ tazobactam	666/300	80/78	3.1/1	0.19/0,40	3 g	>8 × MIC
cefepime	481	84	1.7–2.3	0.3	2 g	c_{ss} > 35 mg/L c_{min} > 20 mg/L
meropenem	383	98	1	0.35	2 g	c_{min} > 64 mg/L
imipenem	317	80	1	0.22	1 g	>8 × MIC
doripenem	420	92	1	0.24	1 g	>8 × MIC
ertapenem	475	20–40	4	0.12	1 g	>8 × MIC

Traitement d'un sepsis





Jason Roberts LID 2016

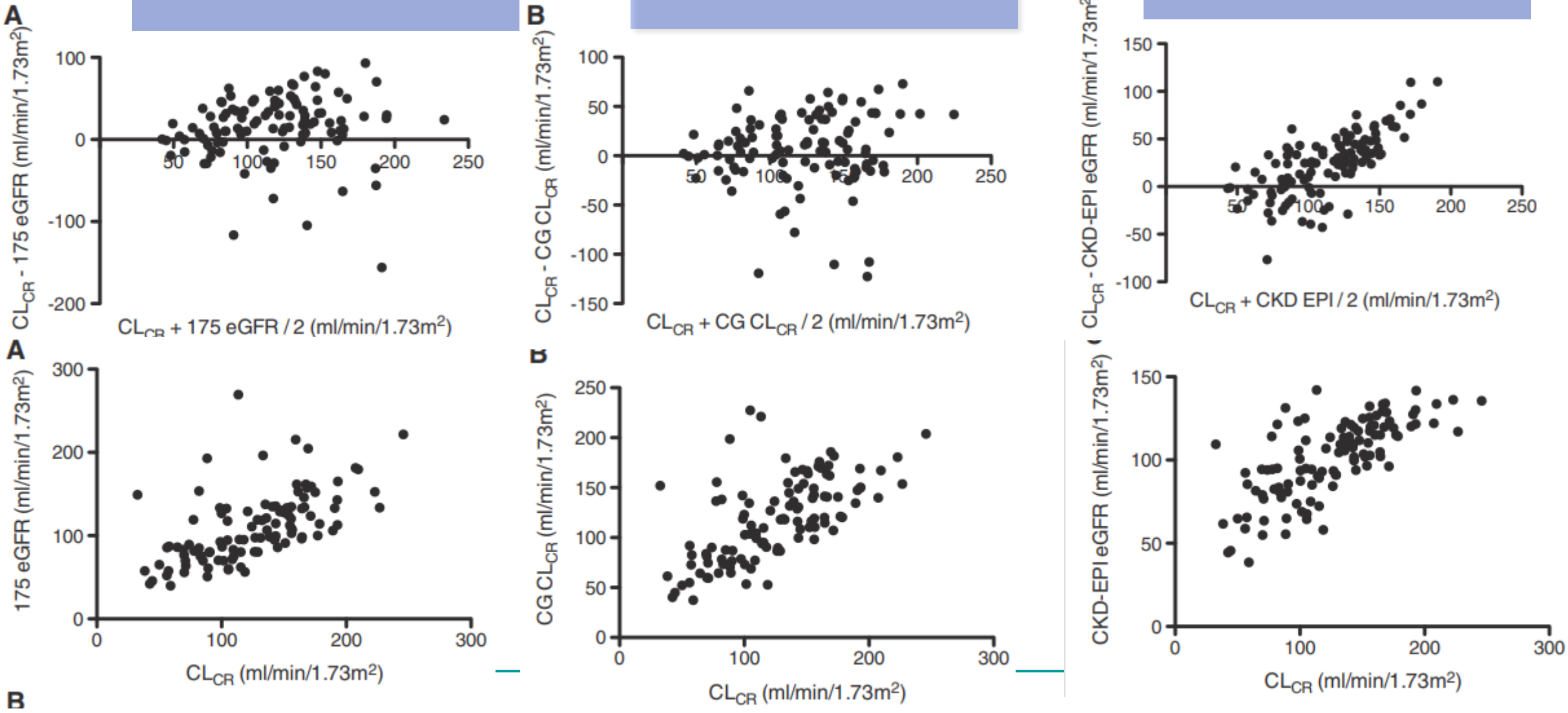

(a)
Increased Vd
Cmax
AUC
Target (MIC)
Serum Concentrations
Injection
Time after injection
(b)
Increased CL
AUC
T>MIC
Target (MIC)
Serum Concentrations
Injection
Time after injection
(c)
Decreased CL
T > target
AUC
Cmin
Target (MIC)
Serum Concentrations
Injection
Time after injection
(d)
Cmax/MIC
AUC/MIC
T>MIC
Increased MIC
Serum Concentrations
Injection
Time after injection

Comment mesurer la fonction rénale?

MDRD

Cockcroft-Gault

CKD EPI



Udy BMC nephro 2013

Table 1 Overview of studies included in this review that analysed the accuracy of methods for diagnosing ARC in critically ill patients

Study	Reference test and definition of ARC	Method assessed	ARC samples [n]	Spearman coefficient[a] [r_S]	Bias ± precision[b] [mL/min/1.73 m^2 or mL/min]	Detection of ARC patients [specificity/sensitivity]	Other information provided
Barletta et al. [9]	CrCl measured in urine > 130 mL/min	mCG CKD-EPI MDRD-4-IDMS	45	NA	mCG: − 52 ± 58 CKD-EPI: NA MDRD-4-IDMS: NA	NA	Underestimation of ARC Inaccurate CrCl estimates became evident when measured CrCl > 160 mL/min
Ruiz et al. [11]	CrCl measured in urine > 130 mL/min/1.73 m^2	CG mCG MDRD-4 CKD-EPI	120	NA	CG: − 35.7 ± 47 mCG: − 78.6 ± 78.6 MDRD-4: − 40.9 ± 51.9 CKD-EPI: − 57.9 ± 58.3	CG: 0.63/0.83 mCG: 0.71/0.67 MDRD-4: 0.61/0.77 CKD-EPI: 0.74/0.75	Underestimation of ARC
Steinke et al. [14]	CrCl measured in urine > 130 mL/min/1.73 m^2	CG CKD-EPI Hoek	16	NA	NA	CG: 0.81/0.69 CKD-EPI: 0.96/0.25 Hoek: 0.96/0.38	Underestimation of ARC
Adnan et al. [17]	CrCl measured in urine > 130 mL/min	CG	19	CG: − 0.04 (NS)	CG: − 57 ± 54	NA	Underestimation of ARC
Baptista et al. [22]	CrCl measured in urine > 130 mL/min/1.73 m^2 in ≥ 50% of measurements	CG CKD-EPI MDRD-4-IDMS	30	NA	NA	NA	Progressive underestimation of CrCl > 120 mL/min/m^2 and overestimation of CrCl < 120 mL/min/m^2
Udy et al. [25]	*Group A:* CrCl measured in urine between 120 and 149 mL/min/1.73 m^2 *Group B:* CrCl measured in urine ≥150 mL/min/1.73 m^2	CG CKD-EPI MDRD-4-IDMS	53	*Group A:* CG: 0.369 (NS) CKD-EPI: 0.347 (NS) MDRD-4-IDMS: 0.047 (NS) *Group B:* CG: 0.399 (p = 0.009) CKD-EPI: 0.46 (p = 0.005) MDRD-4-IDMS:	*Group A:* CG: − 6.62 ± 23.9 CKD-EPI: − 29.2 ± 10.8 MDRD-4-IDMS: − 22.7 ± 26.1 *Group B:* CG: − 27.8 ± 27.2 CKD-EPI: − 55 ± 20.9 MDRD-4-IDMS: − 36.1 ± 31.3	NA	Underestimation of ARC
Baptista et al. [33]	CrCl measured in urine > 130 mL/min/1.73 m^2	CG mCG CKD-EPI MDRD-6	86	CG: 0.26 (p = 0.017) CKD-EPI: 0.21 (p = 0.044) MDRD-4: 0.22 MDRD-6: 0.18 (NS)	CG: − 39 ± 75 mCG: − 84 ± 70 CKD-EPI: − 71 ± 71 MDRD-6: − 68 ± 76	CG: ND/0.62 mCG: ND/0.62 MDRD-4: ND/0.47 MDRD-6: ND/0.29	Underestimation of ARC
May et al. [35]	*Females:* CrCl measured in urine > 120 mL/min/1.73 m^2	CG	20	NA	NA	NA	Underestimation of ARC
[46]	min/1.73 m^2					Larson: NA/0.22	

Sous estime +++

Cockcroft-Gault moins mauvaise

Faire U*V/P

Durée 8h ou 24h

Variation au cours du séjour

RESEARCH Open Access

Augmented renal clearance in the ICU: estimation, incidence, risk factors and consequences—a retrospective observational study

Alexandre Egea[1], Claire Dupuis[2*], Etienne de Montmollin[3,4], Paul-Henry Wicky[3], Juliette Patrier[3], Pierre Jaquet[3], Lucie Lefèvre[5], Fabrice Sinnah[3], Mehdi Marzouk[6], Romain Sonneville[3,7], Lila Bouadma[3,4], Bertrand Souweine[2] and Jean-François Timsit[3,4]

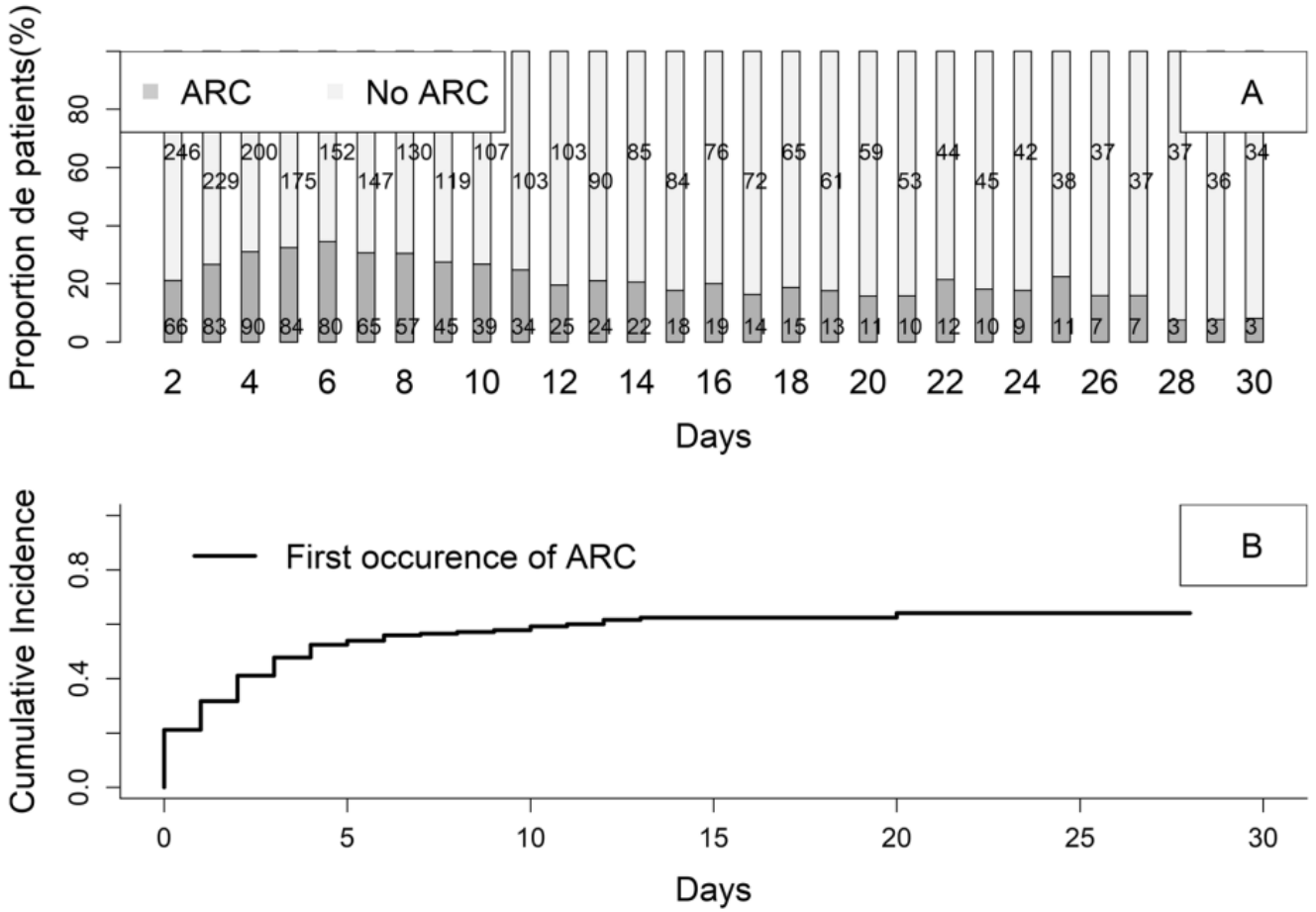


Fig. 1 Daily prevalence (**A**) and cumulative incidence (**B**) of augmented renal clearance in ICU from day 1 to day 30

Comment éviter les sous dosages?

- Perfusions prolongées/continues (toujours après dose de charge)
- Augmenter les doses
- Autres ?

Table 3 Multivariate analysis, with PK/PD target non-attainment as the dependent variable

	p value	Odds ratio	95 % CI	
			Lower	Upper
Factors associated with not reaching concentrations above the MIC during at least 50 % of the dosing interval				
Age (per year)	0.151	0.983	0.960	1.006
Interval between start AB and sampling (per day)	0.086	0.905	0.807	1.014
APACHE II score on admission (per point)	0.879	0.996	0.952	1.043
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Hosmer–Lemeshow goodness of fit, $p = 0.225$				

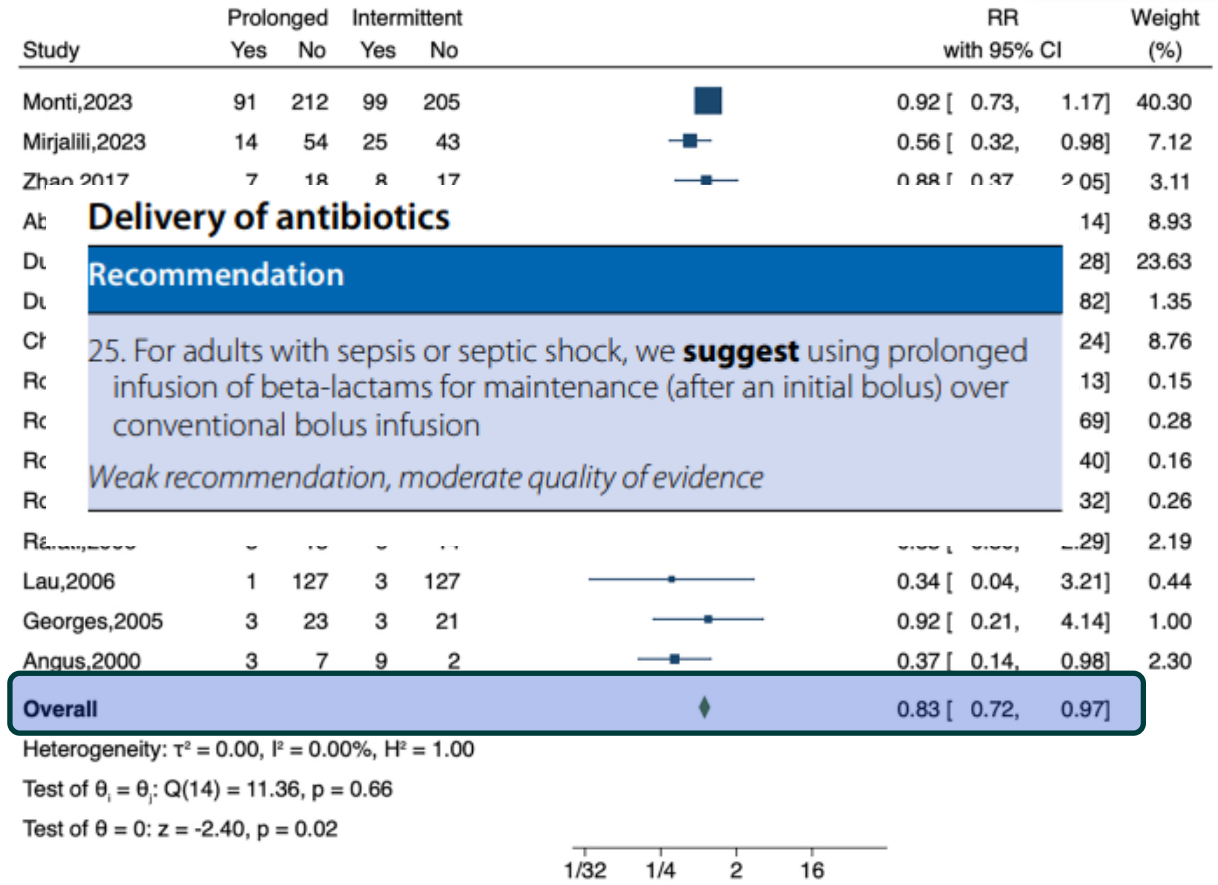
AB antibiotic, *APACHE* acute physiology and chronic health evaluation, CL_{CR} creatinine clearance, *SOFA* sequential organ failure assessment

Perfusions prolongées et mortalité

REVIEW Open Access

Prolonged versus intermittent β-lactam infusion in sepsis: a systematic review and meta-analysis of randomized controlled trials

Yang Zhao[1], Bin Zang[1*] and Qian Wang[2*]



Delivery of antibiotics

Recommendation

25. For adults with sepsis or septic shock, we **suggest** using prolonged infusion of beta-lactams for maintenance (after an initial bolus) over conventional bolus infusion

Weak recommendation, moderate quality of evidence

Fig. 2 Forest plot of all-cause mortality. Prolonged versus intermittent infusion of β-lactam antibiotics among patients with sepsis. The points and the bars represent the relative risk (RR) and 95% confidence intervals (CIs). RR, relative risk; CI, confidence interval

JAMA®

QUESTION Does continuous administration of meropenem reduce a composite of mortality and emergence of drug-resistant bacteria among critically ill patients with sepsis compared with intermittent administration?

CONCLUSION Continuous administration of meropenem, compared with intermittent administration, does not improve clinically relevant outcomes in critically ill patients with sepsis.

POPULATION

404 Men
203 Women

Critically ill adults with sepsis

Mean age: **64** years

LOCATION

31
Intensive care units in Croatia, Italy, Kazakhstan, and Russia

INTERVENTION

607 Patients randomized

303
Continuous administration
3 g of meropenem administered over 24 hours

304
Intermittent administration
1 g of meropenem administered over 30 to 60 minutes every 8 h

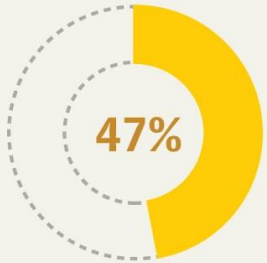
PRIMARY OUTCOME

All-cause mortality and emergence of pandrug-resistant or extensively drug-resistant bacteria at day 28

FINDINGS

Incidence of composite primary outcome at day 28

Continuous administration
142 of 303 patients



Intermittent administration
149 of 304 patients

The between-group difference was not significant:

Relative risk, 0.96 (95% CI, 0.81 to 1.13); *P* = .60

Monti G, Bradić N, Marzaroli M, et al; for the MERCY Investigators. Continuous vs intermittent meropenem administration in critically ill patients with sepsis: the MERCY randomized clinical trial. *JAMA*. Published online June 16, 2023. doi:10.1001/jama.2023.10598

eTable 17. Modified intention to treat analysis of patients with evidence of a multidrug-resistant bacteria on cultures performed between 48 hours before the first study drug dose and randomization

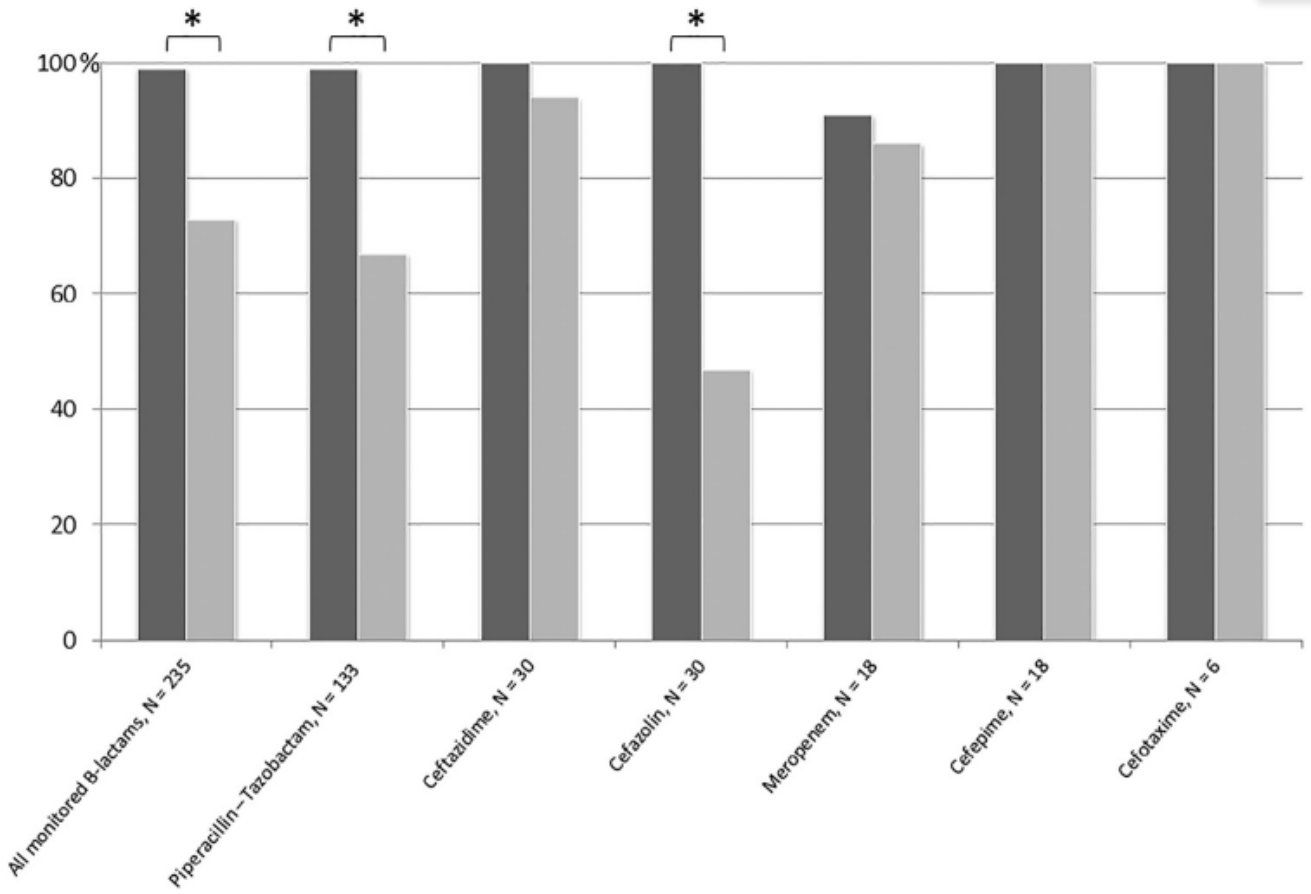
Outcome	Continuous administration (n = 49)	Intermittent administration (n = 48)	Difference (95% CI)	Relative risk (95% CI)	P value
Primary outcome					
28-d mortality and emergence of new pan drug-resistant[a] or extensively drug-resistant[b] bacteria (composite outcome), No. (%)	24 (49)	32 (67)	Absolute, -17.7 (-37.0 to 1.6)	0.73 (0.52 to 1.04)	.08
Components of primary outcome					
28-d mortality, No. (%)	13 (27)	13 (27)	Absolute, -0.6 (-18.2 to 17.1)	0.98 (0.51 to 1.89)	.95
28-d emergence of new pan drug-resistant[a] or extensively drug-resistant[b] bacteria, No. (%)[c]	17/49 (35)	23/46 (50)	Absolute, -15.3 (-35.0 to 4.4)	0.69 (0.43 to 1.12)	.69
Pre-specified secondary outcome					
Days alive and free from antibiotics at day 28, median (IQR)[d]	1 (0-12)	0 (0-8)	Mean, 2.3 (-0.4 to 5.1)		.25
Days alive and free from intensive care unit at day 28, median (IQR)[e]	0 (0 -14)	0 (0-15)	Mean, 0.1 (-3.7 to 3.9)		.83
90-d mortality, No. (%)	23 (47)	16 (33)	Absolute, 13.6 (-5.7 to 32.9)	1.41 (0.86 to 2.32)	.17
28-d cumulative Sequential Organ Failure Assessment -free score, median (IQR)[f]	171 (102 - 290)	136 (76 - 295)	Mean, 17 (-62 to 96)		.47
Post-hoc exploratory outcomes					
Length of intensive care unit stay, median (interquartile range), d	16 (8 – 31)	15 (8 -39)	Mean, -2.7 (-12.7 to 7.3)		.95
in 28-day survivors, days	17 (9 – 44)	22 (10 -48)	Mean, -3.0 (-14.0 to 6.0)		.52
Length of hospital stay, median (interquartile range), d	30 (16 - 49)	37 (12 - 67)	Mean, -4.5 (-16.2 to 7.2)		.62
in 28-day survivors, days	38 (17 – 52)	48 (28 – 86)	Mean, -11.1 (-25.4 to 3.1)		.11
Readmission to intensive care unit, No. (%)[g]	4/36 (11)	4/33 (12)	Absolute, -1.0 (-16.2 to 14.1)	0.92 (0.25 to 3.37)	>.99

Quel est le risque avec des perfusions prolongées/continues?

Risque différent selon le type d'ATB

- Exclusion des I. Rénale

12% de sous dosage



CL creat>170ml/min

Carrié IJAA 2017

Selon vrai CMI

Risque sous dosage

30%

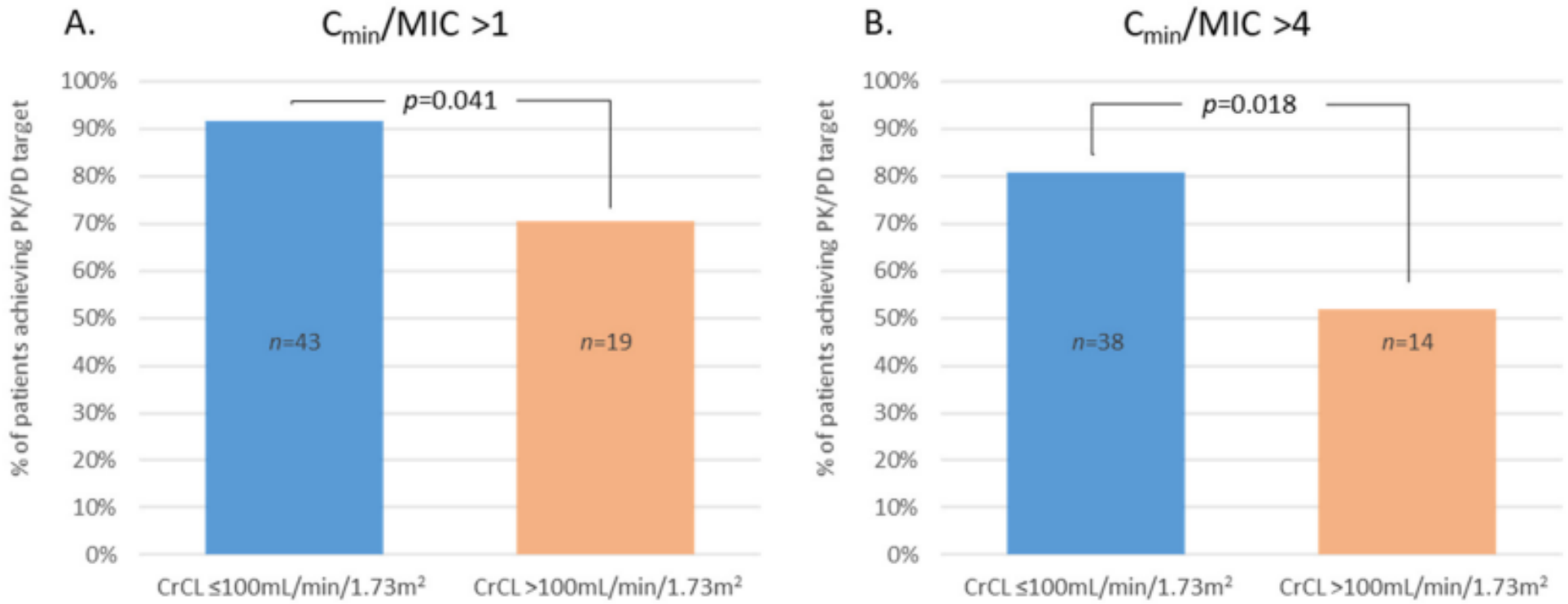
antibiotics

MDPI

Article

Empirical Antibiotic Therapy for Gram-Negative Bacilli Ventilator-Associated Pneumonia: Observational Study and Pharmacodynamic Assessment

Olivier Pajot [1,*], Karim Lakhal [2], Jérome Lambert [3], Antoine Gros [4], Cédric Bruel [5], Thierry Boulain [6], Denis Garot [7], Vincent Das [8], Jean François Timsit [9], Charles Cerf [10], Bertrand Souweine [11], Cendrine Chaffaut [3], Hervé Mentec [1], Jean Ralph Zahar [12], Jean Paul Mira [13] and Vincent Jullien [14]

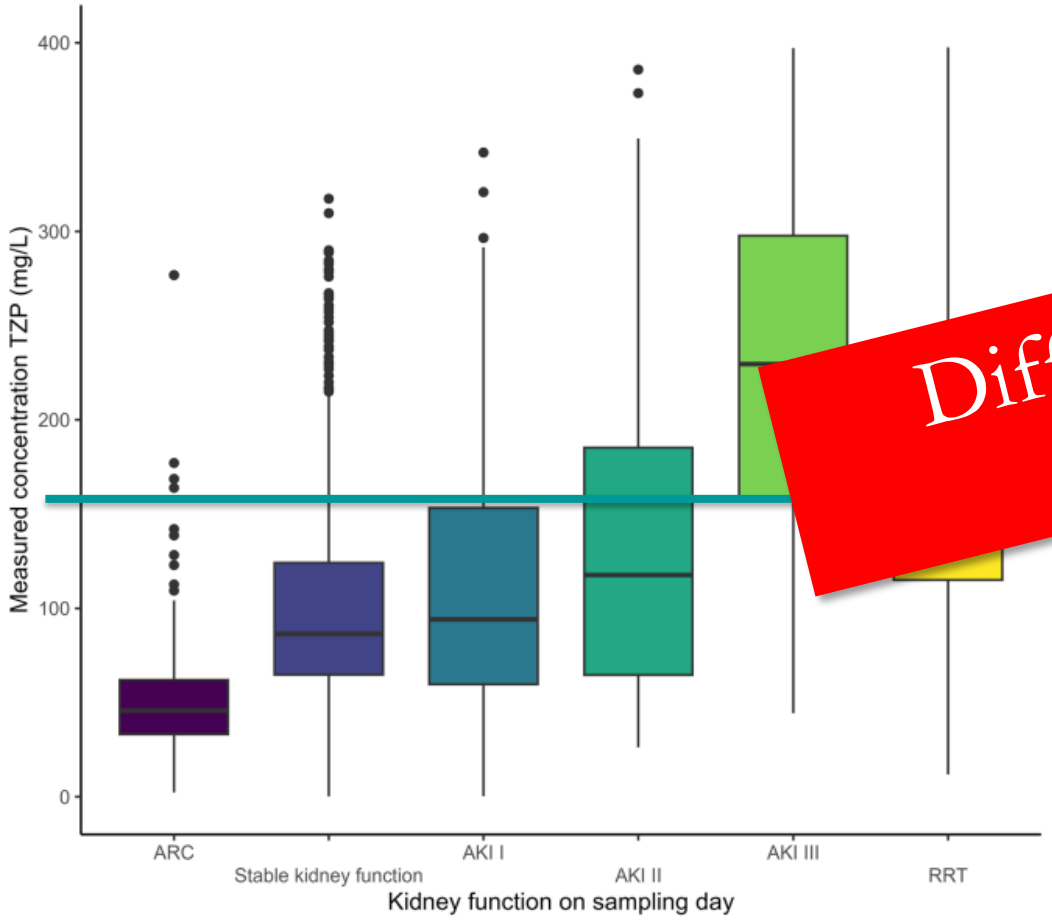


Risque toxicité?

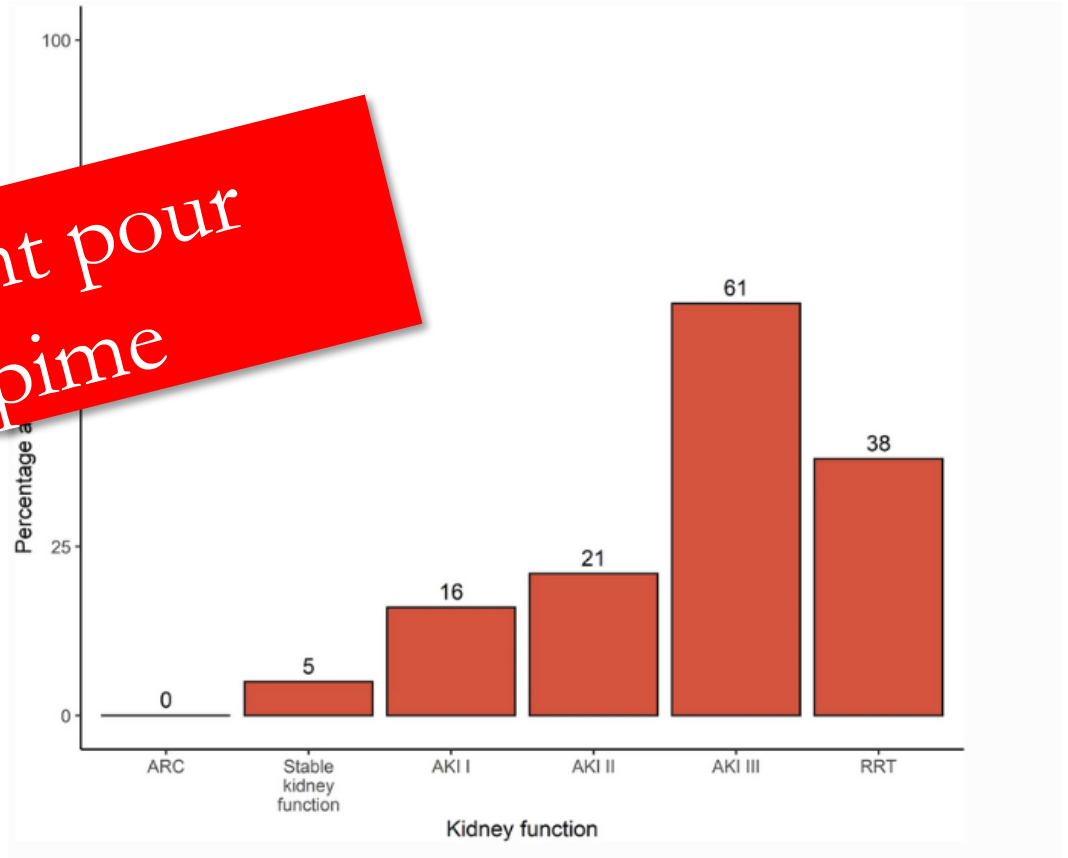
Pathogen-based target attainment of optimized continuous infusion dosing regimens of piperacillin-tazobactam and meropenem in surgical ICU patients: a prospective single center observational study

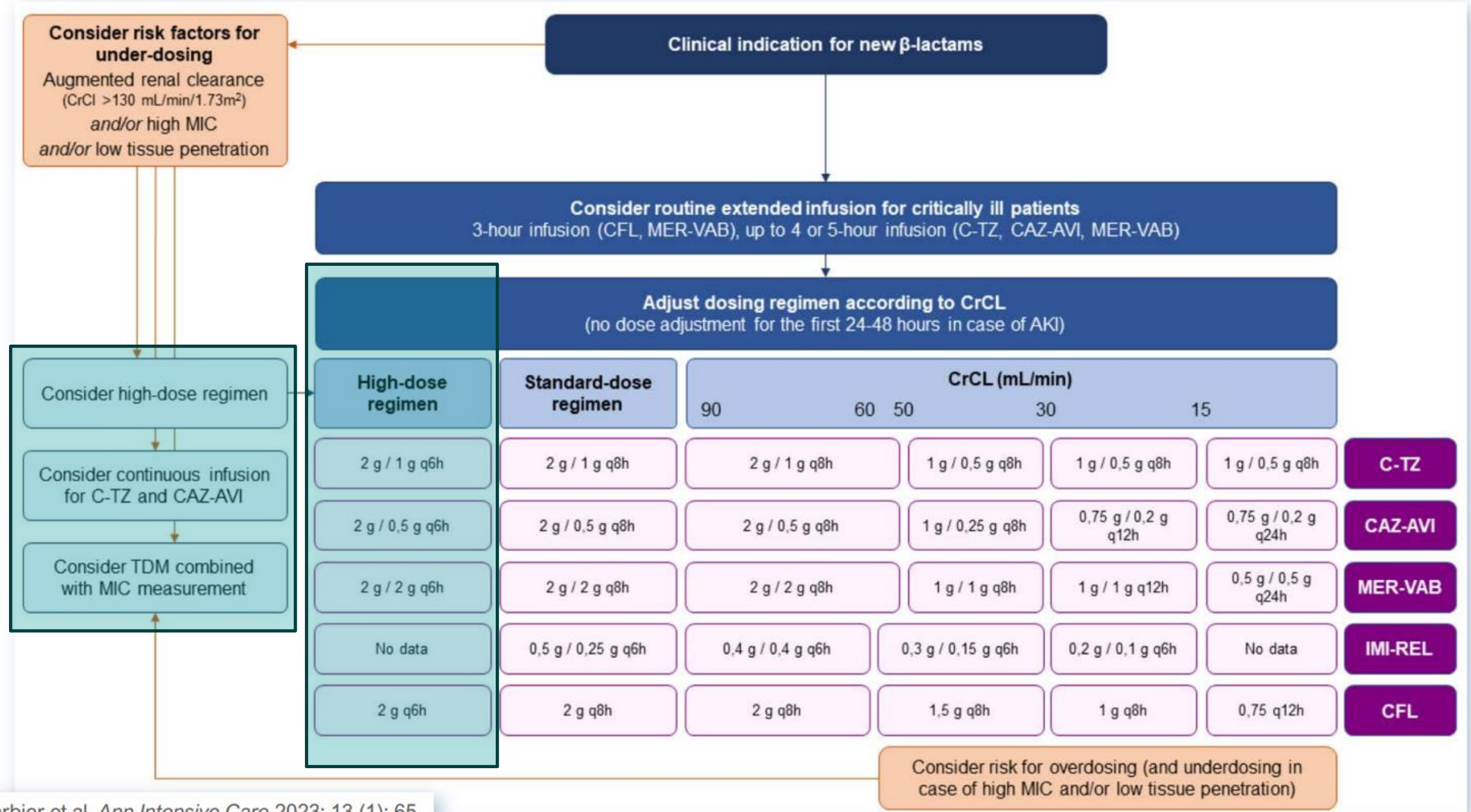
Thomas De Corte, Jarne Verhaeghe, Sofie Dhaese, Sarah Van Vooren, Jerina Boelens, Alain G. Verstraete, Veronique Stove, Femke Ongenae, Liesbet De Bus, Pieter Depuydt, Sofie Van Hoecke & Jan J. De Waele

Annals of Intensive Care **13**, Article number: 35 (2023) | Cite this article



Différent pour cefepime





Barbier et al. *Ann Intensive Care* 2023; 13 (1): 65

Dosage?

ORIGINAL

Effect of therapeutic drug monitoring-based dose optimization of piperacillin/tazobactam on sepsis-related organ dysfunction in patients with sepsis: a randomized controlled trial

Stefan Hagel[1,2*], Friedhelm Bach[3], Thorsten Brenner[4,5], Hendrik Bracht[6], Alexander Brinkmann[7], Thorsten Annecke[8,9], Andreas Hohn[8,10], Markus Weigand[5], Guido Michels[11], Stefan Kluge[12], Axel Nierhaus[12], Dominik Jarczak[12], Christina König[12], Dirk Weismann[13], Otto Frey[14], Dominic Witzke[3], Carsten Müller[15], Michael Bauer[16], Michael Kiehntopf[17], Sophie Neugebauer[2,17], Thomas Lehmann[18], Jason A. Roberts[19,20,21] and Mathias W. Pletz[1,2] on behalf of the TARGET Trial Investigators

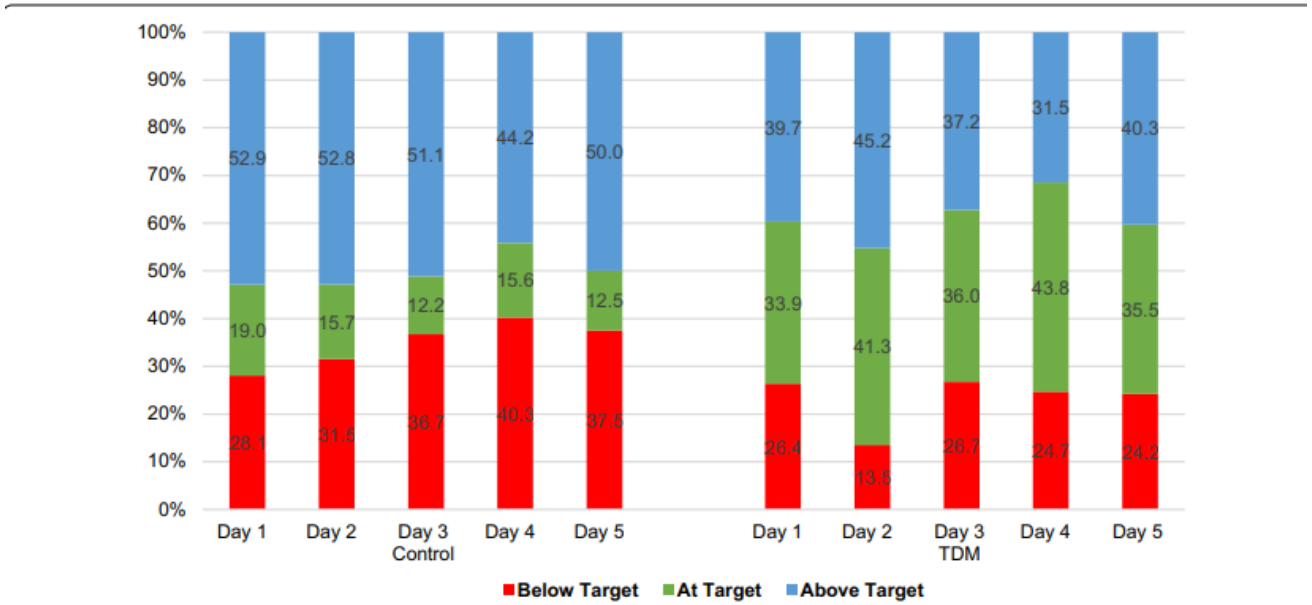


Fig. 3 Attainment of piperacillin target concentration in percent up to day 5 after randomization in patients with piperacillin TDM-guided therapy (TDM, right columns) and patients in the control group (control, left column). Within range (green), above range (blue) or below range (red) per the target range on a given day

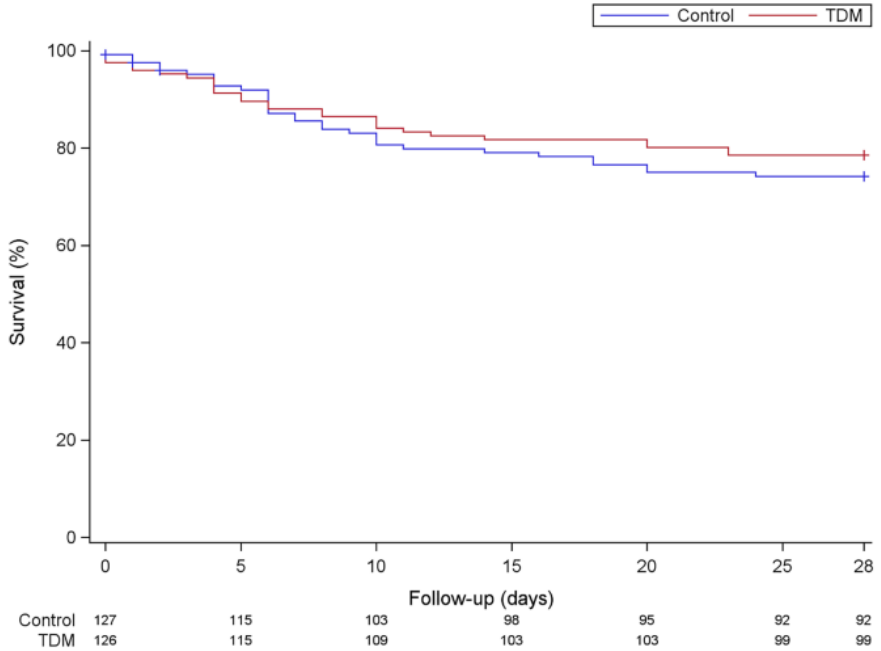


Fig. 2 Kaplan–Meier analysis. Overall survival rates at day 28 among patients with piperacillin TDM-guided therapy (TDM) and patients in the control group (control). Number of patients at risk for each group included in the analysis along the *x*-axis scale

RESEARCH Open Access

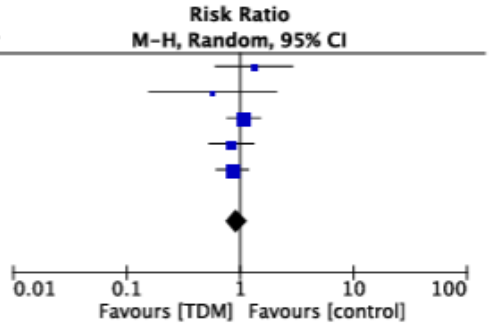
Efficacy of therapeutic drug monitoring-based antibiotic regimen in critically ill patients: a systematic review and meta-analysis of randomized controlled trials

Nozomi Takahashi[1,2*], Yutaka Kondo[3], Kenji Kubo[4], Moritoki Egi[5], Ken-ichi Kano[6], Yoshiyasu Ohshima[7] and Taka-aki Nakada[2]

A. 28-day mortality

Study or Subgroup	TDM Events	TDM Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Bartal 2003	12	43	8	38	6.4%	1.33 [0.61, 2.89]	2003
Waele 2014	3	21	5	20	2.3%	0.57 [0.16, 2.08]	2014
Ewoldt 2022	50	189	49	199	34.0%	1.07 [0.76, 1.51]	2022
Hagel 2022	27	125	32	124	19.6%	0.84 [0.53, 1.31]	2022
Roggeveen 2022	45	132	48	120	37.7%	0.85 [0.62, 1.18]	2022
Total (95% CI)		**510**		**501**	**100.0%**	**0.94 [0.77, 1.14]**	
Total events	137		142				

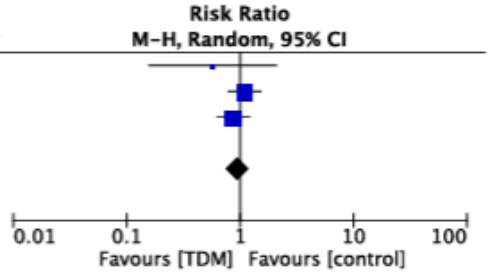
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.52$, df = 4 (P = 0.64); $I^2 = 0\%$
Test for overall effect: Z = 0.65 (P = 0.52)



B. Hospital mortality

Study or Subgroup	TDM Events	TDM Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Waele 2014	3	21	5	20	3.1%	0.57 [0.16, 2.08]	2014
Ewoldt 2022	53	189	51	199	48.0%	1.09 [0.79, 1.52]	2022
Roggeveen 2022	45	132	47	120	48.9%	0.87 [0.63, 1.21]	2022
Total (95% CI)		**342**		**339**	**100.0%**	**0.96 [0.76, 1.20]**	
Total events	101		103				

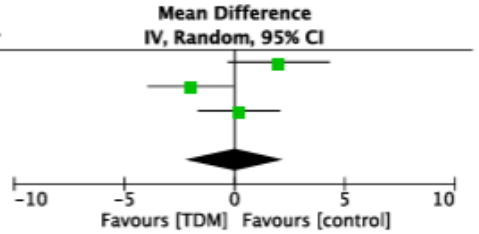
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.57$, df = 2 (P = 0.46); $I^2 = 0\%$
Test for overall effect: Z = 0.36 (P = 0.72)



C. ICU length of stay

Study or Subgroup	TDM Mean	TDM SD	TDM Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI	Year
Ewoldt 2022	10	11.1	189	8	11.9	199	30.8%	2.00 [-0.29, 4.29]	2022
Hagel 2022	9	8.1	125	11	7.4	124	34.2%	-2.00 [-3.93, -0.07]	2022
Roggeveen 2022	3.8	7.5	132	3.6	7.4	120	35.0%	0.20 [-1.64, 2.04]	2022
Total (95% CI)			**446**			**443**	**100.0%**	**0.00 [-2.18, 2.19]**	

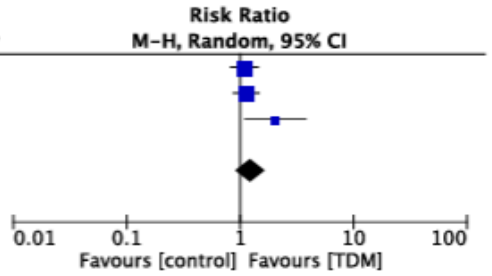
Heterogeneity: $Tau^2 = 2.66$; $Chi^2 = 7.07$, df = 2 (P = 0.03); $I^2 = 72\%$
Test for overall effect: Z = 0.00 (P = 1.00)



D. Clinical cure

Study or Subgroup	TDM Events	TDM Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Bartal 2003	32	43	26	38	40.4%	1.09 [0.82, 1.44]	2003
Waele 2014	19	21	16	20	42.3%	1.13 [0.87, 1.47]	2014
Hagel 2022	21	59	12	69	17.3%	2.05 [1.10, 3.80]	2022
Total (95% CI)		**123**		**127**	**100.0%**	**1.23 [0.91, 1.67]**	
Total events	72		54				

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 4.63$, df = 2 (P = 0.10); $I^2 = 57\%$
Test for overall effect: Z = 1.35 (P = 0.18)

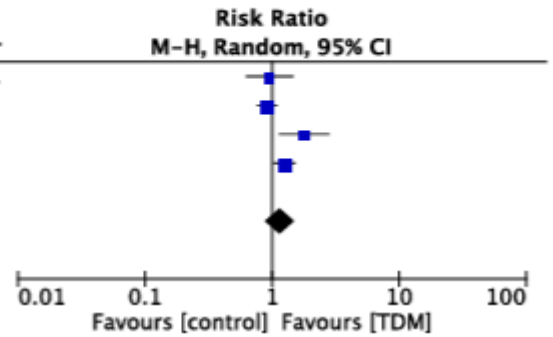


E. Target attainment in day 1

Study or Subgroup	TDM Events	TDM Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Waele 2014	14	21	14	20	19.0%	0.95 [0.63, 1.44]	2014
Ewoldt 2022	105	189	120	197	32.0%	0.91 [0.77, 1.08]	2022
Hagel 2022	41	121	23	121	17.9%	1.78 [1.14, 2.78]	2022
Roggeveen 2022	90	115	57	91	31.1%	1.25 [1.04, 1.50]	2022
Total (95% CI)		**446**		**429**	**100.0%**	**1.14 [0.88, 1.48]**	
Total events	250		214				

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 11.54$, df = 3 (P = 0.009); $I^2 = 74\%$

Test for overall effect: Z = 1.01 (P = 0.31)

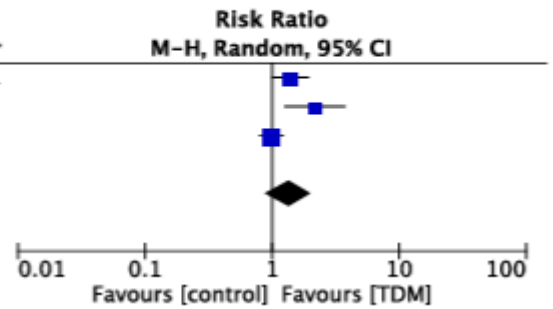


F. Target attainment at day 3

Study or Subgroup	TDM Events	TDM Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Waele 2014	18	19	13	19	35.0%	1.38 [1.00, 1.91]	2014
Hagel 2022	31	86	15	90	25.1%	2.16 [1.26, 3.72]	2022
Ewoldt 2022	69	116	64	106	39.9%	0.99 [0.79, 1.22]	2022
Total (95% CI)		**221**		**215**	**100.0%**	**1.35 [0.90, 2.03]**	
Total events	118		92				

Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 8.71$, df = 2 (P = 0.01); $I^2 = 77\%$

Test for overall effect: Z = 1.45 (P = 0.15)



Aide d'un logiciel?

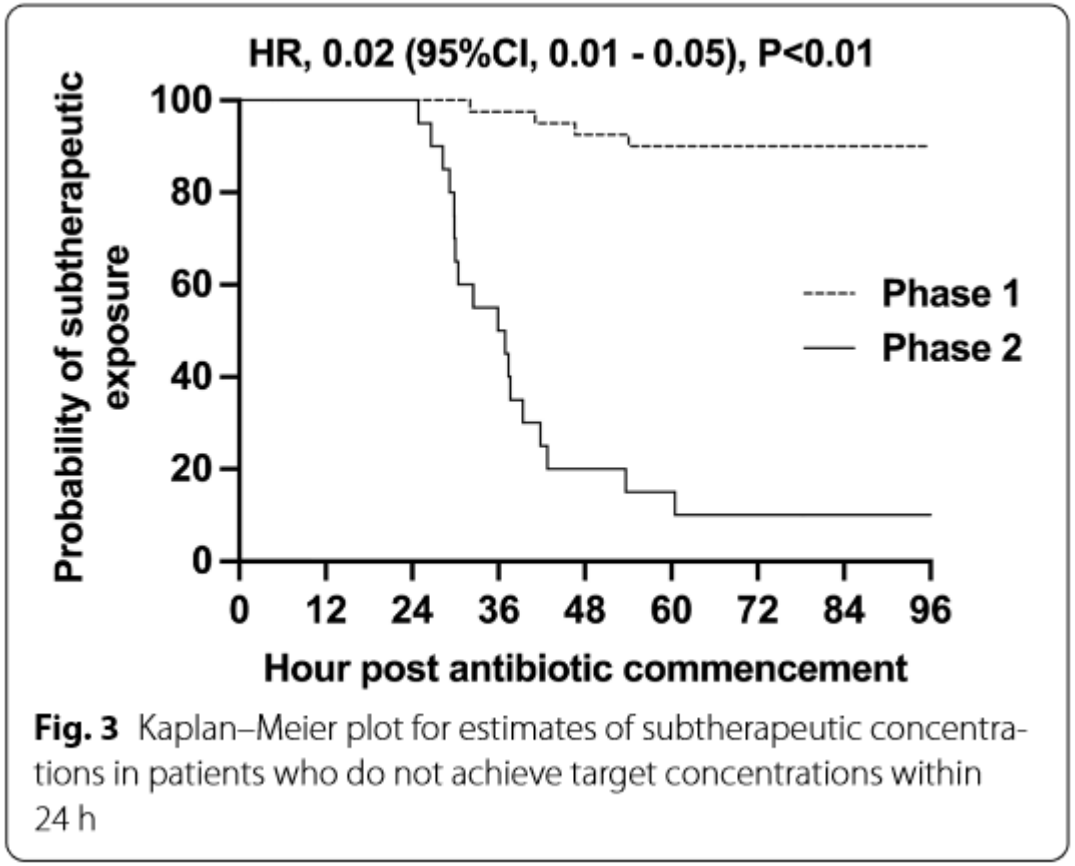
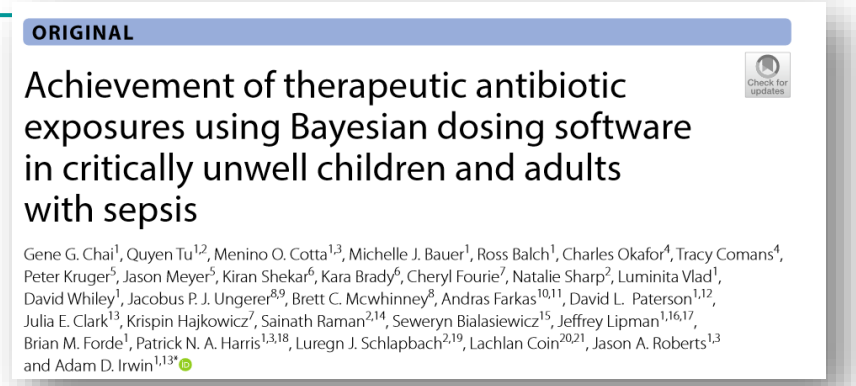


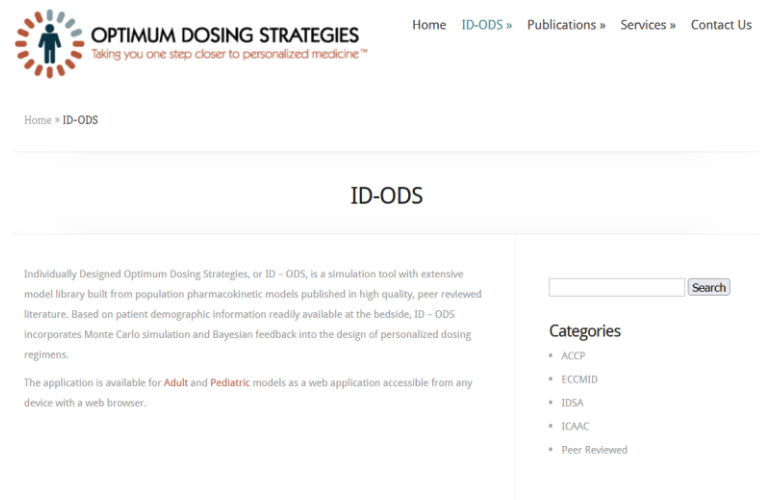
Fig. 3 Kaplan–Meier plot for estimates of subtherapeutic concentrations in patients who do not achieve target concentrations within 24 h



ORIGINAL

Achievement of therapeutic antibiotic exposures using Bayesian dosing software in critically unwell children and adults with sepsis

Gene G. Chai[1], Quyen Tu[1,2], Menino O. Cotta[1,3], Michelle J. Bauer[1], Ross Balch[1], Charles Okafor[4], Tracy Comans[4], Peter Kruger[5], Jason Meyer[5], Kiran Shekar[6], Kara Brady[6], Cheryl Fourie[7], Natalie Sharp[2], Luminita Vlad[1], David Whiley[1], Jacobus P. J. Ungerer[8,9], Brett C. Mcwhinney[8], Andras Farkas[10,11], David L. Paterson[1,12], Julia E. Clark[13], Krispin Hajkowicz[7], Sainath Raman[2,14], Seweryn Bialasiewicz[15], Jeffrey Lipman[1,16,17], Brian M. Forde[1], Patrick N. A. Harris[1,3,18], Luregn J. Schlapbach[2,19], Lachlan Coin[20,21], Jason A. Roberts[1,3] and Adam D. Irwin[1,13*]



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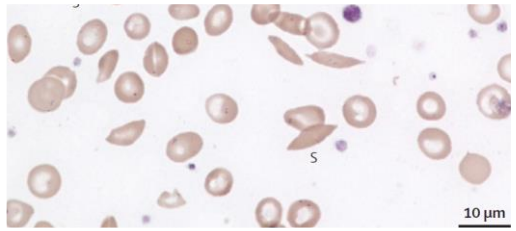
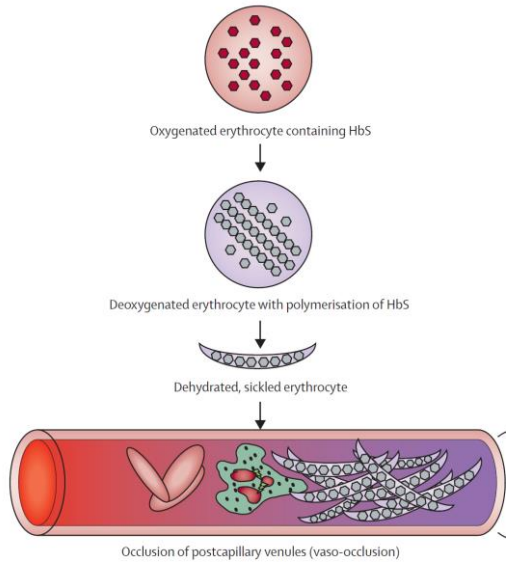
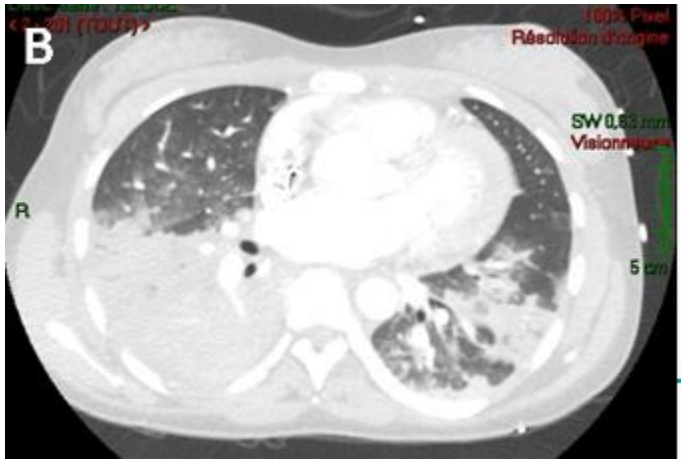
En dehors de la réanimation?

Drépanocytose





- Jeune
- Asplénie
- Infection rapidement fatale
- Antibiotique fréquent
- Anémie avec hyperdébit cardiaque
- 80% hyperclairant



Rees, Lancet 2010

Increased vancomycin dosing requirements in sickle cell disease due to hyperfiltration-dependent and independent pathways

Table 1. Clinical characteristics in the sickle cell disease and non-sickle cell disease groups.

	HgbSS	HgbAA control	*P*	
N	96	96		
Age (years)	29 (24-34)	30 (22-34)	0.370	
Gender (male %)	53	53	NS	
Weight (kg)	69 (59-78)	70 (60-76)	0.671	
Race (AA %)	97	97	NS	
Length of treatment (days)	5 (3-7)	5 (3-7)	0.794	
Doses received during treatment	12 (7-18)	10 (7-16)	0.165	
Baseline SCr (mg/dL)	0.59 (0.52-0.73)	0.69 (0.57-0.82)	0.002	0.
Baseline CrCl (mL/min)	137 (114-165)	120 (102-150)	0.018	
Baseline eGFR (mL/min/1.73 m^2)	149 (138-160)	141 (126-154)	0.002	1
Trough level at steady state (mg/L)	8.7 (6.5-11.5)	8.8 (6.5-12.4)	0.557	9
Daily dose to reach trough level (gram/day)	3 (2.3-3.5)	2.5 (2.0-3.0)	0.013	
Daily dose/weight at trough level (gram/day/kg)	0.043 (0.034-0.049)	0.036 (0.032-0.044)	0.003	(
Acute kidney injury (%)	4.2	5.2	0.749	

Median (interquartile range) or percent is shown. Patients' characteristics were compared using Mann-Whitney U for categorical variables.

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CLINICAL THERAPEUTICS

Population Pharmacokinetics of Cefotaxime and Dosage Recommendations in Children with Sickle Cell Disease

Elsa Maksoud,[a] Berengere Koehl,[b,c] Aude Facchin,[a] Phuong Ha,[a] Wei Zhao,[a] Florentia Kaguelidou,[a,d,f] Malika Benkerrou,[b] Patricia Mariani,[e] Albert Faye,[c,f] Mathie Lorrot,[c,f*] Evelyne Jacqz-Aigrain[a,d,f]

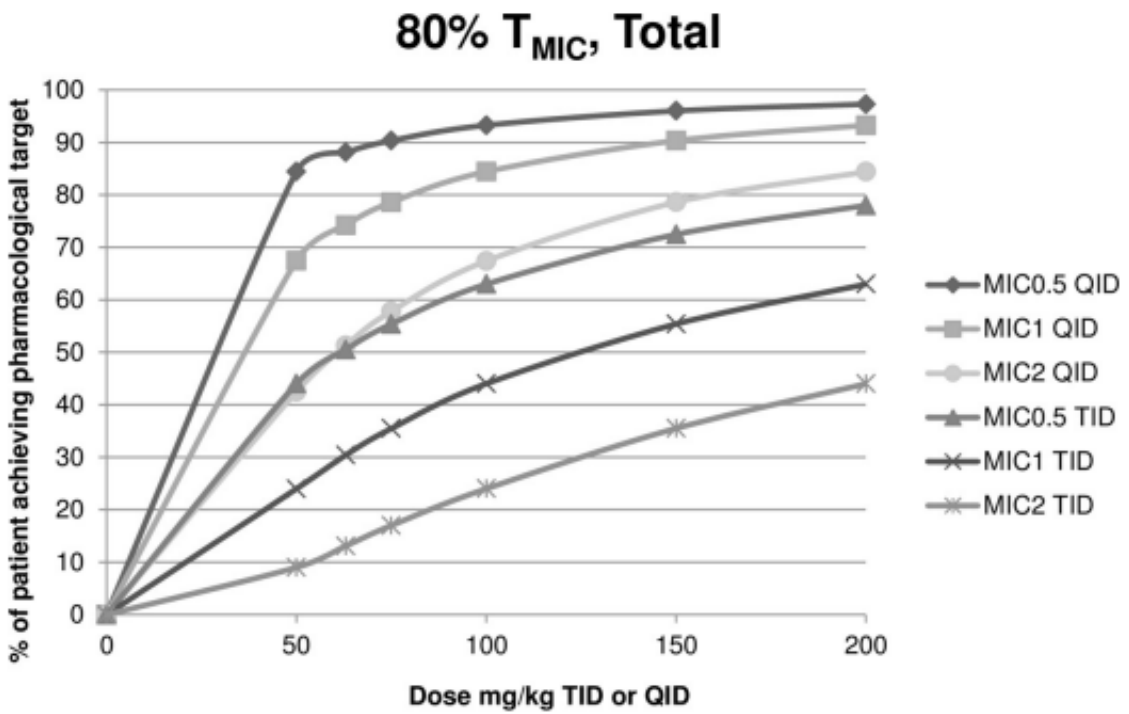


FIG 3 Target attainment rates for the 1,000 simulated trials for MICs of 0.5 mg/liter, 1 mg/liter, and 2 mg/liter are presented as a function of dose (in milligrams per kilogram) administered three times per day (TID) or four times per day (QID). The T_{MIC} target was 80%.

Profound underdosing of β-lactams in patients with sickle-cell disease

Jérôme Cecchini[1,2]*, Anne Hulin[3], Anoosha Habibi[4,5], Armand Mekontso Dessap[1,2]† and Keyvan Razazi[1,2]†

Journal of Antimicrobial Chemotherapy

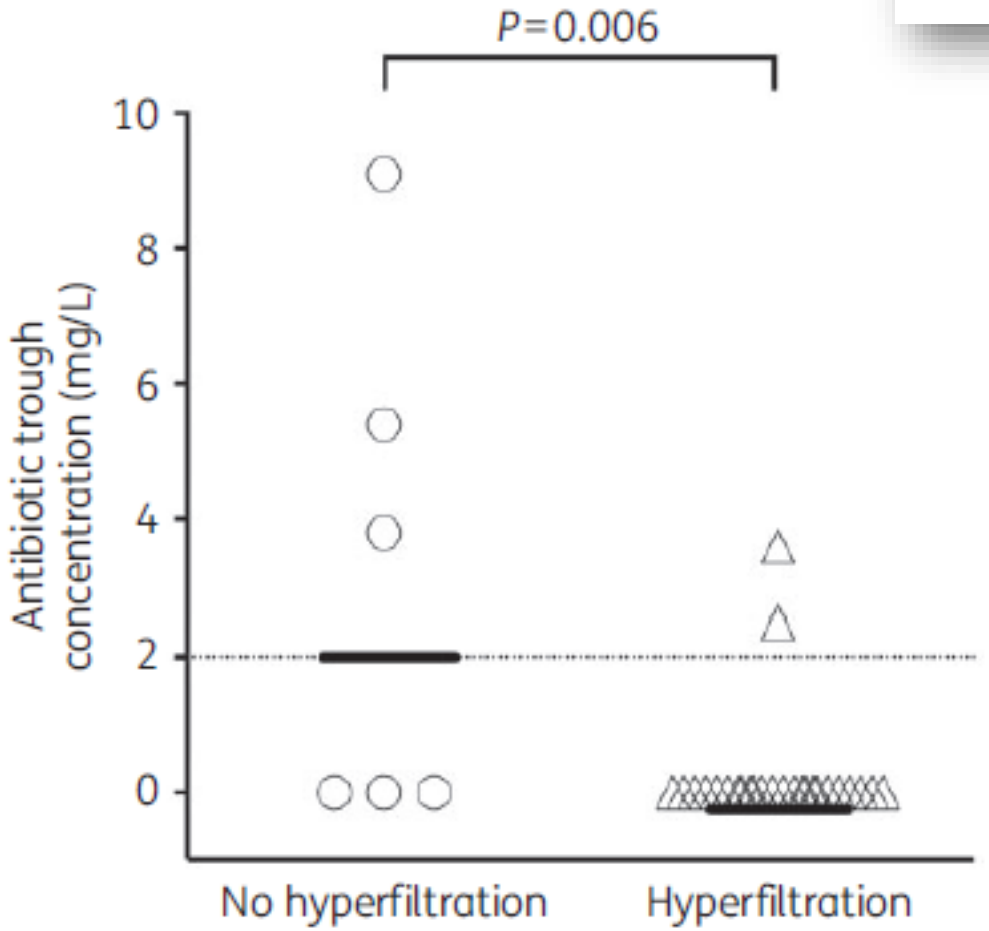
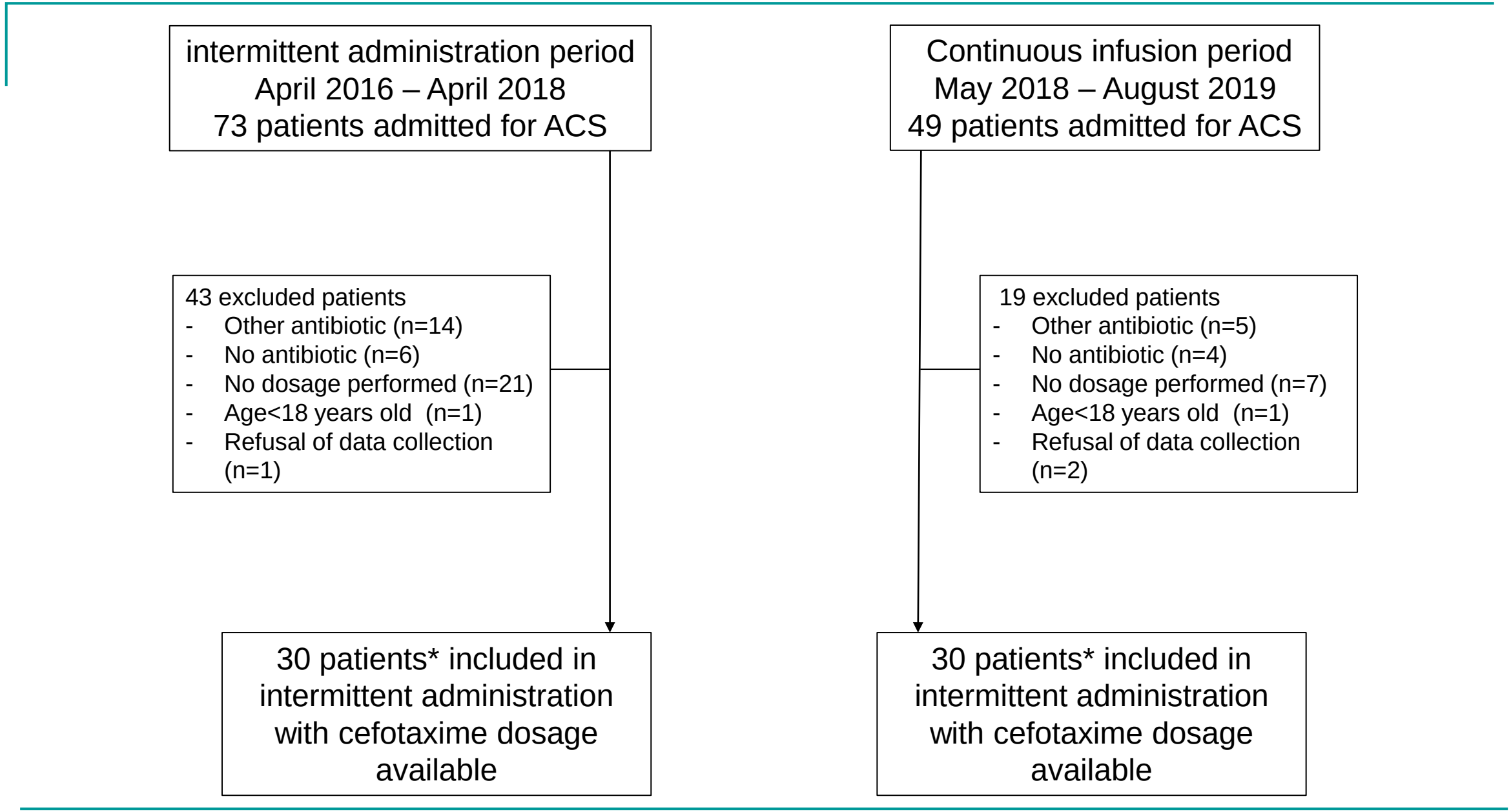
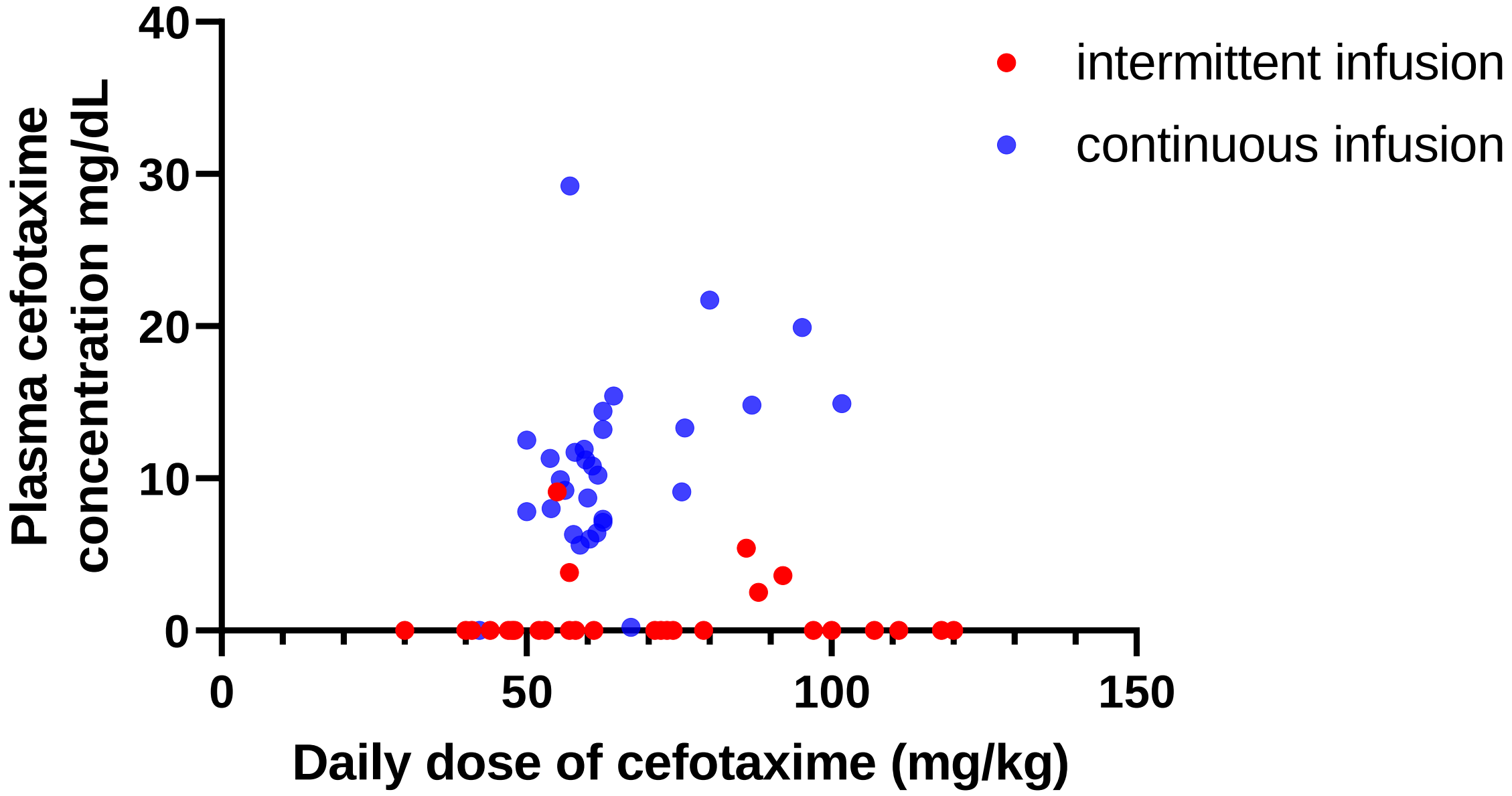
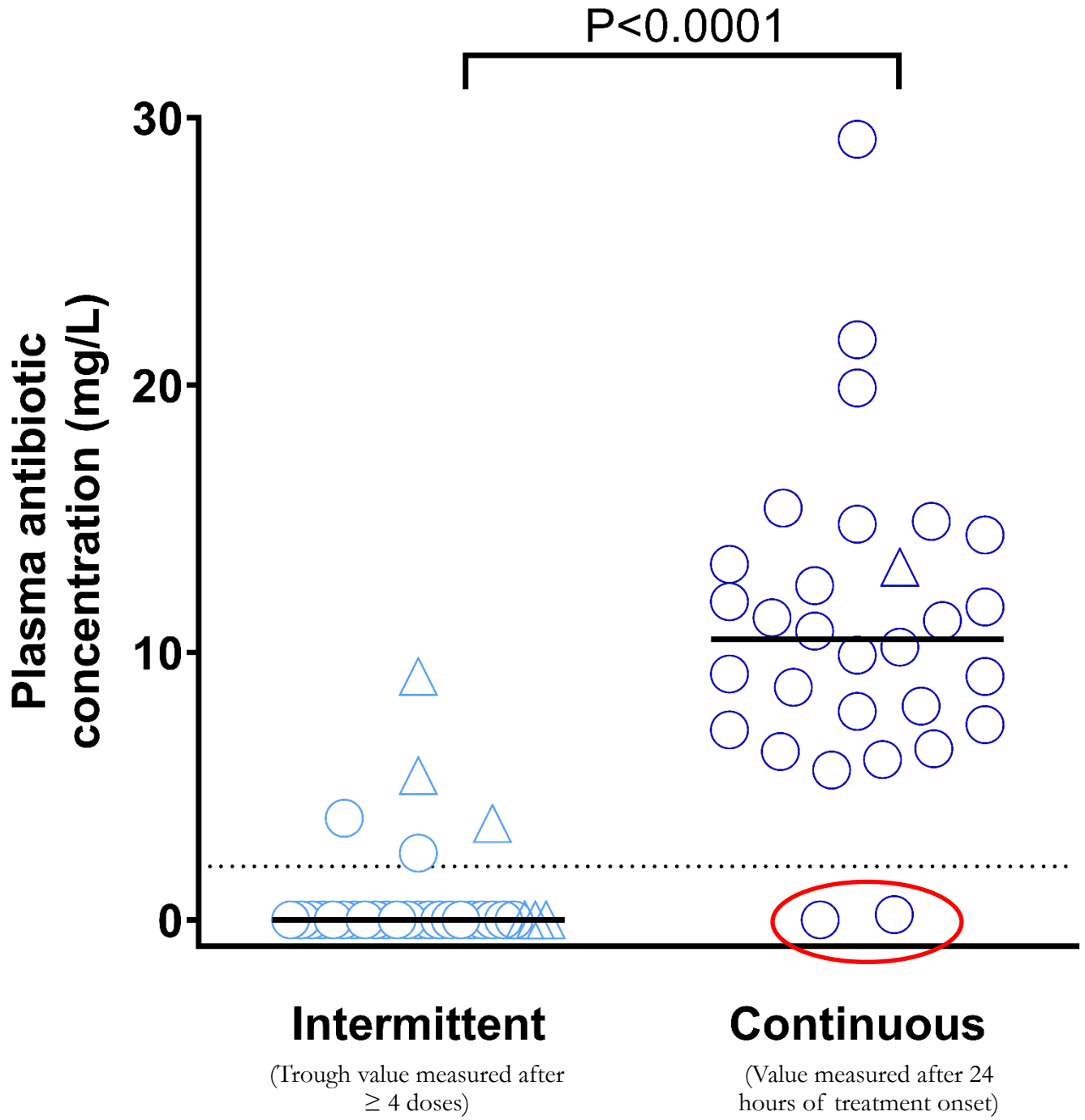


Figure 1. Antibiotic trough concentration in patients with (triangles) or without (circles) hyperfiltration, with median values (bars). The Mann–Whitney test was used to compare data.



*Two patients got the two infusion methods

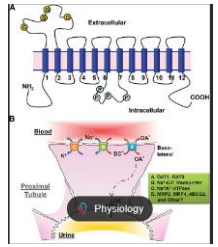

Plasma cefotaxime concentration mg/dL
40
30
20
10
0
0
50
100
150
Daily dose of cefotaxime (mg/kg)
intermittent infusion
continuous infusion

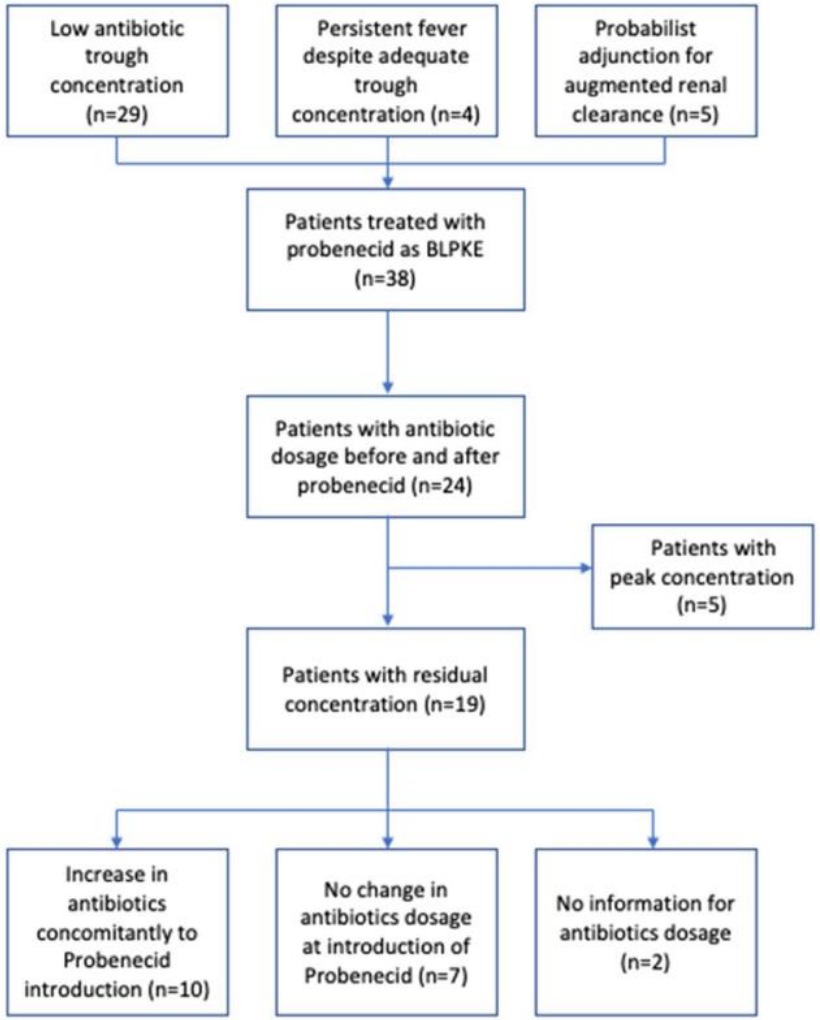

P<0.0001
30
20
10
0
Plasma antibiotic concentration (mg/L)
Intermittent
(Trough value measured after ≥ 4 doses)
Continuous
(Value measured after 24 hours of treatment onset)

Original article

Probenecid, an old β-lactams pharmacokinetic enhancer for a renewed use: A retrospective study

P. Huriez[a,*], C. Ourghanlian[b], K. Razazi[c], W. Vindrios[a], A. Hulin[d], R. Lepeule[e], A. Habibi[f], S. Gallien[g]





Variation après probenecid

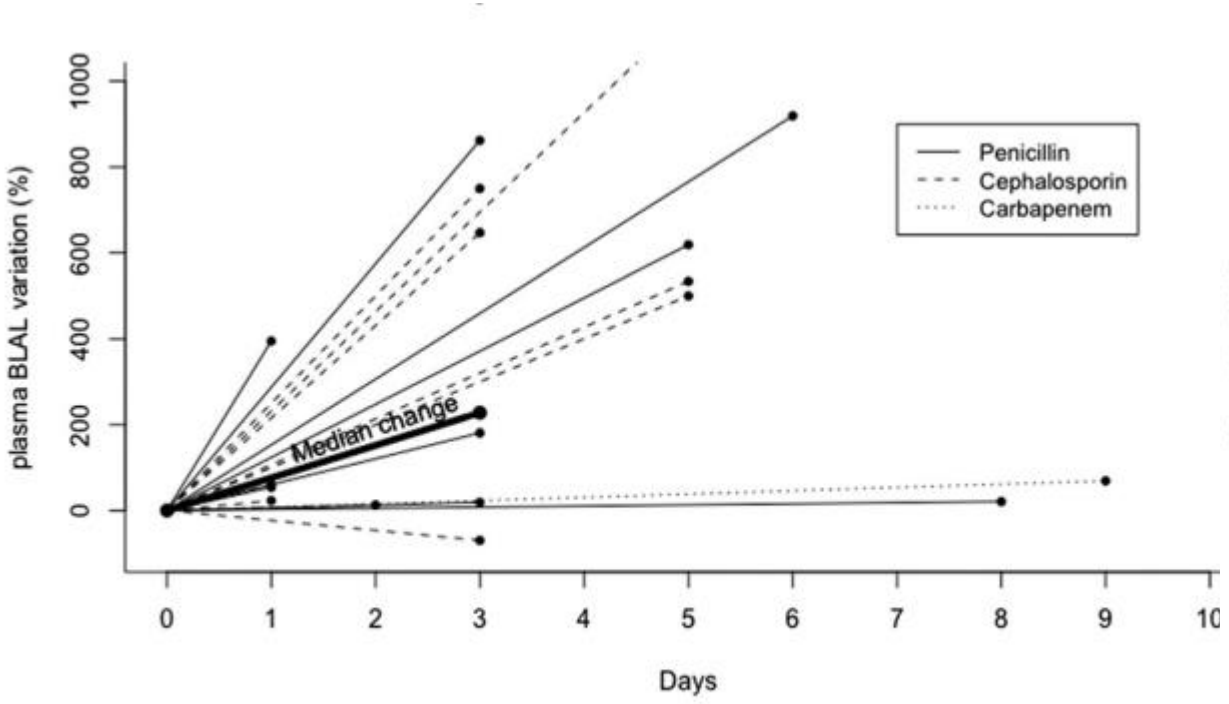


Fig. 2. Change In plasma antibiotic trough concentration with probenecid.

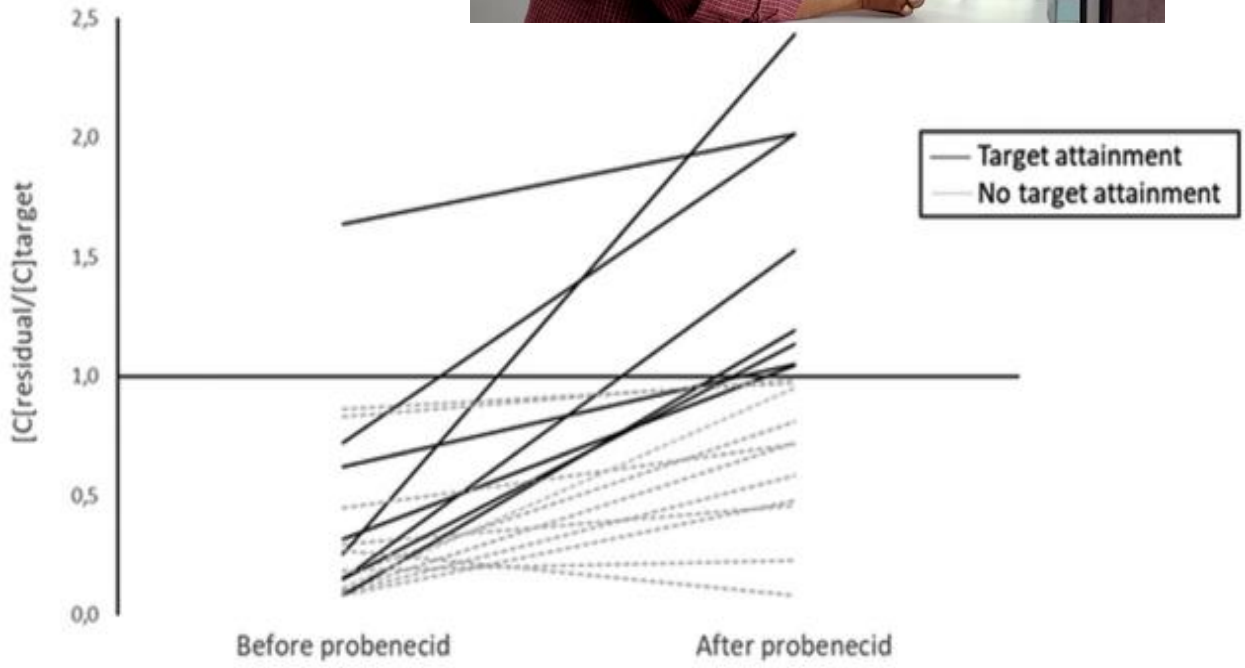


Fig. 3. Pharmacological target reached after probenecid introduction.

En onco-hématologie

- 10%-100% of patients

- FDR:
  - aplasie fébrile
  - age <50-65 years,
  - Malade d’hématologie
  - Créatininémie basse

Conclusion

- Fréquent: jeune avec créat basse
- Diurèse sur 8h
- Associée à des sous dosages (voir indosable)
- Non associée à un mauvais pronostic
- Doser au moindre doute ou si index thérapeutique faible ou bactérie difficile à traiter (BGN++)
- Stratégies pour optimiser ATB chez les patients avec ARC
  - Administration dose maximale approuvée et au délà
  - Administration prolongée ou continue
  - Probenecid?
  - Changer pour ATB alternatif non à élimination rénale?