HYPERCLAIRANCE RÉNALE:

PHYSIOPATHOLOGIE ET IMPACT CLINIQUE

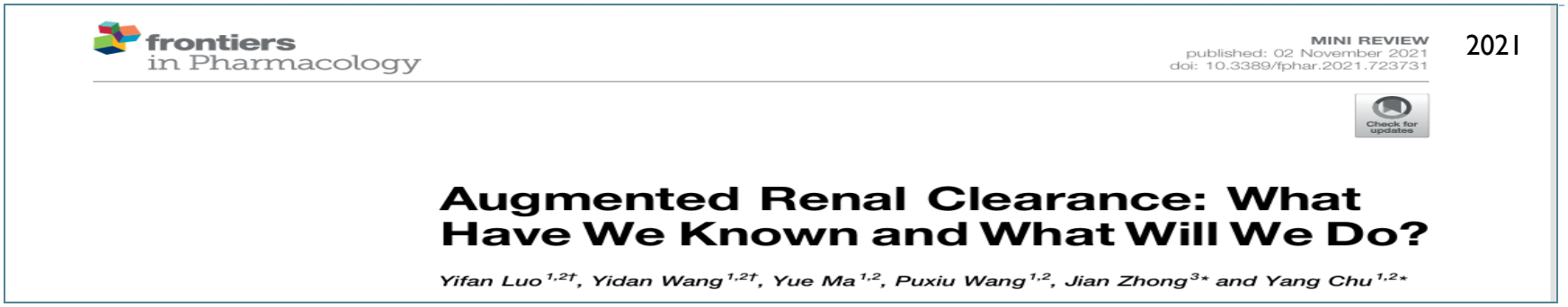
Pr Amel MOKLINE

Service de Réanimation des Brûlés

Centre de Traumatologie
Et de Grands
Brulés

☑ Je n'ai pas de lien d'intérêt potentiel à déclarer

HYPERCLAIRANCE RÉNALE (HCR)



2021

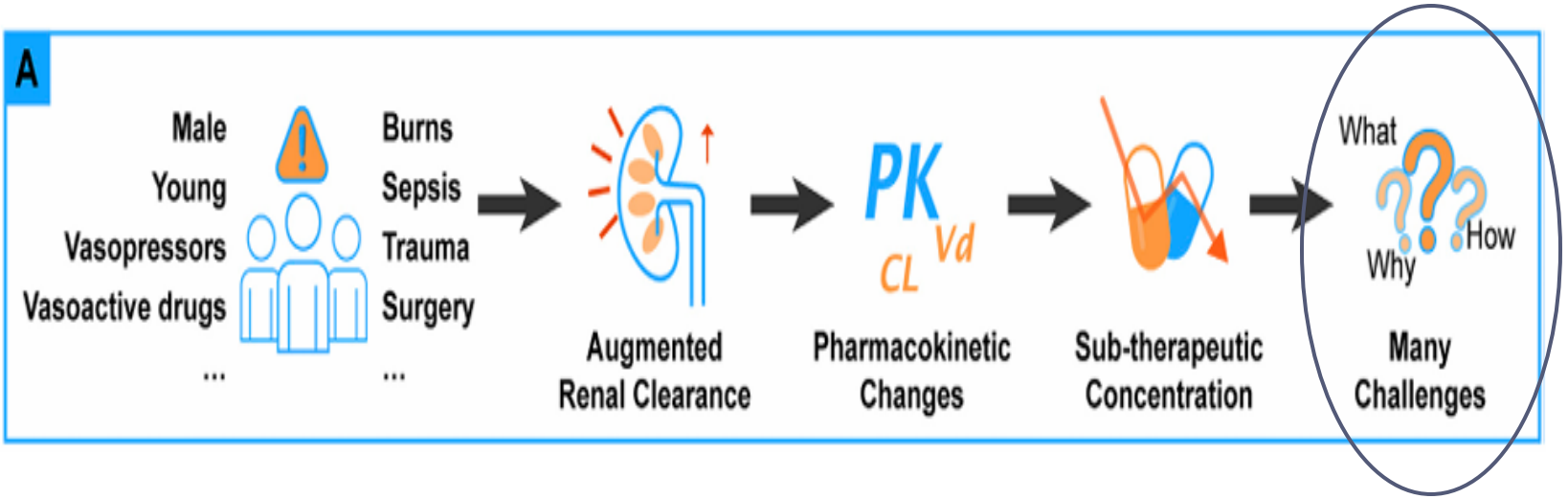
HCR:

- Entité clinique sous estimé, et sous diagnostiquée en ICU jusqu'au 2010 (concept individualisé par Udy et al en 2010) .
- correspond à une augmentation supra-physiologique de la clairance de la créatinine.
- définie par une clairance de la créatinine supérieure à 130 mL/min/1,73m2

Bilbao-Meseguer et al., 2018; Dhaese et al., 2021; Nicolau et al., 2021; Tang et al., 2021

HYPERCLAIRANCE RÉNALE (HCR)

- HCR a suscité l'intérêt des cliniciens et des pharmacologues
- Elle expose à un risque de sous dosage des médicaments pour les patients de réanimation et d'échec thérapeutique



INCIDENCE DE L'HYPERCLAIRANCE RÉNALE (HCR)

Augmented renal clearance in critical illness: "The Elephant in the ICU"?

J. P. BAPTISTA [1], A. A. UDY [2, 3]

TABLE I.—*Selected epidemiological data from recent studies investigating ARC - only studies with more than 200 CL_{CR} measurements were included.*

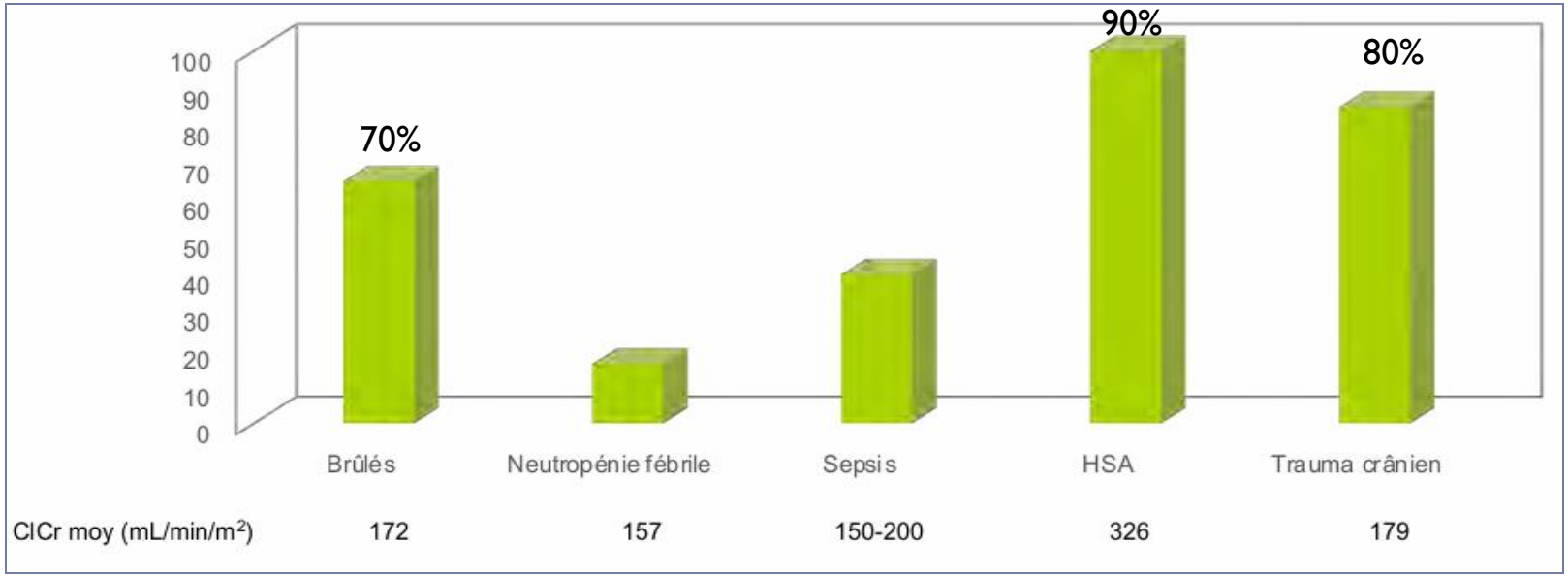
First author	Publication year	Country	ICU Patients (N.)	Measurements (N.)	ARC criteria (mL/m)	Urine time collection (h)	ARC incidence
Campassi [10]	2014	Brasil	363	363	>120	24	28%
Grootaert [18]	2012	Belgium	1317	4019	≥120	24	41%
Lautrette [19]	2012	France	32	224	>140	24	47%
Claus [12]	2013	Belgium	128	599	≥130	24	51.6%
De Waele [13]	2015	Belgium	1081	4472	≥130	24	55.8%
Baptista [6]	2014	Portugal	54	644	>130	8	55.6%
Udy [2]	2013	Australia	71	213	≥130	2	57.7%
Udy [5]	2014	Australia, Portugal, Malasya, Hong-Kong	281	1660	≥130	8	65.1%

ICU: intensive care unit; ARC: augmented renal clearance; h: hours.

INCIDENCE DE L'HYPERCLAIRANCE RÉNALE (HCR)

Selon la catégorie des patients

22es JNI, Montpellier du 30/08 au 1er/09/2021



En tunisie (Sce Rea brulés): Etude 29 mois (Octobre 2017 – Février 2020)

- ✓Prévalence 77%
- ✓Age: 40 ans dont 72% des hommes
- ✓SCB=39%

PHYSIOPATHOLOGIE DE L'HYPERCLAIRANCE RÉNALE

2019

Anaesth Crit Care Pain Med 38 (2019) 335–336

SFAR
Société Française d'Anesthésie et de Réanimation

Editorial

Augmented renal clearance: A real phenomenon with an uncertain cause

Physiopathologie :

- complexe, non univoque*
- Facteurs multiples :
  - intrinsèques liées au patient (âge, sexe, creatinine sg…)
  - extrinsèques (cause d'hospitalisation en USI ; gravité; mesures de réanimation…)

PHYSIOPATHOLOGIE DE L'HYPERCLAIRANCE RÉNALE

Physiopathologie :

- Etat hyperkinétique (sepsis, brulures, trauma…)

  Augmentation du débit cardiaque → hausse du flux rénal → **hyperfiltration**

- conséquences de la réanimation :

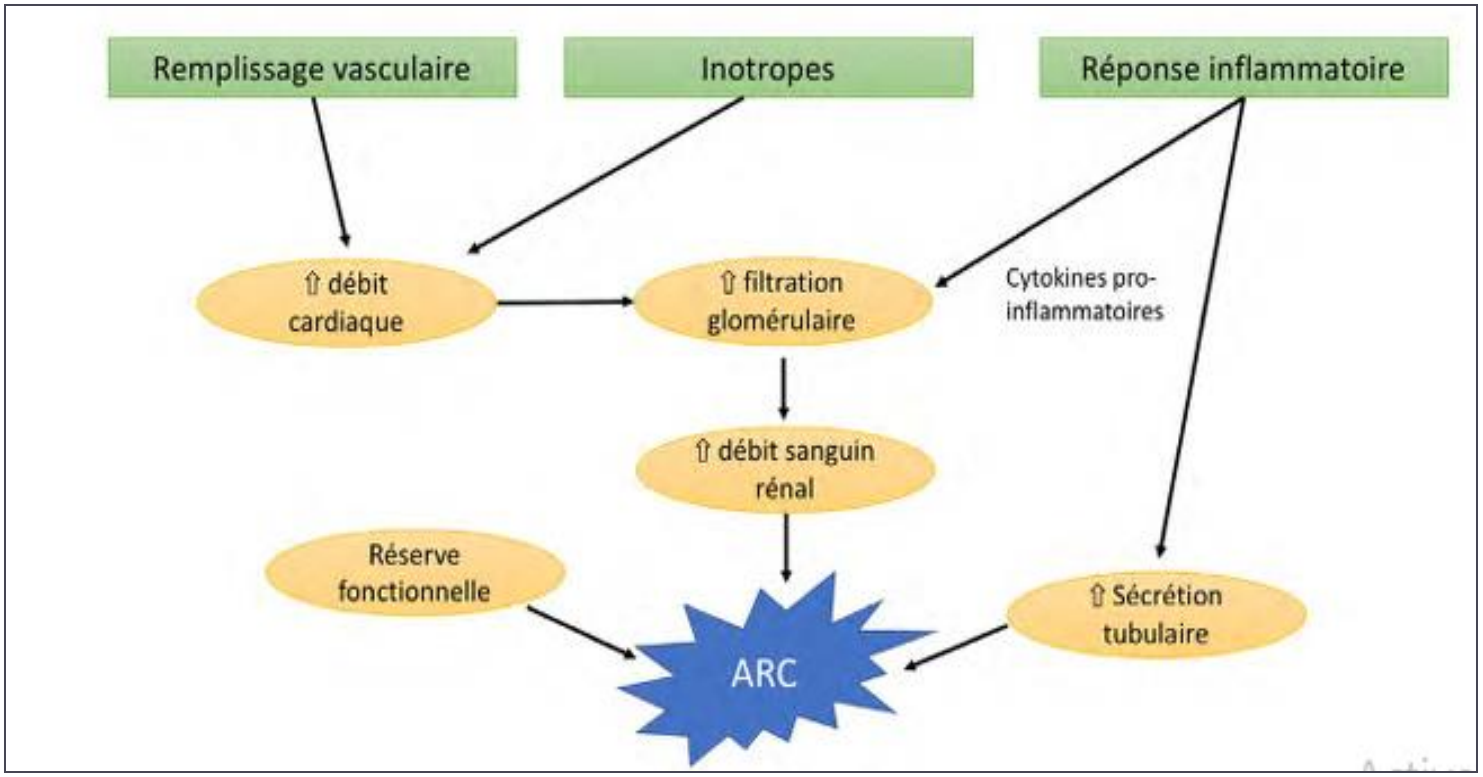
  Inflation hydrique, vasopresseurs, sepsis → **vasodilatation artériolaire rénale paradoxale**.

- **Reserve fonctionnelle rénale** par inhibition de la vasomotricité artériolaire

  capacité du rein à augmenter DFG face à des stimuli++ avec VD par liberation de PG et endotheline relaxante like)

PHYSIOPATHOLOGIE DE L'HYPERCLAIRANCE RÉNALE

Mécanismes de l'hyperclairance en USI



PHYSIOPATHOLOGIE DE L'HYPERCLAIRANCE RÉNALE

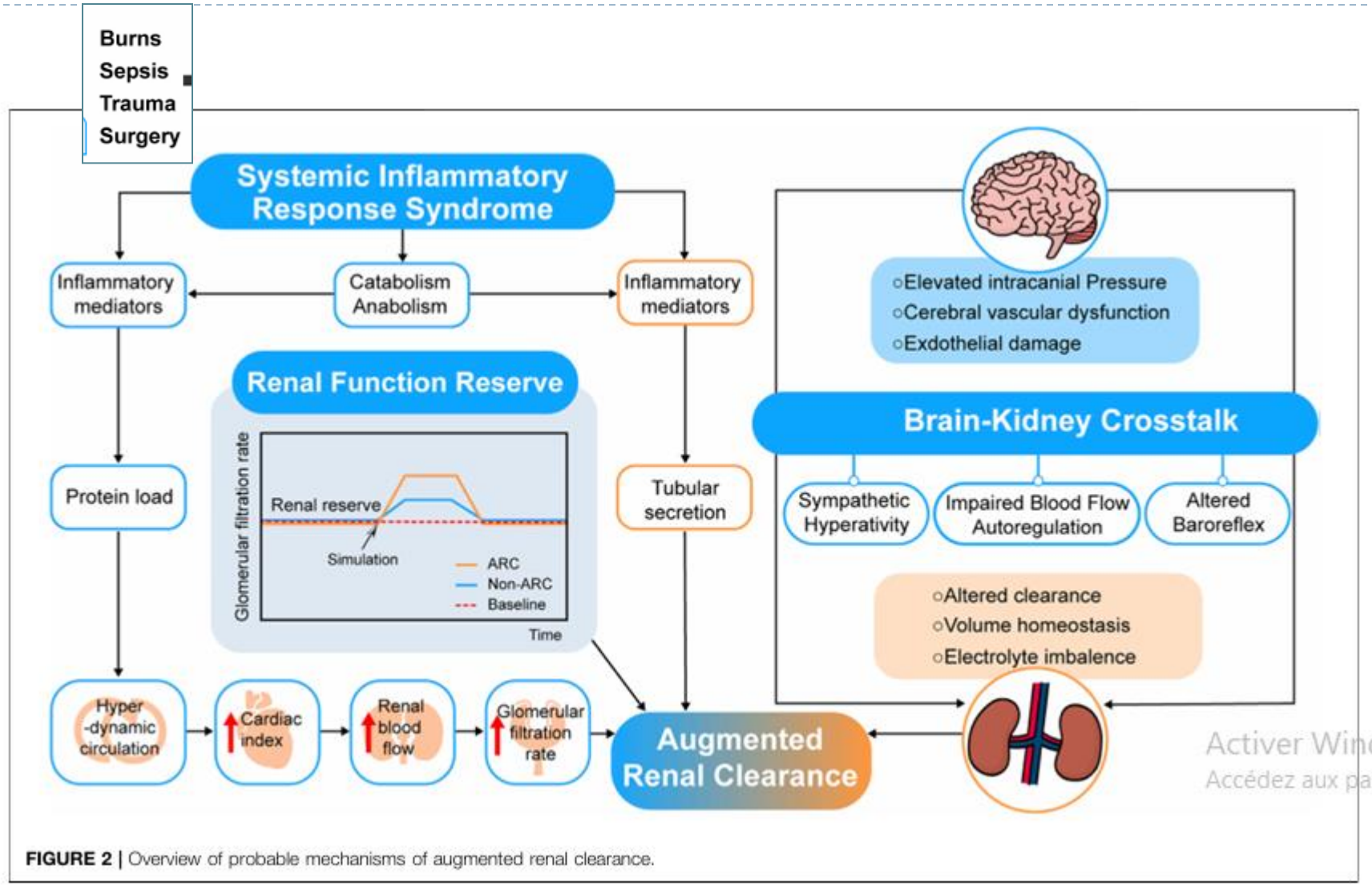


FIGURE 2 | Overview of probable mechanisms of augmented renal clearance.

Yifan Luo1,and al . Frontiers Pharmaco. 2021

FACTEURS DE RISQUE DE L'HYPERCLAIRANCE RÉNALE

Udy et al. Critical Care 2013, 17:R35
http://ccforum.com/content/17/1/R35

CRITICAL CARE

2013

RESEARCH Open Access

Augmented renal clearance in septic and traumatized patients with normal plasma creatinine concentrations: identifying at-risk patients

Andrew A Udy[1,2*], Jason A Roberts[1,2,3], Andrew F Shorr[4], Robert J Boots[1,2] and Jeffrey Lipman[1,2]

- ✓ 71 patients (sepsis n = 43, multi-trauma n = 28)
- ✓ **In multivariate analysis**:
  - -age ≤50 years,
  - - trauma,
  - - SOFA score ≤4

were identified as significant risk factors.

SCORES DE PREDICTION D'HYPERCLAIRANCE RÉNALE

ARC SCORE

PARAMETERS	SCORE
Age ≤ 50	6
Trauma	3
Modified SOFA ≤ 4	1
Interpretation: 0–3: Low Risk; 4–6: Intermediate Risk; ≥ 7: High Risk	

Udy AA, and al. Critical Care. 2013;17(1):1–9. doi: 10.1186/cc12544.

ARCTIC SCORE[10]

PARAMETERS	SCORE
Age < 56	4
Age b/w 56 - 75	3
S.Cr < 0.7 mg/dL	3
Male patient	2
Interpretation: ≥ 6: Increased risk for augmented renal clearance	

Saran S, and al. Indian J Crit Care Med. 2020;24(Suppl 3):S129–S134.

SCORES DE PREDICTION D'HYPERCLAIRANCE RÉNALE

Table 2. 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%

ARC = augmented renal clearance; ARCTIC = augmented renal clearance in trauma intensive Care (ARCTIC); SOFA = sequential organ failure assessment score; SCr = serum creatinine concentration; pt = point; pts = points.

Sherif Hanafy Mahmoud and al. Pharmaceutics 2017, 9, 36;

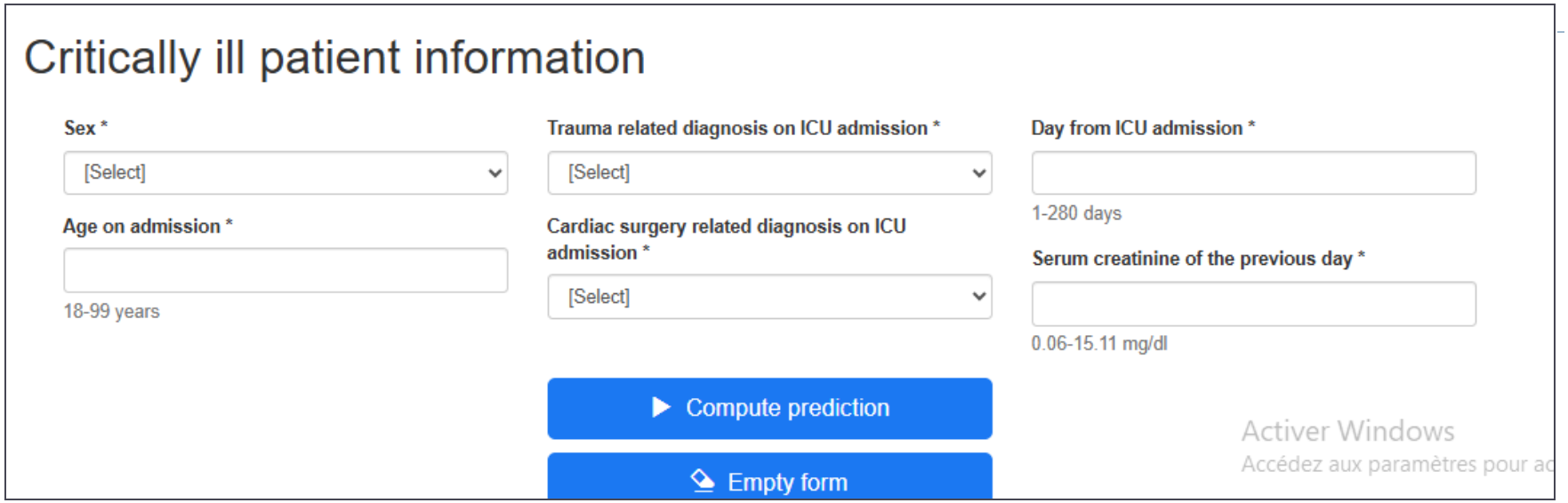
Development and External Validation of an Online Clinical Prediction Model for Augmented Renal Clearance in Adult Mixed Critically Ill Patients: The Augmented Renal Clearance Predictor

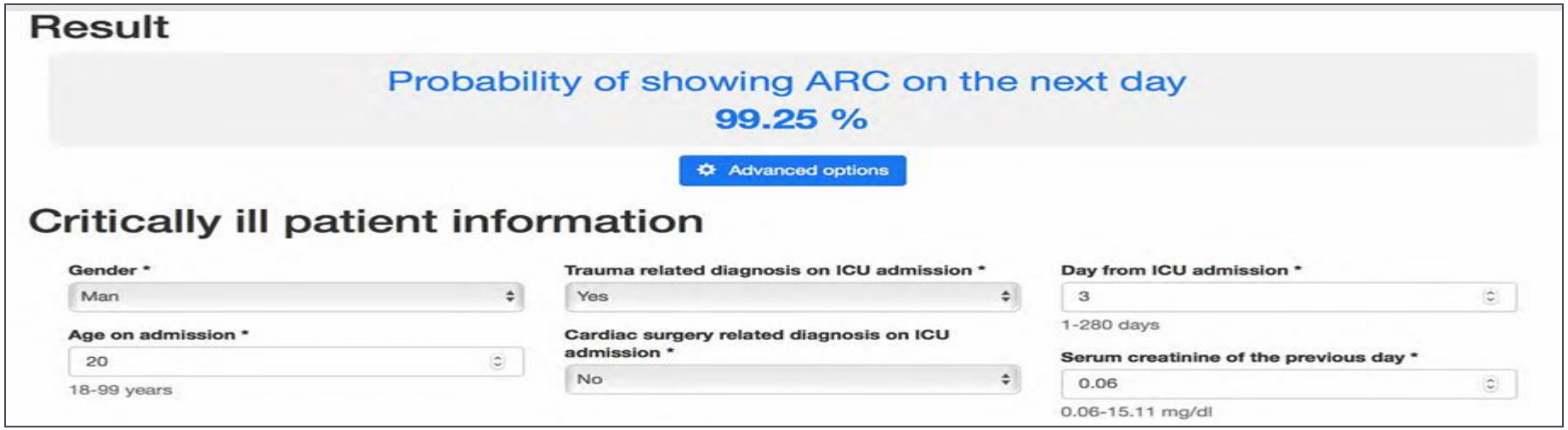
Critical Care Medicine 48(12):p e1260-e1268, December 2020. | ***DOI:*** 10.1097/CCM.0000000000004667

Augmented renal clearance on the next day can be predicted with good performance during ICU stay, using routinely collected clinical information that is readily available at bedside. Our augmented renal clearance predictor is available at www.arcpredictor.com.

ARC PREDICTOR

www.arcpredictor.com





Sunder et al. Journal of Intensive Care 2014, 2:31
http://www.jintensivecare.com/content/2/1/31

JOURNAL OF INTENSIVE CARE

REVIEW Open Access

2014

Estimation of renal function in the intensive care unit: the covert concepts brought to light

Sham Sunder, Rajesh Jayaraman*, Himanshu Sekhar Mahapatra, Satyanand Sathi, Venkata Ramanan, Prabhu Kanchi, Anurag Gupta, Sunil Kumar Daksh and Pranit Ram

Table 1 Salient features of various methods that could be employed to measure GFR in ICU setup

Sl no	Methods	Merits	Demerits
1	CG formula	Easily computable	Highly inaccurate in the critical care setup. Considerable degree of GFR overestimation
2	4-variable MDRD	More accurate than CG. May offer value close to 6-variable MDRD in healthier patients with preserved BUN/Cr ratio	Dependency on creatinine. May not be accurate when BUN/Cr ratio is increased. Does not take into account blood urea nitrogen and albumin. Overestimation of GFR when baseline GFR is high
3	6-variable MDRD	BUN and serum albumin are taken into account. More accurate when BUN/CR ratio is increased. Better concordance correlation coefficient when compared with CG and 4-variable MDRD	Dependency on creatinine. Ongoing creatinine production and its fluid balance variations are not taken into account. Less accurate when compared with cystatin C and novel methods
4	CKD-EPI formula	Greater precision and reliability when compared with MDRD. More accurate when GFR >60 ml/min/1.73 m^2	Not validated extensively in hospitalized and sick individuals. Dependency on serum creatinine
5	24-h creatinine clearance	More accurate when compared to CG and MDRD formulae	Collection of urine is an issue. Cannot provide immediate results. Becomes a problem when rapid administration of drugs is essential

Sunder et al. Journal of Intensive Care 2014, 2:31
http://www.jintensivecare.com/content/2/1/31

JOURNAL OF INTENSIVE CARE

REVIEW Open Access

Estimation of renal function in the intensive care unit: the covert concepts brought to light

2014

Sham Sunder, Rajesh Jayaraman*, Himanshu Sekhar Mahapatra, Satyanand Sathi, Venkata Ramanan, Prabhu Kanchi, Anurag Gupta, Sunil Kumar Daksh and Pranit Ram

Table 1 Salient features of various methods that could be employed to measure GFR in ICU setup

Sl no	Methods	Merits	Demerits
1	CG formula	Easily computable	Highly inaccurate in the critical care setup. Considerable degree of GFR overestimation
2	4-variable MDRD	More accurate than CG. May offer value close to 6-variable MDRD in healthier patients with preserved BUN/Cr ratio	Dependency on creatinine. May not be accurate when BUN/Cr ratio is increased. Does not take into account blood urea nitrogen and albumin. Overestimation of GFR when baseline GFR is high
3	6-variable MDRD	BUN and serum albumin are taken into account. More accurate when BUN/CR ratio is increased. Better concordance correlation coefficient when compared with CG and 4-variable MDRD	Dependency on creatinine. Ongoing creatinine production and its fluid balance variations are not taken into account. Less accurate when compared with cystatin C and novel methods
4	CKD-EPI formula	Greater precision and reliability when compared with MDRD. More accurate when GFR >60 ml/min/1.73 m^2	Not validated extensively in hospitalized and sick individuals. Dependency on serum creatinine
5	24-h creatinine clearance	More accurate when compared to CG and MDRD formulae	Collection of urine is an issue. Cannot provide immediate results. Becomes a problem when rapid administration of drugs is essential

Mesure>>Estimation de la clairance de la créatinine

Mesurer la clairance à partir d'un échantillon d'urines sur 8h ou 24h++++

$$\text{Créatinine urinaire} \quad \frac{U\ V}{P}$$

U : Volume d'urines sur 8h ou 24h

P : Créatinine plasmatique

Ichai et al. Ann Intensive Care 2016; 6:48
Cherry et al. J Trauma 2002; 53:267-271

DEBUT ET DURÉE DE L'HYPERCLAIRANCE RÉNALE IN ICU ?

Mikami *et al. Journal of Intensive Care* (2023) 11:13
https://doi.org/10.1186/s40560-023-00660-9

Journal of Intensive Care

2023

RESEARCH Open Access

Onset timing and duration of augmented renal clearance in a mixed intensive care unit

Methods Data were retrospectively obtained from the medical records of 2592 critically ill patients admitted to the intensive care unit (ICU) from January 2019 to June 2022 at a tertiary emergency hospital. Among these, patients with continuously measured urinary CrCl were selected and observed over time. We evaluated the onset timing and duration of ARC by plotting Kaplan–Meier curves. Furthermore, by multivariate analyses, factors associated with the onset and persistence of ARC were analyzed, and the association between the ARC time course and clinical outcomes was evaluated.

Mikami et al. Journal of Intensive Care (2023) 11:13
https://doi.org/10.1186/s40560-023-00660-9

Journal of Intensive Care

2023

RESEARCH Open Access

Onset timing and duration of augmented renal clearance in a mixed intensive care unit

Onset timing of ARC:
- 3 days: 50%
- 1st week:

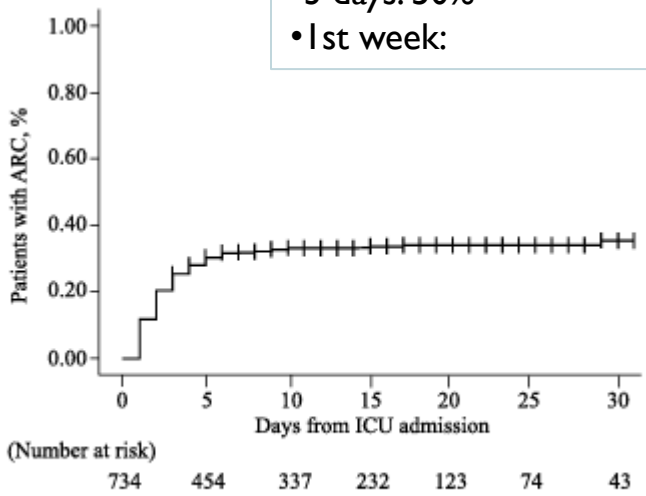


Fig. 2 Cumulative incidence rate of ARC ($n = 734$). *ARC* augmented renal clearance, *ICU* intensive care unit

Duration of ARC
- The median duration: 5 days
- ended within 3 weeks

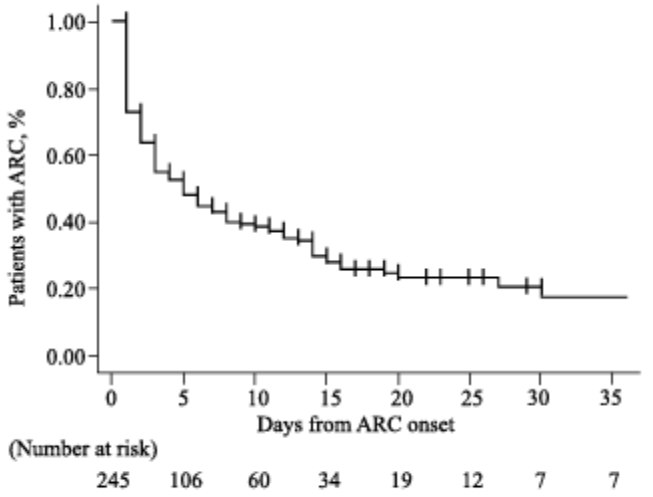


Fig. 4 Cumulative persistence rate of ARC ($n = 245$). *ARC* augmented renal clearance

Mikami et al. Journal of Intensive Care (2023) 11:13
https://doi.org/10.1186/s40560-023-00660-9

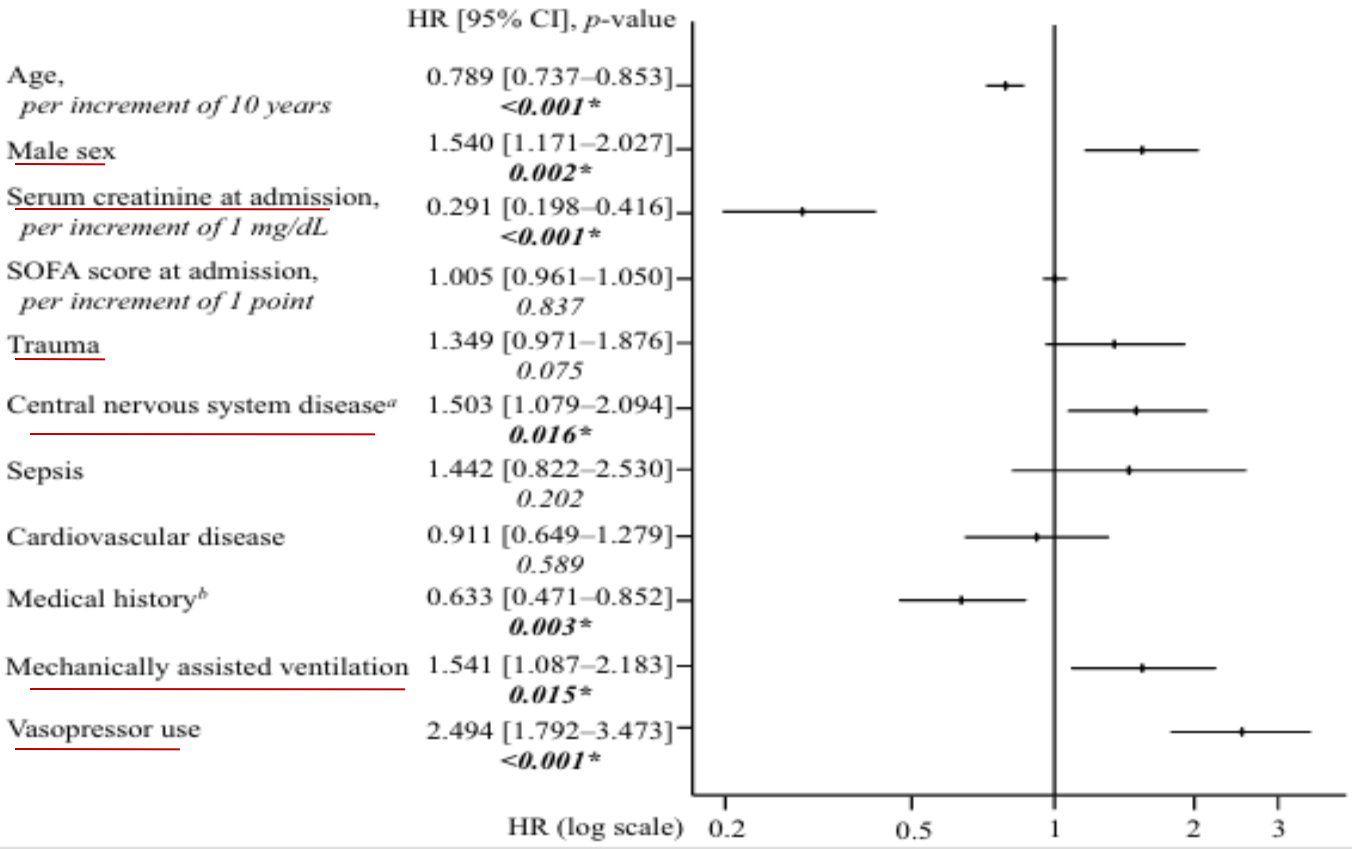
Journal of Intensive Care

2023

RESEARCH Open Access

Onset timing and duration of augmented renal clearance in a mixed intensive care unit

Factors associated with onset of ARC



Mikami et al. Journal of Intensive Care (2023) 11:13
https://doi.org/10.1186/s40560-023-00660-9

Journal of Intensive Care

2023

RESEARCH Open Access

Onset timing and duration of augmented renal clearance in a mixed intensive care unit

Factors associated with persistant of ARC

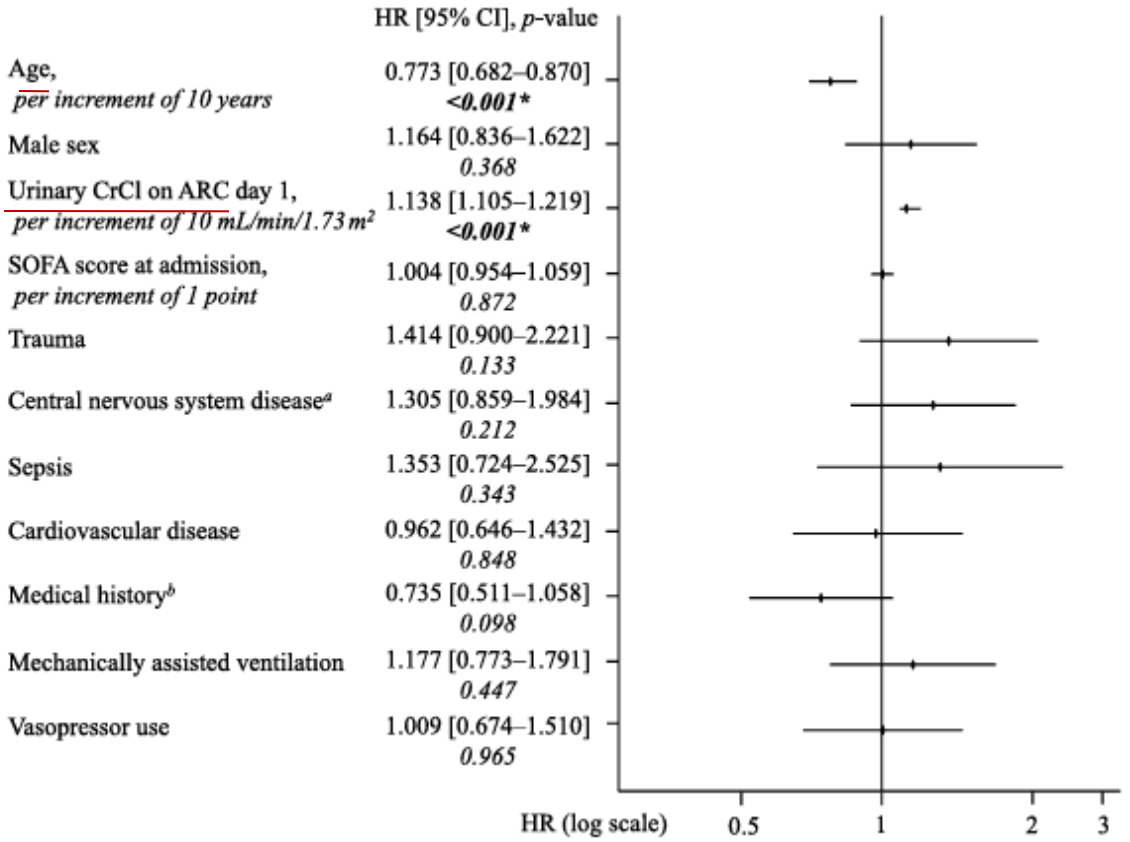


Fig. 5 Factors associated with persistence of ARC ($n = 245$). [a]Central nervous system disease refers to hospitalization for any of the following

HYPERCLAIRANCE RÉNALE = IMPACT CLINIQUE

2024

J Crit Care 84 (2024) 154541

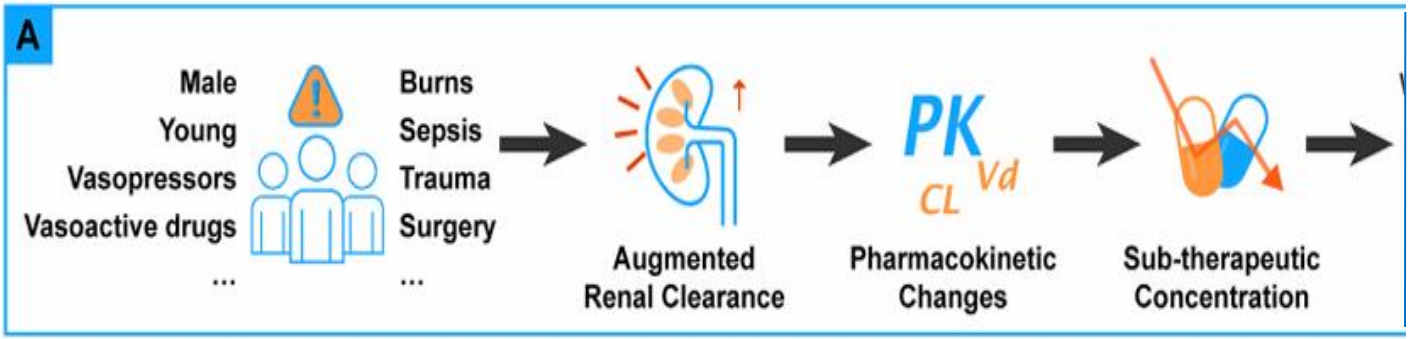
Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

What every intensivist should know about augmented renal clearance (ARC)

ARC est une problématique en USI :
✓Fréquente en réanimation mais sous diagnostiquée

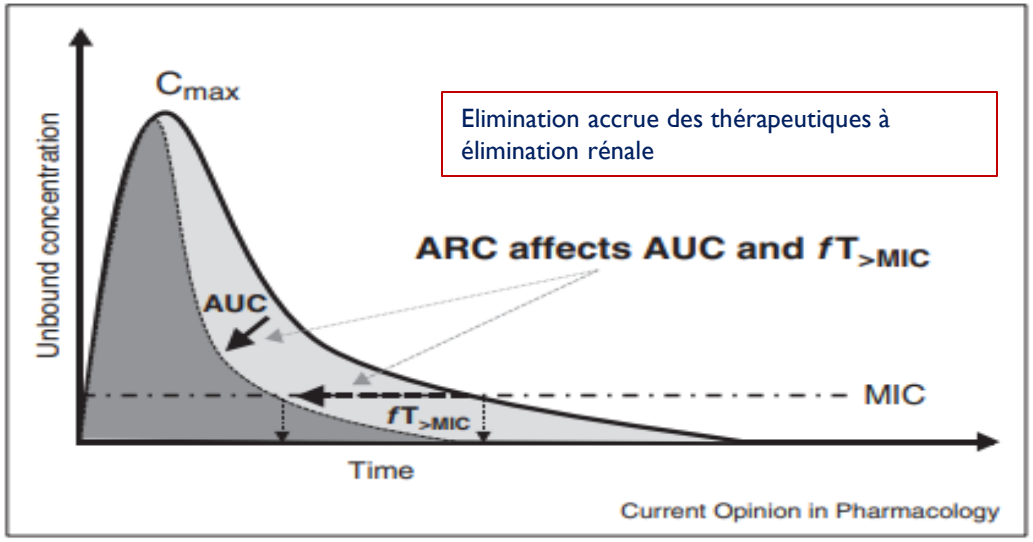


Poor Prognosis

Available online at www.sciencedirect.com
ScienceDirect
Current Opinion in Pharmacology
2015

Augmented renal clearance in critically ill patients: etiology, definition and implications for beta-lactam dose optimization

Fekade Bruck Sime[1], Andrew A Udy[1,2,3] and Jason A Roberts[1,4]



1. **Sous dosage en antibiotiques à élimination rénale** (temps dépendants)

2. **Echec des thérapeutiques anti-infectieuses**
   - surmorbidité avec acquisition des resistances
   - surconsommation des ATB
   - surmortalité

QUELS ANTI-INFECTIEUX SONT A RISQUE ?

	Antibiotique hydrophile	Antibiotique lipophile
PK	Faible volume de distribution Principalement éliminé par le rein Faible pénétration tissulaire et intra cellulaire	Large volume de distribution Principalement métabolisé par le foie Bonne pénétration tissulaire et intra cellulaire
Exemples	Beta lactamines Aminosides Vancomycine Colistine Fluconazole	Macrolides Fluoroquinolones Tigecycline Echinocandines Azoles

Higher than standard dosing regimen are needed to achieve optimal antibiotic exposure in critically ill patients with augmented renal clearance receiving piperacillin-tazobactam administered by continuous infusion.

Cédric Carrié, M.D.[1], Rachel Legeron, Pharm.D Ph.D.[2,3], Laurent Petit, M.D.[1], Julien Ollivier[2], Vincent

J Crit Care 2018

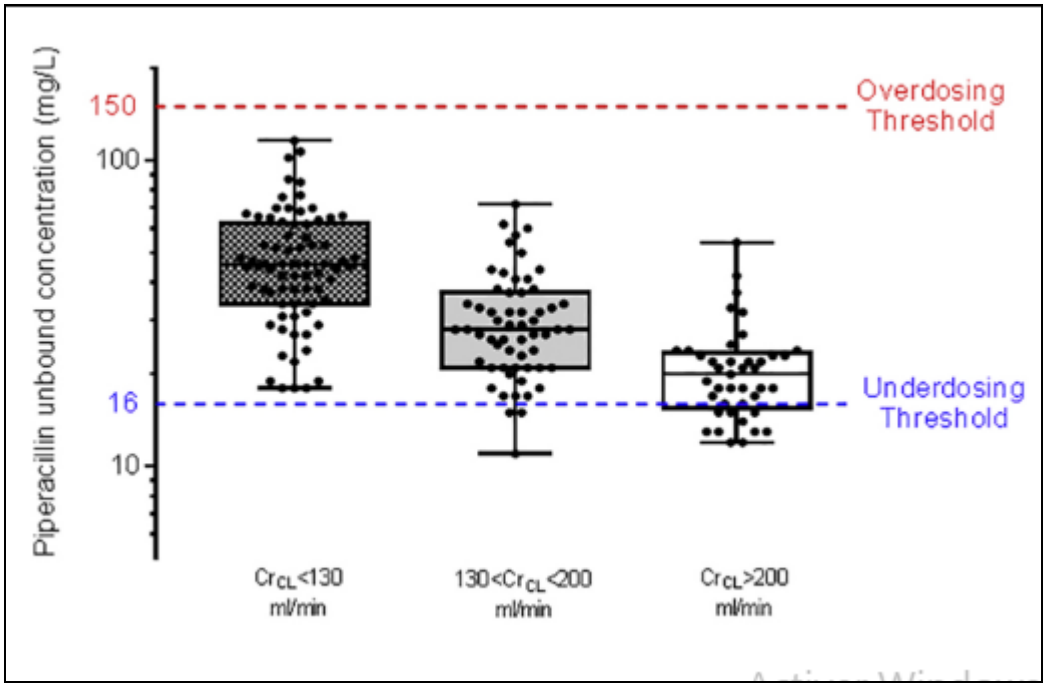


Fig: Relation between pipera concentration and Cl creat

Higher than standard dosing regimen are needed to achieve optimal antibiotic exposure in critically ill patients with augmented renal clearance receiving piperacillin-tazobactam administered by continuous infusion.

Cédric Carrié, M.D.[1], Rachel Legeron, Pharm.D Ph.D.[2,3], Laurent Petit, M.D.[1], Julien Ollivier[2], Vincent

Résultats:

- **Administration continue en IVSE:**

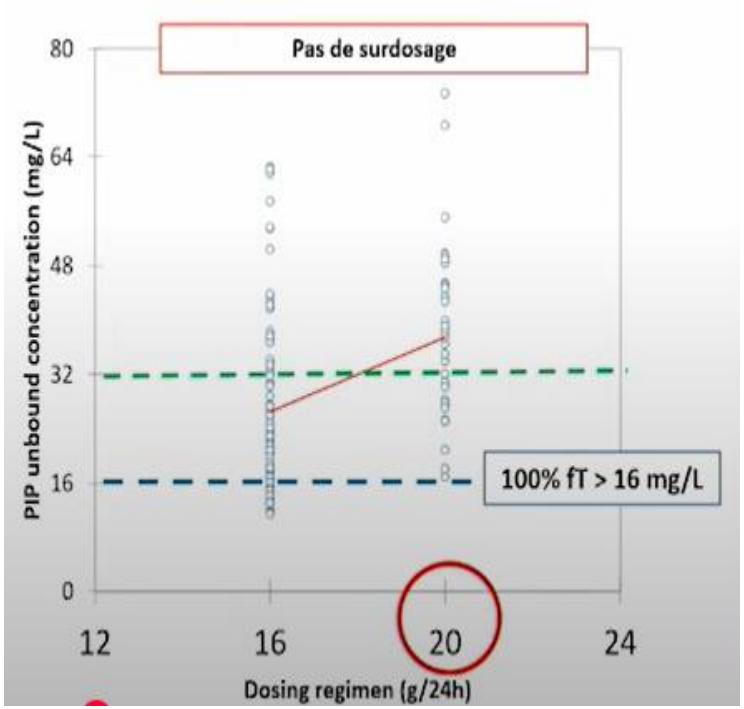
permet de limiter le risque de sous dosage

(Dose de charge 4g puis 16 g/j)

- Seuil **CLCr à risque≥ 150ml/min**

(PIP en probabiliste en IVSE à 16g/l)

- Risque de sous dosage si cible thérapeutique ≥ 4CMI max pour les germes les moins sensibles (Dose 20 g/j)



Observational Study > Int J Antimicrob Agents. 2018 Mar;51(3):443-449.

2018

doi: 10.1016/j.ijantimicag.2017.11.013. Epub 2017 Nov 24.

Association between augmented renal clearance, antibiotic exposure and clinical outcome in critically ill septic patients receiving high doses of β−lactams administered by continuous infusion: a prospective observational study

Messages clés:

- In patients with augmented renal clearance, PK/PD targets may not be reached using high-dose continuous-infusion β-lactams.
- **Mean CL_{Cr} values ≥170 mL/min** remain associated with higher rates of subexposure for β-lactams.
- •Subexposure$_{<4\times MIC}$ is associated with higher rates of therapeutic failure.

Observational Study > Int J Antimicrob Agents. 2018 Mar;51(3):443-449.

2018

doi: 10.1016/j.ijantimicag.2017.11.013. Epub 2017 Nov 24.

Association between augmented renal clearance, antibiotic exposure and clinical outcome in critically ill septic patients receiving high doses of β−lactams administered by continuous infusion: a prospective observational study

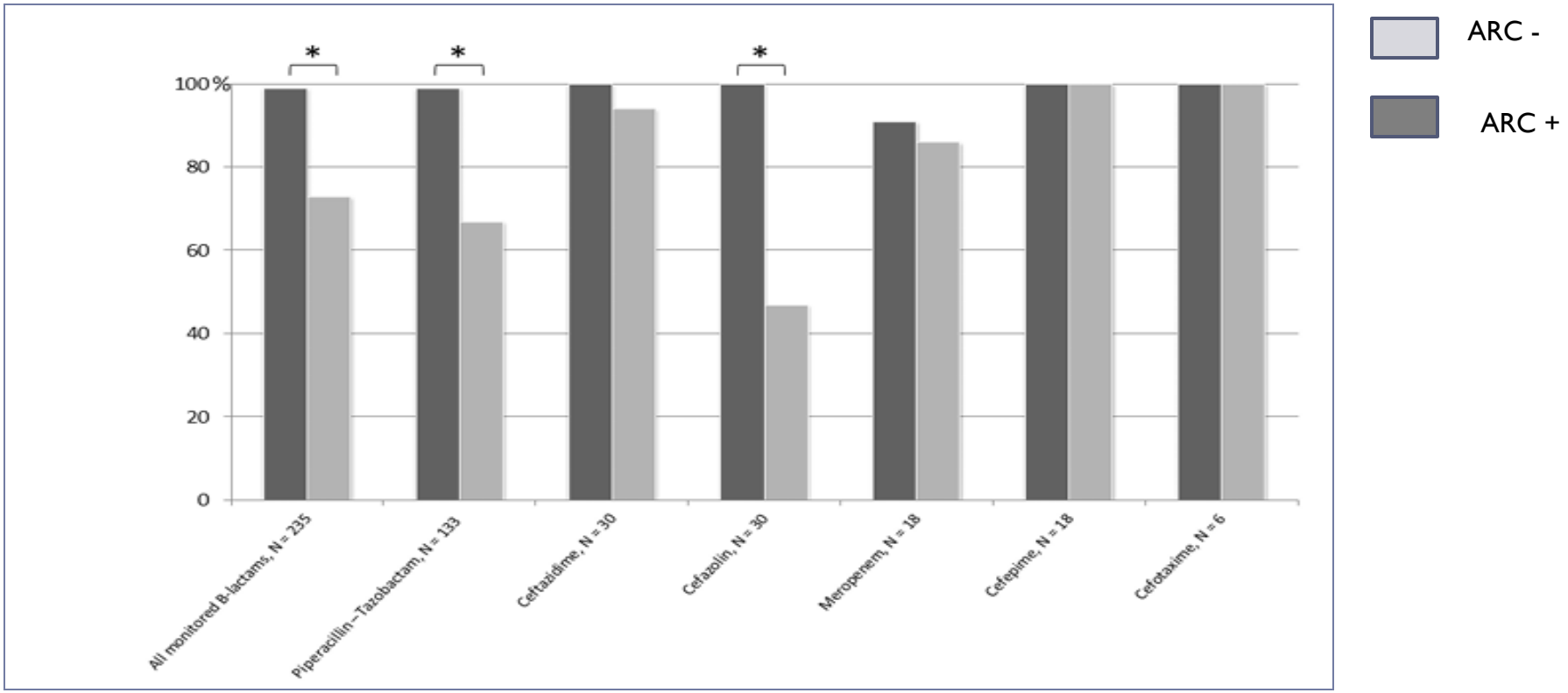


Fig: Dosage regimes of ATB between ARC+ and ARC-

Observational Study > Int J Antimicrob Agents. 2018 Mar;51(3):443-449.
doi: 10.1016/j.ijantimicag.2017.11.013. Epub 2017 Nov 24.

Association between augmented renal clearance, antibiotic exposure and clinical outcome in critically ill septic patients receiving high doses of β−lactams administered by continuous infusion: a prospective observational study

- Risque de sous dosage si cible thérapeutique ≥ 4CMI max pour les germes les moins sensibles
- Aucun sous dosage documenté pour FEP et CAZ

  (Dose de charge 2g puis 6 g/J)
- Sécurité pour le meropenème en perfusion intermittente (3H)

  (Dose de charge 2g puis 6 g/J
- Risque sous dosage pour Cefazoline avec effet inoculum

  (Dose de 100 mg/Kg/j)

Antimicrob Agents Chemother. 2019 Feb 26;63(3):e02134-18. doi: 10.1128/AAC.02134-18

Are Standard Dosing Regimens of Ceftriaxone Adapted for Critically Ill Patients with Augmented Creatinine Clearance?

- **Ceftriaxone et hyperclairance**

  Objectif PK/PD= 100% fT ≥ 2mg

  2g x 2/ J si **CL_{Cr} ≥170 mL/min**

J Antimicrob Chemother. 2013 Nov;68(11):2600-8. doi: 10.1093/jac/dkt240. Epub 2013 Jun 25.

Population pharmacokinetics and dosing simulations of amoxicillin/clavulanic acid in critically ill patients

- **Amox-Ac Clav et hyperclairance**

  Objectif PK/PD= 50% fT ≥ 2mg

  2g x 4/ J si **CL_{Cr} ≥190 mL/min**

Optimization of B-lactamin Dosing Regimens in critically Ill Patients with Augmented Renal Clearance

Deux stratégies pour prévenir le sous dosage

- ✓ Monitorage Pharmacologique
- ✓Etat d'équilible si IVSE
- ✓Vallée si administration ponctuelle

Limites
- ✓Disponibilité, couts
- ✓Délais dosage, analyse, résultat

- ✓ Adaptation des doses selon Cl creat mesurée sur iono urinaire/24H

Limites
- ✓Raisonnement spéculatif
- ✓Monitorage quotidien CLcr

Problématique Cl creat
- Dépend du type de molécule
  dose modalités d'administration)
- Dépend de la CMI (probabiliste ou documentée).

Comment optimiser l'exposition aux antibiotiques en cas d'hyperclairance rénale?

✓ **Stratégies de l'optimisation de l'antibiothérapie si hyperclairance**

- Monitorer la Clcr toute la durée de l'antibiothérapie
- Dose de charge puis perfusion continue, respect stabilité et dilution
- Ajuster doses quotidiennes pour les antibiotiques à risque
- Idéal dosages plasmatiques quotidiens

Conséquences de l'hyperclairance rénales en réanimation?

✓ Augmentation de la clairance des thérapeutiques à élimination rénale (sedatifs, anticonvulsivants)

Sime et al. Clin Pharmaocokine 2021

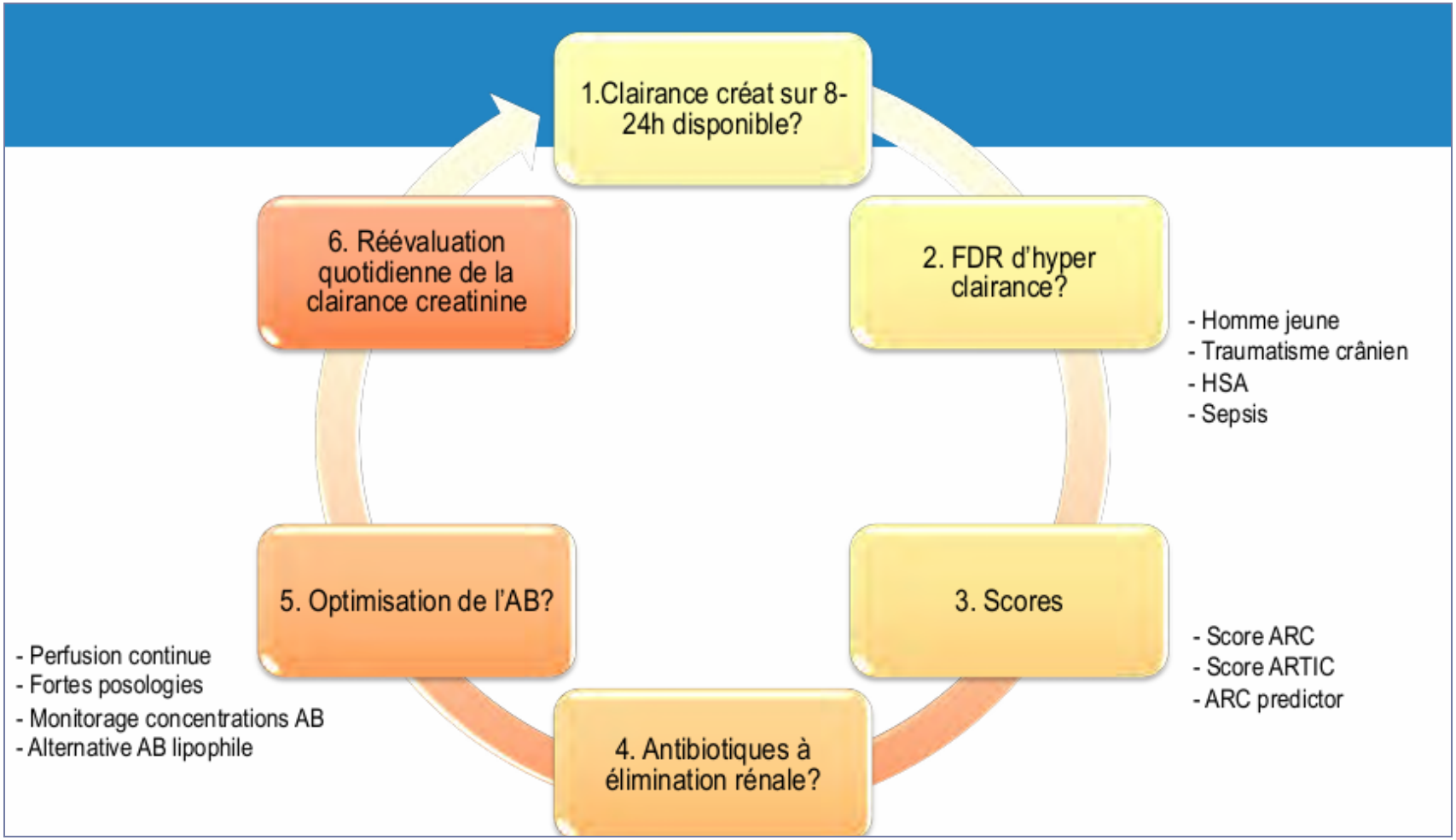
✓ Troubles hydroélectrolytiques et pertes rénales accrues (hypoNa et Hypoph de réa....)

Lanou et al. BMC 2021

✓ Hypercatabolismes et pertes azotées accrues

Dreydemi et al. Nutrients 2021

HCR EN PRATIQUE CLINIQUE ?



TAKE HOME MESSAGES

MERCI POUR VOTRE ATTENTION

VOS QUESTIONS ???