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# Comparison of different equations for renal function evaluation as proxies for antibiotic drug clearance: the examples of amoxicillin and cloxacillin.

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## Abstract:

The most appropriate renal function estimation equation to predict drug clearance is a matter of debate. In this study, we compare the Modification of Diet in Renal Disease (MDRD), the Chronic Kidney Disease Epidemiology collaboration (CKD-EPI) and the Cockcroft-Gault (CG) equations to predict amoxicillin and cloxacillin clearance among hospitalized patients receiving high doses of these antibiotic treatments. This study aimed to compare different equations used to predict amoxicillin and cloxacillin clearance among hospitalized patients receiving amoxicillin or cloxacillin treatments outside the intensive care unit. Data from 128 patients contributing 268 plasma samples was analyzed, and correlations between the equations and the amoxicillin and cloxacillin antibiotic clearance rates were calculated. We found a correlation between antibiotic clearance and all the renal function estimation

equations, CG being the best, with a  $R^2$  of 0.35 for amoxicillin and 0.29 for cloxacillin (compared to 0.26 and 0.21 for MDRD and 0.12 and 0.24 for CKD-EPI). CG should be preferentially used as a proxy for amoxicillin and cloxacillin drug clearance, but the use of completely different tools such as therapeutic drug monitoring could help individualize antibiotic dosage.

**Keywords:** Antibiotics; Chronic Kidney Disease; Betalactams; Drug Monitoring; Pharmacokinetics

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**Text [1475/1500 words]**

### **1. Introduction:**

There is controversy regarding the best renal function estimation equation to use to adjust antibiotic drug dosage. Some authors have proposed the Cockcroft-Gault (CG) equation as the preferred option following its initial use in phase II clinical trials involving patients with decreased renal function [1]. While it provides only an estimation of creatinine clearance, and is therefore a proxy for glomerular filtration rate (GFR), the CG equation could also capture the tubular secretion, since creatinine is also partly eliminated by this route and in this case, it would correspond to an estimate of creatinine clearance ( $eCl_{\text{creat}}$ ) [2]. On the other hand, the Modification of Diet in Renal Disease (MDRD) and the Chronic Kidney Disease Epidemiology collaboration equations (CKD-EPI) are thought to provide a better estimation of GFR. Kidney Disease Improving Global Outcomes (KDIGO) previously recommends reporting estimated GFR (eGFR) using the 2009 CKD-EPI, but it also states that other equations are acceptable [3]. However, these equations, depending on the specific population, could underestimate or overestimate GFR compared to CG, and finally result in different drug dosage adjustments [4]. It can be noted that these eGFR equations are not recommended for patients with unstable creatinine, for

patients under 18 years of age and in cases of extreme body weight, muscular mass or altered dietary intake.

Regarding betalactam antibiotics, several studies have reported pharmacokinetic data, but either dosage adjustment did not rely on eGFR with the above equations, or the studies were specifically focused on critically ill patients [5]. Among betalactam antibiotics, amoxicillin and cloxacillin are also used at high doses outside the intensive care unit (ICU) (e.g. for the treatment of infective endocarditis, bone and joint infections...). These antibiotics are mainly eliminated through the renal route, and eGFR or  $eCl_{creat}$  are used as proxies for their clearance to choose the starting dose. It can be noted that the actual antibiotic clearance is easily obtained for patients receiving continuous infusion by simply measuring their plasma concentrations. However, to date, none of the equations used to approximate antibiotic clearance can be recommended over another.

The aim of this study was to compare the different equations to predict amoxicillin and cloxacillin clearance among hospitalized patients receiving amoxicillin or cloxacillin treatments outside the ICU.

## **2. Material and methods:**

Over a period of 21 months, all consecutive adult patients receiving continuous intravenous infusion of amoxicillin or cloxacillin at the Rennes University Hospital and undergoing therapeutic drug monitoring (TDM) based on plasma concentration measurement were retrospectively included in the study. Concentrations were measured in plasma at steady state (i.e. at least 24 hours after antibiotic treatment initiation). A validated high-performance liquid chromatography method coupled with ultraviolet detection was used to quantify plasma amoxicillin and cloxacillin levels [6]. Intra-day precision (coefficient of variation) and accuracy (bias) at three concentration (5, 100 and 200  $\mu\text{g}/\text{mL}$ ) using spiked plasma quality controls were: 3.1, 3.1, 1.8% and 102.0, 104.1, 105.3% for amoxicillin and 5.1, 2.6, 1.9% and 86.0, 103.8, 99.4% for cloxacillin. Inter-day precision (coefficient of variation) and

accuracy (bias) at three concentration (5, 100 and 200 µg/mL) using spiked plasma quality controls were: 2.7, 1.6, 1.3% and 86.0, 98.2, 98.9% for amoxicillin and 5.5, 1.8, 1.4% and 84.0, 99.2, 101.2% for cloxacillin. Gender, age, weight, height, body mass index (BMI, calculated using the following equation):

$$BMI = \frac{Weight}{Height^2}$$

drug dose, drug dose per kg, steady-state plasma antibiotic concentrations and serum creatinine were also gathered. Serum creatinine was measured using an automated enzymatic method on a Roche Cobas 8000 with Roche Diagnostics reagent and an Isotope Dilution Mass Spectrometry (IDMS) - standardized calibrator. ICU patients, extreme BMI values (<18.5kg/m<sup>2</sup>; >35kg/m<sup>2</sup>) and plasma concentrations outside the method range (5-250µg/mL) were excluded. The area under the curve of drug concentrations over 24 hours (AUC<sub>0-24h</sub>) and antibiotic drug clearance (Cl<sub>ATB</sub>) were determined using the following equations (1-2):

$$AUC_{0-24h} = 24 \times C_{ss} \quad (1)$$

$$CL_{ATB} (L/h) = \frac{Dose (mg)}{AUC_{0-24h} (mg \cdot h/L)} \quad (2)$$

where C<sub>ss</sub> represents the steady-state plasma antibiotic concentrations.

Renal function was estimated using the equations displayed in table 1.

eGFR was calculated for each patient using MDRD and CKD-EPI and adjusted to patient body surface area [7,8]. eCl<sub>creat</sub> was calculated for each patient using CG [9].

A non-linear regression was performed to assess the correlation between Cl<sub>ATB</sub> and eGFR<sub>MDRD</sub> and eGFR<sub>CKD-EPI</sub> or eCl<sub>creat</sub> (CG). Coefficients of determination between each renal function estimation and Cl<sub>ATB</sub> were calculated and compared for amoxicillin and cloxacillin and for each equation.

All the analyses were conducted using Prism 5 software (version 5.0.3, Dec 10 2009).

### 3. Results:

One hundred and twenty-eight patients provided 268 plasma samples. In the amoxicillin group, (n=107 samples), 55 patients received a median daily dose of 142.9 mg.kg<sup>-1</sup>. Median body weight, age and Cl<sub>ATB</sub> were 71 kg, 66 years and 208.3 mL/min, respectively. There were 14 patients over the age of 80 (25.4%). In this group, the infections were mainly endocarditis (38.8%), bone and joint infections (32.0%) and bacteremia/sepsis (20.4%). The bacteria isolated were *Streptococcus sp.* for more than half the patients (54.1%) with *Enterococcus sp.* the second most frequently isolated bacterium (19.4%).

In the cloxacillin group (n=161 samples), 73 patients received a median daily dose of 131.2 mg.kg<sup>-1</sup>. Median body weight, age and Cl<sub>ATB</sub> were 73 kg, 71 years and 171.5 mL/min, respectively. Demographic and treatment parameters are reported in table 2. There were 14 patients over the age of 80 (19.2%). In this group, the infections were mainly bone and joint infections (44.4%), endocarditis (24.3%) and bacteremia/sepsis (20.1%). The bacteria isolated were almost exclusively *Staphylococcus sp.* (98.3%).

We found a correlation between Cl<sub>ATB</sub> and all the renal function estimation equations (p<0.05), CG being the best, with a R<sup>2</sup> of 0.35 for amoxicillin and 0.29 for cloxacillin (compared to 0.26 and 0.21 for MDRD and 0.12 and 0.24 for CKD-EPI) (Figure 1).

### 4. Discussion:

This study aimed to evaluate the performance of equations estimating renal function as proxies for antibiotic clearance calculated from betalactam concentration measurements. Estimations of betalactam drug clearance among patients enables individual adjustment of drug dosage to maximize treatment success and minimize adverse drug reactions (ADR). We thus focused on a population of non-ICU patients receiving high doses of amoxicillin and cloxacillin (i.e. a population with severe

infection, a risk of treatment failure and a risk of drug accumulation/ADR), and we compared the  $Cl_{ATB}$  to  $eGFR_{MDRD}$  and  $eGFR_{CKD-EPI}$  or  $eCl_{creat}$  (CG) equations. We showed that, compared to the MDRD and CKD-EPI equations, the CG equation correlated better with amoxicillin and cloxacillin clearance. Even for drugs mainly eliminated via the kidneys, drug clearance mechanisms not only rely on filtration but entail tubular secretion and reabsorption. Measuring clearance of creatinine, which is filtered and also secreted, could thus be a better reflection of renal function than  $eGFR$ . For cloxacillin, tubular secretion is thought to be particularly important, as highlighted by the mean  $Cl_{ATB}$  of the drug (208.4 mL/min). Indeed, the  $R^2$  was significantly higher for the CG equation (0.35) than for the MDRD and CKD-EPI equations (0.12 and 0.24 respectively). However, it should be noted that MDRD has limited performance among elderly patients, while CKD-EPI has been shown to perform adequately in studies among patients with a mean age >70. Thus, the design of the study could have disadvantaged the MDRD equation [10]. Another limitation in the use of CG is the need to obtain patients' body weight, while this is not required for MDRD and CKD-EPI. MDRD and CKD-EPI can be calibrated to  $1.73m^2$  body size but this requires both weight and size to be fitted for each specific patient.

Similar levels of correlation between  $eGFR/eCl_{creat}$  and drug clearance have been reported for other anti-infective drugs. Palacio-Lacambra *et al.* reported that the CKD-EPI equation correlated better with ganciclovir clearance, which is consistent with its almost exclusive excretion by filtration [11]. Charhon *et al.* showed that the CG equation had equal or even better performance than the MDRD equation for estimation of gentamicin clearance, possibly related to the non-renal clearance route of the drug [12].

Finally, CG is preferable to evaluate initial kidney function and to calculate amoxicillin and cloxacillin starting doses. However, because in our study none of the equations correlated strongly with  $Cl_{ATB}$ , subsequent dose adjustment should be based on early TDM.

## 5. Conclusion:

Despite a largely imperfect relationship with  $Cl_{ATB}$ , renal function estimation using equations could be used to adjust cloxacillin and amoxicillin drug dosage at least at the beginning of treatment. In our population of non-ICU patients receiving high doses of antibiotics, the CG equation should be preferentially used as a proxy for amoxicillin and cloxacillin drug clearance. However, as none of the renal function equations appear ideal for amoxicillin or cloxacillin clearance estimation, individualizing antibiotic dosage when administered via continuous infusion should also rely on complementary tools such as TDM. A common-sense approach, for the first antibiotic dose, would be to choose patients' doses using the GC equation and then to quickly adjust the dose using TDM at the end of the first day of treatment. This could help reduce the variability in amoxicillin and cloxacillin exposure among patients treated with high antibiotic doses.

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**Table 1: Renal function estimation equations**eCL<sub>creat</sub> Estimated creatinine clearance; Scr: Serum creatinine; GFR: Glomerular Filtration Rate

Cockcroft-Gault (CG)	$eCL_{\text{creat}} \text{ (ml.min}^{-1}\text{)} = \left[ \frac{(140 - \text{age (years)}) \times \text{bodyweight (kg)} \times (0.85 \text{ if female})}{72 \times \text{Scr (mg.dL}^{-1}\text{)}} \right]$
Modification of Diet in Renal Disease (MDRD)	$eGFR \text{ (ml.min}^{-1}\text{/1.73 m}^2\text{)} = 175 \times \text{Scr}^{-1.154} \text{ (mg.dL}^{-1}\text{)} \times \text{age}^{-0.203} \text{ (years)} \\ \times 1.212 \text{ (if African - American)} \\ \times 0.742 \text{ (if female)}$
Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)	<p style="text-align: center;"><b>Black</b></p> <p><b>Female</b>  <math>SCr \leq 0.7 \text{ mg dl}^{-1} : GFR \text{ (ml.min}^{-1}\text{/1.73 m}^2\text{)} = 166 \times (SCr \text{ (mg.dl}^{-1}\text{)}/0.7) - 0.329 \times (0.993)^{\text{age (years)}}</math>  <math>SCr &gt; 0.7 \text{ mg.dl}^{-1} : GFR \text{ (ml.min}^{-1}\text{/1.73 m}^2\text{)} = 166 \times (SCr \text{ (mg.dl}^{-1}\text{)}/0.7) - 1.209 \times (0.993)^{\text{age (years)}}</math></p> <p><b>Male</b>  <math>SCr \leq 0.9 \text{ mg dl}^{-1} : GFR \text{ (ml.min}^{-1}\text{/1.73 m}^2\text{)} = 163 \times (SCr \text{ (mg.dl}^{-1}\text{)}/0.9) - 0.411 \times (0.993)^{\text{age (years)}}</math>  <math>SCr &gt; 0.9 \text{ mg.dl}^{-1} : GFR \text{ (ml.min}^{-1}\text{/1.73 m}^2\text{)} = 163 \times (SCr \text{ (mg.dl}^{-1}\text{)}/0.9) - 1.209 \times (0.993)^{\text{age (years)}}</math></p> <p style="text-align: center;"><b>White or other</b></p> <p><b>Female</b>  <math>Cr \leq 0.7 \text{ mg.dl}^{-1} : GFR \text{ (ml.min}^{-1}\text{/1.73 m}^2\text{)} = 144 \times (SCr \text{ (mg.dl}^{-1}\text{)}/0.7) - 0.329 \times (0.993)^{\text{age (years)}}</math>  <math>SCr &gt; 0.7 \text{ mg.dl}^{-1} : GFR \text{ (ml.min}^{-1}\text{/1.73 m}^2\text{)} = 144 \times (SCr \text{ (mg.dl}^{-1}\text{)}/0.7) - 1.209 \times (0.993)^{\text{age (years)}}</math></p> <p><b>Male</b>  <math>SCr \leq 0.9 \text{ mg.dl}^{-1} : GFR \text{ (ml.min}^{-1}\text{/1.73 m}^2\text{)} = 141 \times (SCr \text{ (mg.dl}^{-1}\text{)}/0.9) - 0.411 \times (0.993)^{\text{age (years)}}</math>  <math>SCr &gt; 0.9 \text{ mg dl}^{-1} : GFR \text{ (ml.min}^{-1}\text{/1.73 m}^2\text{)} = 141 \times (SCr \text{ (mg.dl}^{-1}\text{)}/0.9) - 1.209 \times (0.993)^{\text{age (years)}}</math></p>

**Table 2: Demographic, biological and treatment characteristics of study participants.**

BMI: Body Mass Index;  $eCl_{\text{creat}}$ : Estimated creatinine clearance; GFR MDRD-BSA: Glomerular filtration Rate using Modification of Diet in Renal Disease normalized on Body Surface Area; GFR MDRD: Glomerular filtration Rate using Modification of Diet in Renal Disease; GFR CKD-EPI: Glomerular filtration Rate using Chronic Kidney Disease Epidemiology Collaboration; N: normal values.

Parameters	Amoxicillin (n= 55)	Cloxacillin (n= 73)
	Median [min-max] for continuous variables	
	Number (%) for categorical variables	
Age (years)	66 [23 – 91]	71 [27 – 92]
Gender (n), men/women	41/14	56/17
Weight (kg)	71 [48 – 102]	73 [50 – 109]
Height (cm)	170 [130 – 192]	170 [153 – 190]
Body surface area (m <sup>2</sup> ) (Mosteller equation)	1.8 [1.3 – 2.3]	1.9 [1.5 – 2.3]
BMI (kg.m <sup>-2</sup> )	25.0 [18.9 – 34.9]	25.3 [19.1 – 34.0]
PK samples (n)	107	161
PK samples / patient	1 [1-6]	2 [1-7]
Plasma concentration (mg.L <sup>-1</sup> )	34.8 [9.7 – 212.7]	36.6 [9.6 – 247.6]
Antibiotic daily dose (mg.kg <sup>-1</sup> )	142.9 [36.1 – 653.1]	131.2 [42.8 – 205.5]
Antibiotic clearance: $Cl_{ATB}$ (mL.min <sup>-1</sup> )	208.3 [20.7 – 929.2]	171.5 [26.0 – 626.6]
Serum creatinine (μmol/L) (N: men: 59-104; women: 45-84)	75.0 [42.0-547.0]	87.0 [39.0-612.0]
$eCl_{\text{creat}}$ Cockcroft-Gault (mL.min <sup>-1</sup> )	81.9 [9.9 – 198.1]	68.9 [12.4 – 209.5]
eGFR MDRD (mL.min <sup>-1</sup> .1.73m <sup>-2</sup> )	87.1 [8.9 – 179.3]	71.9 [8.55 – 187.9]
eGFR MDRD-BSA (mL.min <sup>-1</sup> )	88.3 [10.5 – 201.8]	80.9 [9.1 – 192.9]
eGFR CKD-EPI (mL.min <sup>-1</sup> .1.73m <sup>-2</sup> )	84.7 [8.21 – 136.61]	73.7 [8.54 – 130.8]
eGFR CKD-EPI-BSA (mL.min <sup>-1</sup> )	86.4 [9.7-163.1]	80.3 [9.1-149.0]

**Figure 1.** Correlations between antibiotic drug clearance ( $\text{mL}\cdot\text{min}^{-1}$ ) (amoxicillin (A) and cloxacillin (B)) and Cockcroft-Gault estimated creatinine clearance

