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The kinetic glomerular filtration rate is not interchangeable with measured creatinine clearance for prediction of piperacillin underexposure in critically ill patients with augmented renal clearance

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In the critical care setting, augmented renal clearance (ARC) is increasingly recognized as one of the leading causes of subtherapeutic antibiotic exposure [1]. However, commonly used formulas for estimating glomerular filtration rate (GFR) are inaccurate in patients with ARC and the 24-h urinary creatinine clearance (Cr_{CL}) remains the best available approach for optimizing empirical antimicrobial therapy [2]. On the other hand, no study has evaluated the clinical and prognostic value of the kinetic estimated GFR (KeGFR) in this context. We thus aimed to determine whether KeGFR could be a reliable alternative to measured Cr_{CL} in critically ill patients needing early initiation of an appropriate piperacillin dosing regimen.

For this purpose, we retrospectively analyzed 60 consecutive patients who underwent 24-h urinary Cr_{CL} measurements and therapeutic drug monitoring during the first 3 days of antimicrobial therapy of piperacillin administered 16 g/day continuously. The protocol pertaining to this substudy has been published elsewhere [3]. As previously described, the corresponding KeGFR was calculated as follows: $\frac{\text{Baseline sCr x eGFR}}{\text{Mean sCr}} \times \left(1 - \frac{24 \text{ x } \Delta\text{sCr}}{\Delta\text{t x MaxΔsCr/Day}}\right)$ with eGFR derived from the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation using serum creatinine (sCr) before admission, Δt fixed at 24 h between two sCr measurements, and maximal sCr increase per day approximated to 133 μmol/L [4]. ARC was defined by a measured $Cr_{CL} \geq 130$ mL/min/1.73 m^2. Piperacillin underdosing was arbitrarily defined by a free drug concentration ≤ 32 μg/ml at steady state.

Among the 180 samples analyzed, the incidence of ARC was 48% (median Cr_{CL} values = 124 [83–170] ml/min/1.73 m^2) and the incidence of piperacillin underdosing was 51% (median piperacillin concentrations = 32 [22–47] μg/ml). The diagnostic agreement between KeGFR and Cr_{CL} was only moderate (κ = 0.48 [95% confidence interval 0.4–0.55]) (Fig. 1). Comparison between KeGFR and Cr_{CL} showed a mean bias of −8.7 ml/min/1.73 m^2 and limit of agreement from −99 ml/min/1.73 m^2 to 82 ml/min/1.73 m^2. Finally, the area under the ROC curve generated for KeGFR was significantly lower than the one generated for measured Cr_{CL} for prediction of piperacillin underdosing (0.76 [0.68–0.83] vs 0.85 [0.79–0.91], $p = 0.03$; Fig. 2).

In conclusion, KeGFR is not interchangeable with measured Cr_{CL} for prediction of piperacillin underexposure in critically ill patients with ARC. Also, scarce data may suggest a better predictive value of Cockcroft-Gault compared to MDRD (Modification of Diet in Renal Disease Study) or CKD-EPI for identifying patients with ARC [5]; a measured CL_{CR} should be performed to accurately guide drug dosing. This study emphasizes the need for dosing adjustment and therapeutic drug monitoring in patients with ARC.

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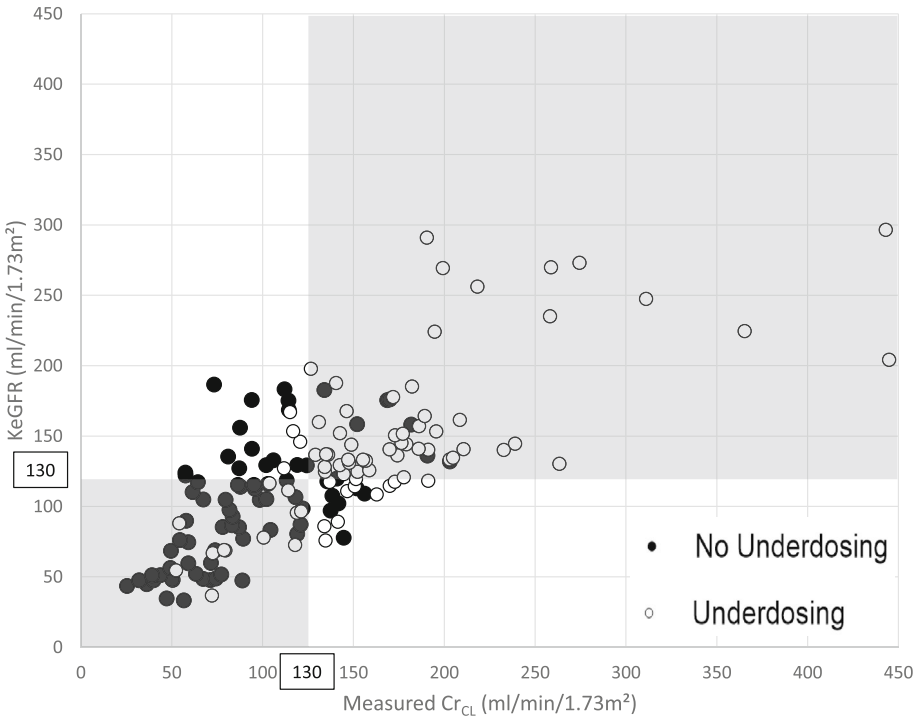

Fig. 1 Correlation between measured Cr_{CL} and KeGFR ($r^2 = 0.54$, $p < 0.0001$) and repartition of samples with (*white circles*) or without (*black circles*) piperacillin underdosing, defined by an unbound concentration ≤ 32 μg/ml. ARC was defined by a measured Cr_{CL} or a KeGFR ≥ 130 ml/min/1.73 m^2. Samples in the *gray shaded area* are considered to be well classified

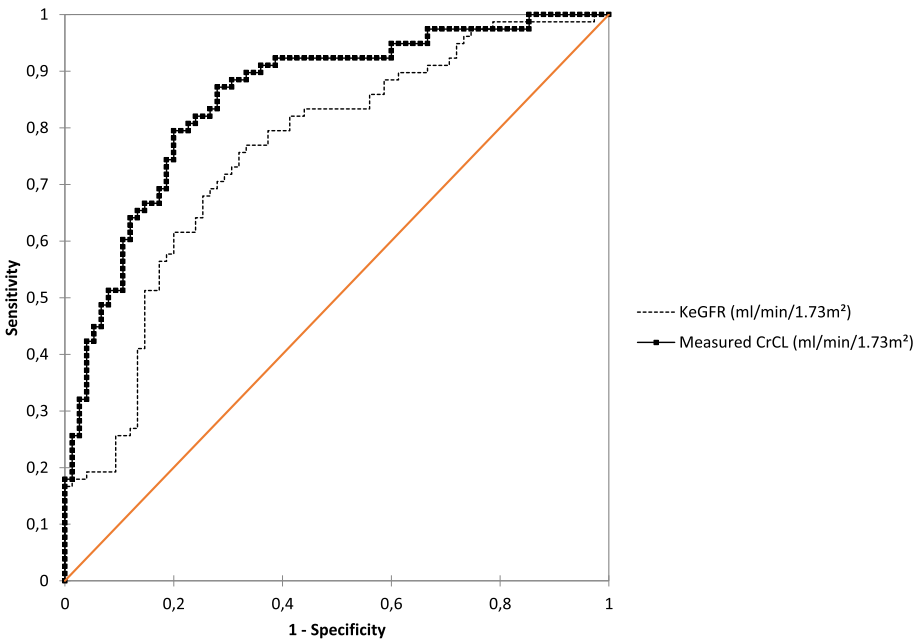

Fig. 2 Receiver operating characteristics (ROC) curves evaluating the ability of KeGFR and measured Cr_{CL} to predict piperacillin underdosing. Areas under ROC curves between KeGFR and measured Cr_{CL} were compared using the Handley approach. Piperacillin underdosing was defined by a free drug concentration ≤ 32 μg/ml

Abbreviations
ARC: Augmented renal clearance; Cr_{CL}: Creatinine clearance; GFR: Glomerular filtration rate; KeGFR: Kinetic estimated glomerular filtration rate; MIC: Minimum inhibitory concentration; ROC: Receiver operating characteristic; sCr: Serum creatinine

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions
CC and SR designed the study. CC and PS recruited patients and collected the data. CC and MB performed statistical analysis and wrote the manuscript. DB was in charge of sample preparation, storage and quantification. SR, DB, and MB have personally reviewed the data and confirmed that the methods are clearly described and that they are a fair way to report the results. All authors read and approved the final manuscript.

Ethics approval and consent to participate
Ethics approval was obtained from the Institutional Review Board (Comite de Protection des Personnes Sud-Ouest et Outre Mer III, Bordeaux, France; protocol number DC 2016/147), which waived the need for written consent. Patients or next of kin were orally informed of the goal and design of the study.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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References
1. Udy AA, Lipman J, Jarrett P, Klein K, Wallis SC, Patel K, Kirkpatrick CM, Kruger PS, Paterson DL, Roberts MS, Roberts JA. Are standard doses of piperacillin sufficient for critically ill patients with augmented creatinine clearance? Crit Care. 2015;19:28.
2. Barletta JF, Mangram AJ, Byrne M, Hollingworth AK, Sucher JF, Ali-Osman FR, Shirah GR, Dzandu JK. The importance of empiric antibiotic dosing in critically ill trauma patients: are we under-dosing based on augmented renal clearance and inaccurate renal clearance estimates? J Trauma Acute Care Surg. 2016;81(6):1115–21.
3. Carrié C, Petit L, d'Houdain N, Sauvage N, Cottenceau V, Lafitte M, Foumenteze C, Hisz Q, Menu D, Legeron R, Breilh D, Sztark F. 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. Int J Antimicrob Agents. 2018;51(3):443–9.
4. Dewitte A, Joannès-Boyau O, Sidobre C, Fleureau C, Bats ML, Derache P, Leuillet S, Ripoche J, Combe C, Ouattara A. Kinetic eGFR and novel AKI biomarkers to predict renal recovery. Clin J Am Soc Nephrol. 2015;10(11):1900–10.
5. Baptista JP, Udy AA, Sousa E, Pimentel J, Wang L, Roberts JA, Lipman J. A comparison of estimates of glomerular filtration in critically ill patients with augmented renal clearance. Crit Care. 2011;15(3):R139.