The Impact of Different Renal Function Measuring Methods on the Dosages of Meropenem, Piperacillin/Tazobactam and Cefepime in Critically Ill Patients

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Abstract

Objective: Assessment of dosage deviations of 3 β-lactam antibiotics eliminated through the kidneys (meropenem, piperacillin/tazobactam, and cefepime) by comparison of 2 prediction formulae, Cockroft-Gault (CG) and Modification of Diet in Renal Disease (MDRD) with 24 h urinary creatinine clearance ($CrCl_{24h}$), as a reference method.

Method: 125 samples of 61 critically ill patients (each one with CG, MDRD and $CrCl_{24h}$ values) were classified in one of the 5 stages of the National Kidney Foundation (NKF) according to $CrCl_{24h}$. Dosage discrepancies for each antibiotic based on CG and MDRD were studied in reference to $CrCl_{24h}$ by percentage agreement and weighted kappa. At each of the NKF stages, daily dosage differences (Δ=DoseCG-Dose$CrCl_{24h}$; Δ=DoseMDRD-Dose$CrCl_{24h}$) and percentage of samples with dosage discrepancies by CG and MDRD in reference to $CrCl_{24h}$ were calculated.

Results: There were no statistically significant differences between the 2 prediction formulae in respect to $CrCl_{24h}$, achieving good degrees of concordance. Deviation percentages fluctuated between 15.2% and 28% and occurred mainly by underdosing on stages 1 and 2 and by overdosing on stages 4 and 5.

Conclusions: The 2 renal function prediction formulae can be indistinctly used to optimize the β-lactam antibiotics dose regimen, CG being the easiest one.

Key words: β-lactam antibiotics. Glomerular filtration. Cockcroft-Gault. MDRD. Critically ill patients.

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Impacto de distintos métodos de estimación de la función renal en la dosificación de meropenem, piperacilina/tazobactam y cefepima en pacientes críticos

Objetivo: Evaluar las desviaciones de dosificación de 3 antibióticos betalactámicos eliminados por vía renal (meropenem, piperacilina/ tazobactam y cefepima) mediante la comparación de 2 fórmulas de predicción de función renal, Cockroft-Gault (CG) y Modification of Diet in Renal Disease (MDRD), con el aclaramiento de creatinina en orina de 24 h ($ClCr_{24h}$) como método de referencia.

Método: Las 125 muestras de 61 pacientes (cada una con sus valores de CG, MDRD y $ClCr_{24h}$) de una unidad de cuidados intensivos (UCI) se clasificaron en los 5 estadios definidos por la National Kidney Foundation (NKF) en función del $ClCr_{24h}$. Se estudiaron las discrepancias de dosificación de cada antibiótico según CG o MDRD en referencia al $ClCr_{24h}$ por acuerdo porcentual e índice kappa ponderado. En cada estadio de NKF se cuantificaron las diferencias de dosificación diaria (Δ = DosisCG-Dosis$ClCr_{24h}$; Δ = DosisMDRD-Dosis$ClCr_{24h}$) y el porcentaje de muestras con discrepancias de dosificación por CG y MDRD en referencia al $ClCr_{24h}$.

Resultados: En ningún caso se observaron diferencias estadísticamente significativas entre ambas fórmulas con respecto al $ClCr_{24h}$, obteniendo grados de concordancia buenos. Los porcentajes de desviaciones oscilaron del 15,2% al 28% y ocurrieron mayoritariamente por infradosificación en los estadios 1 y 2, y por sobredosificación en los estadios 4 y 5.

Conclusiones: Las dos predicciones de función renal en pacientes de la UCI pueden ser empleadas indistintamente para la dosificación de betalactámicos, aunque la de CG es la más sencilla.

Palabras clave: Antibióticos betalactámicos. Filtrado glomerular. Cockcroft-Gault. MDRD. Pacientes críticos.

INTRODUCTION

Glomerular filtration rate (GFR) is measured as the urinary clearance of an ideal filtration marker such as inulin, ^{125}I-iothalamate, ^{51}Cr-EDTA (^{51}Cr-ethylene diamine tetraacetic acid), ^{99m}Tc-diethylene-triamine-penta-acetic acid, or iohexol. The basic quality of an ideal marker is it almost totally filtrating in its passing through the renal glomerulus, without experiencing subsequent tubular processes of reabsorption and secretion. However, in clinical practice, exogenous filtration markers are hardly used given their high cost, the work involved, complex measurement, and in some, radioactivity.[1,2] In the case of a required exact measurement of a glomerular filtration value, the use of iohexol as a contrast agent is highly recommended, considering it is relatively inexpensive, non-radioactive, has a very good correlation with glomerular filtration rate values obtained with inulin,[3,4] insurance for special populations of patients, including those with serious renal insufficiency,[4] and it is relatively simple, considering that urinary samples are not required.[5] Furthermore, in patients with a GFR >40 mL/min · 1.73 m^2 only a plasma sample is required a few hours after its administration[5] which, compared with inulin, means saving cost and time derived from the need for a bolus and infusion until reaching a state of stable equilibrium, and obtaining blood and urine collections.[6] As an alternative to exogenous markers, the quantification of an endogenous filtration marker was prescribed, which is 24 h urinary creatinine, coming from catabolism of muscular creatine, or hepatic, in low proportion. Even though it is the most widely used reference method in clinical treatment, it is a suboptimal marker[7] due to some limitations, considering that its production is inconstant, and its analytical quantification is not without difficulties. Creatinine production varies according to age, sex, race, pregnancy, nutritional state, diet, muscular mass and muscular diseases, immobilization, diabetes mellitus, and some medicines (increase of serum creatinine due to inhibition of tubular secretion from cimetidine, probenecid or trimethoprim, and nephrotoxic drugs), among others. Analytical quantification is influenced by the obtainment process, laboratory techniques (analytical interferences of reagents with physiological substances, etc), and physiopathologic situations (dehydration, edemas, cirrhosis, cardiovascular disease, cancer, diabetes, use of vasoactive, and diuretic substances), which significantly affect the resulting value of 24 h urinary creatinine clearance ($CrCl_{24h}$) and, consequently, the estimation of actual glomerular filtration rate (aGFR).[1,8] This presents complications in unstable patients in intensive care units (ICU)[9,10] because of the high variability inherent in these situations related to morbidity, perfusion of diuretic and vasoactive substances,[9] and hemodynamic and renal instability throughout the 24 h of urine collection[9,10] (correct measurement of $CrCl_{24h}$ requires stable renal function).[11]

In an attempt to resolve the mentioned problems, it has been proposed that urinary clearance collected in 2 h ($CrCl_{2h}$) compared with $CrCl_{24h}$ be measured in ICU patients, but with the scarcity of studies, this is still not generalizable.[9] Other authors decided upon 1 ($CrCl_{1h}$)[10] in place of $CrCl_{24h}$ as a reference for the evaluation of predictors of glomerular filtration. Considering the complexity and limitations of quantification of 24 h urinary creatinine, and with the purpose of simplifying it regarding assistance, various formulas of glomerular filtration estimation were proposed based on serum creatinine, of which the most used in dosage of medicines are, first, Cockcroft-Gault (CG), and secondly, Levey or Modification of Diet in Renal Disease (MDRD).[1,12] Creatinine clearance (CrCl) supposes a systematic overestimation of 10% or 20% of the GFR, due to the fact that creatinine goes through a tubular secretion process, a reason why some researchers proposed a correction of this bias through the product GFR = 0.84 · CrCl.[13] Regardless of this, creatinine clearance values and GFR are interchangeable[2] in clinical practice.

There is another endogenous marker of glomerular filtration, similar to serum cystatin-C, which appears to be more precise in quantification of glomerular filtration, even though an improvement regarding equations of estimation of glomerular filtration based on the serum creatinine value has still not been demonstrated with adequate certainty,[1] and it has not been validated in special populations.[2,14,15]

The importance of evaluation of renal function in critically ill patients for a correct individualization of pharmacotherapeutic regimens is unquestionable.[16] In a recent study, with a main objective of comparing critically ill ICU patients with 2 formulas for estimating creatinine clearance as a marker of glomerular filtration, *a)* Cockcroft-Gault (CG), and *b)* MDRD, using 24 h urinary creatinine clearance values ($CrCl_{24h}$) as a reference, expressed in mL/min, no significant differences were observed among them.[17] In the study, it was concluded that either of the formulas could be used in this population of patients. However, an individualized data analysis demonstrated that in some patients notable differences were observed between creatinine clearance values obtained by the reference method ($ClCr_{24h}$) and values of estimated GFR (eGFR) for each one of the 2 formulas, CG and MDRD.

The objective of this study is to analyze possible clinical consequences regarding of the dosage of antibiotic medicines such as cefepime, piperacillin/tazobactam, and meropenem, which are principally eliminated through the kidneys.

METHOD

Patients

Observational and retrospective study carried out on adult patients admitted into various ICU's of a university hospital with 800 beds. In the study, 125 samples from 61 patients were included during a period of 2 years, and those who received extracorporeal purification techniques (hemodialysis, hemofiltration, etc) were excluded.

Data Collection

For each sample, demographic (age, sex, weight, height) and biochemical (24 h urinary creatinine, serum creatinine, nitrogen uremic balance [NUB], and albumin) information was collected. eGFR values were calculated according to CG formulas (eq. 1) and MDRD (eq. 2). That is, each sample had 3 values for renal function (CG, MDRD, $CrCl_{24h}$). Body surface areas were found by the Mosteller formula (eq. 3), by using height averages by sex, all of them not being available. The values $CrCl_{24h}$ values 1.73 m^2 of body surface area (eq. 4) were standardized for classifying patients, as will be subsequently shown, and MDRD values were converted from mL/min · 1.73 m^2 to mL/min (eq. 5).

Eq. 1

CG (mL/min) = [(140 – age [years]) · actual weight (kg)] / [72 · serum creatinine (mg/dL)] · (0.85 if female)

Eq. 2

MDRD (mL/min · 1.73 m^2) = 170 · [serum creatinine (mg/dL)]$^{-0.999}$ · [age (years)]$^{-0.176}$ · [0.762 if female] · [1.180 if of black race] · [NUB (mg/dL)]$^{-0.170}$ · [albumin (g/dL)]$^{+0.318}$

Eq. 3

SC (m^2) = [(actual weight (kg) · (height (cm)/3600)]$^{0.5}$, with an average height in males of 176.8 cm and in females of 162.1 cm.

Eq. 4

Standardization $CrCl_{24h}$ times 1.73 m^2 = $CrCl_{24h}$ · 1.73/SC

Eq. 5

Conversion of MDRD from mL/min · 1.73m^2 to mL/min = MDRD · SC/1.73

Dosage of antibiotics

For dosage recommendations of antibiotic medicines studied—cefepime, piperacillin/tazobactam, and meropenem—on the basis of the patient's renal function (estimation of glomerular filtration) 2 bibliographic sources were consulted: *a)* Micromedex database (September 2006);[18-21] and *b)* Drug Information Handbook 2004-2005[22] (Table 1).

Table 1. Daily Dosage Adjusted by Renal Function According to the Bibliography, Drug Information Handbook 2004-2005 and Micromedex September 2006

Meropenem		
Creatinine Clearance, mL/min	**Drug Information Handbook 2004-2005 Meropenem Adults**	**Micromedex Meropenem Adults: Complicated Infectious Abdominal Disease**
>50		3 g/day i.v.
26-50		2 g/day i.v.
10-25		1 g/day i.v.
<10		0.5 g/day i.v.
Piperacillin/Tazobactam		
Creatinine Clearance, mL/min	**Drug Information Handbook 2004-2005 Piperacillin/Tazobactam Adults: Severe Infection, Except Nosocomial Pneumonia**	**Micromedex Piperacillin/Tazobactam Adults: Infection, Except Nosocomial Pneumonia**
>40	12 g/day i.v.	13.5 g/day i.v.
20-40	8 g/day i.v.	9 g/day i.v.
<20	6 g/day i.v.	6.75 g/day i.v.
Cefepime		
Creatinine Clearance, mL/min	**Drug Information Handbook 2004-2005 Cefepime Adults: Infection, Except Febrile Neutropenia and Mild to Moderate Urinary Infection**	**Micromedex Cefepime Adults: Infection, Except Febrile Neutropenia and Mild to Moderate Urinary Infection (in Moderate to Severe Pneumonia and With Normal Renal Function, Dosage May Vary From 2 to 4 g/day)**
<60		4 g/day i.v.
30-60		2 g/day i.v.
11-29		1 g/day i.v.
<11		0.5 g/day i.v.

i.v. indicates intravenous.

Data Analysis

Comparison of the Glomerular Filtration Estimations According to the 2 Formulas Described

Renal function data ($CrCl_{24h}$, MDRD, and CG) were collected and saved in an Excel database. Patients were ordered and classified according to $CrCl_{24h}$ standardized by body surface area, according to the National Kidney Foundation (NKF)[23] regulation: stage 1 (GFR >90 mL/min · 1.73 m^2) (n_1=22); stage 2 (GFR 60-89 mL/min · 1.73 m^2) (n_2=39); stage 3 (GFR 30-59 mL/min · 1.73 m^2) (n_3=40); stage 4 (GFR 15-29 mL/min · 1.73 m^2) (n_4=15), and stage 5 (GFR <15 mL/min · 1.73 m^2) (n_5=9). Next, daily dosages corresponding to each of the renal function values ($CrCl_{24h}$, MDRD, and CG) were assigned in mL/min, obtained for each patient and estimation method, and the correlation or discrepancy of daily dosages adjusted according to CG and MDRD corresponding with $CrCl_{24h}$. In patients with clear discrepancies observed regarding dosage of these medicines, causes of this and possible implications in clinical treatment were evaluated.

Dosage Analysis

In each NKF classification stage, *a)* quantity of daily overdosing and underdosing in grams (g) (Δ = dosage CG – dosage $CrCl_{24h}$; Δ = MDRD dosage – $CrCl_{24h}$ dosage), and *b)* the percentage of patients who presented with deviations.

The value $CrCl_{24h}$ was always employed during the study period for the dosage of these medicines in clinical practice. The estimated glomerular filtration values were only considered in a "theoretical" way to establish comparisons between them and possible clinical implications which could be drawn from them.

Statistics

The comparison of distinct creatinine clearance estimations for one subject was carried out through tests based on the study of concordance between ordered categorical variables (c>2), such as the concordance observed by percentage agreement (po) and by weighted kappa (κp). The interpretation of value κp is arbitrary; in this study, the proposal by Landis y Koch (1977) is used: <0.20: very low; 0.21-0.40: low; 0.41-0.60: moderate; 0.61-0.80: good; 0.81-1.00: excellent.

The percentages of multi-organ failure and of each NKF stage of the 2 eGFR's were compared by the test of χ^2 or Fisher's exact test. A *P* value less than .05 was considered statistically significant. The confidence intervals were calculated in each case.

RESULTS

Meropenem

In Table 2 results are shown from the within-subject statistical concordance tests between the 2 glomerular estimation methods, which indicate a degree of good concordance with respect to the reference method ($CrCl_{24h}$) for CG and excellent for MDRD, without statistically significant differences.

Multi-organ failure from meropenem dosage is slightly higher in creatinine clearance estimation with MDRD. Likewise, statistically significant differences in the percentages of failure in different NKF stages were not observed either. In stage 1, it is fitting to point out the absence of failures in estimation by CG and in stage 2, a small percentage of discrepancy is observed with MDRD (3%). In stage 3, variance is similar for the 2 estimation methods, although it is a little greater with MDRD. On the other hand, in stage 4, the percentage of disagreement is

Table 2. Within-Subject Tests

Beta-Lactamase Antibiotic	Parameter	CG Compared With $CrCl_{24h}$	MDRD Compared With $CrCl_{24h}$	*P*	95% CI
Meropenem	Observed concordance by percentage agreement	80.8%	80%	>.05	−9.0 to 10.6
	Weighted kappa	0.77	0.81	–	–
Piperacillin/tazobactam	Observed concordance by percentage agreement	83.2%	84.8%	>.05	−10.7 to 7.5
	Weighted kappa	0.72	0.73	–	–
Cefepime	Observed concordance by percentage agreement	74.4%	72%	>.05	−8.6 to 13.4
	Weighted kappa	0.78	0.79	–	–

CG indicates Cockcroft-Gault formula; CI, confidence interval; $CrCl_{24h}$, 24 h urinary creatinine clearance; MDRD, Modification of Diet in Renal Disease.

less with the estimation by MDRD. Ultimately, in stage 5, percentages of failure are higher and reach values of 44% for CG and MDRD, although MDRD is safer considering that the risk of overdosing of Δ = (+ 1.5 g/day) is 11% compared to 33% with CG (Figure 1).

Failures from estimation of glomerular filtration with MDRD in stage 2 are due to underdosing of Δ = (–1 g/day), while in stages 4 and 5, they are caused by overdosing.

Piperacillin/Tazobactam

In Table 2, the degree of within-subject concordance of piperacillin/tazobactam in the 2 revised methods is collected, which is good and without statistically significant differences.

In reference to the percentages of patients with dosage deviations, no statistically significant differences were detected between both methods. The overall dosage deviation reaches a proportion slightly greater with CG. In stages 1 and 2, dosage discrepancies were not shown in any patients and methods. In stages 3, 4, and 5, there were variances observed in the 2 methods used, and higher proportions of deviations with CG in stages 4 and 5 (Figures 2 and 3).

The piperacillin/tazobactam graphs reflect that in the stage 3 discrepancies there is a predominance of underdosing with MDRD, while with CG, the same proportion of underdosing and overdosing is shown. In stages 4 and 5, discrepancies are produced mostly by overdosing (Figures 2 and 3).

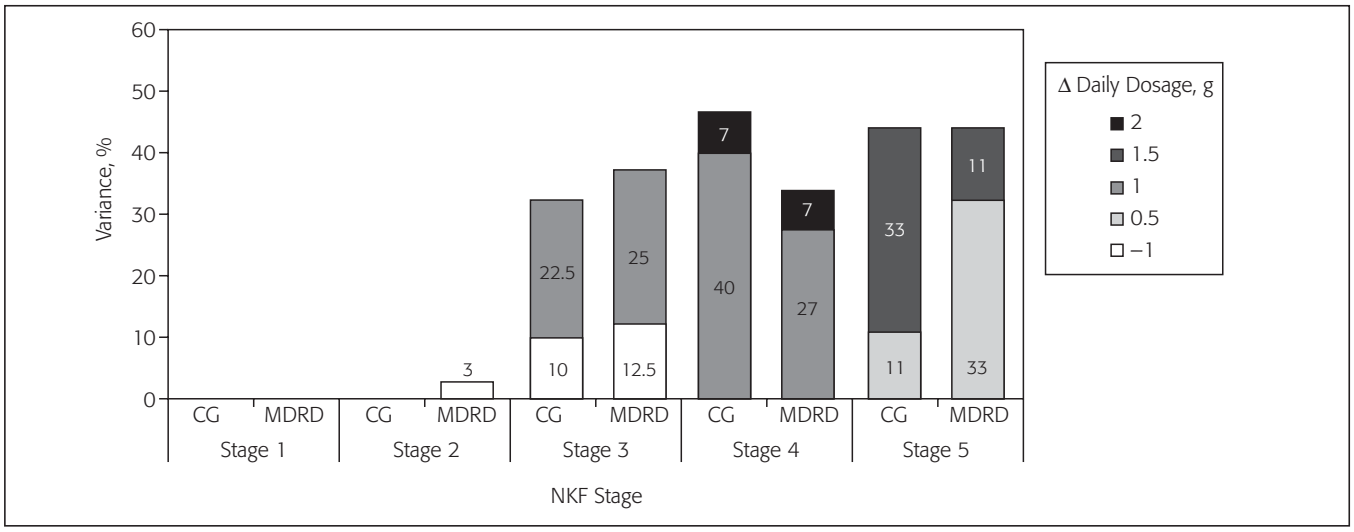

Figure 1. *Percentage of variance of meropenem according to NKF stage and dosage difference (g): Cockcroft-Gault (CG) compared with Modification of Diet in Renal Disease (MDRD).*

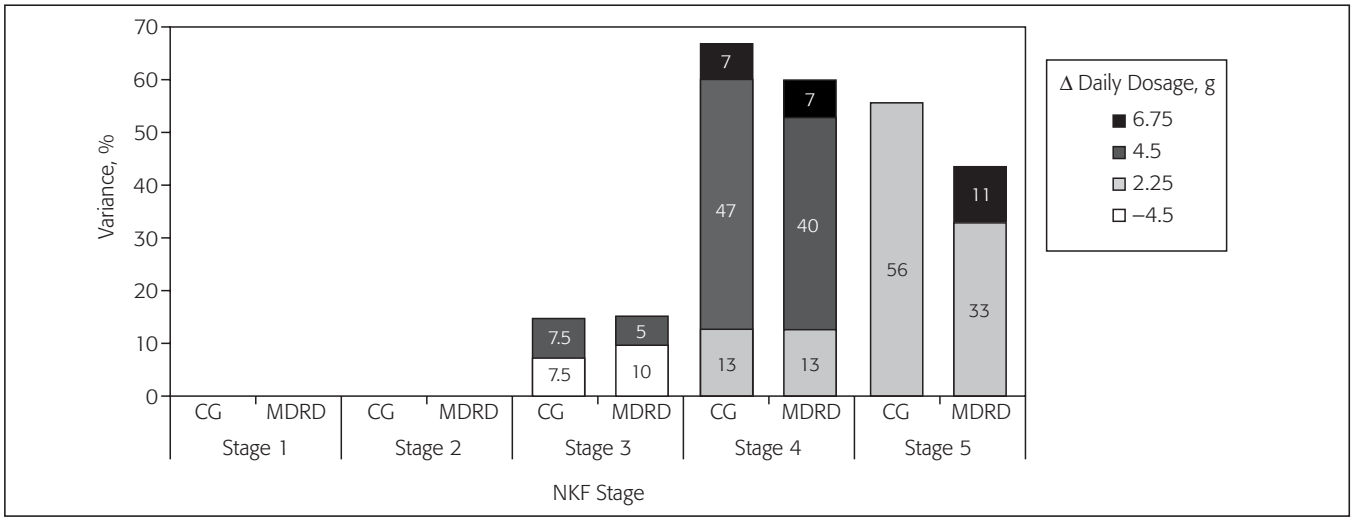

Figure 2. *Percentage of variance of piperacillin/tazobactam according to NKF stage and dosage difference (g) (Micromedex dosage): Cockcroft-Gault (CG) compared with Modification of Diet in Renal Disease (MDRD).*

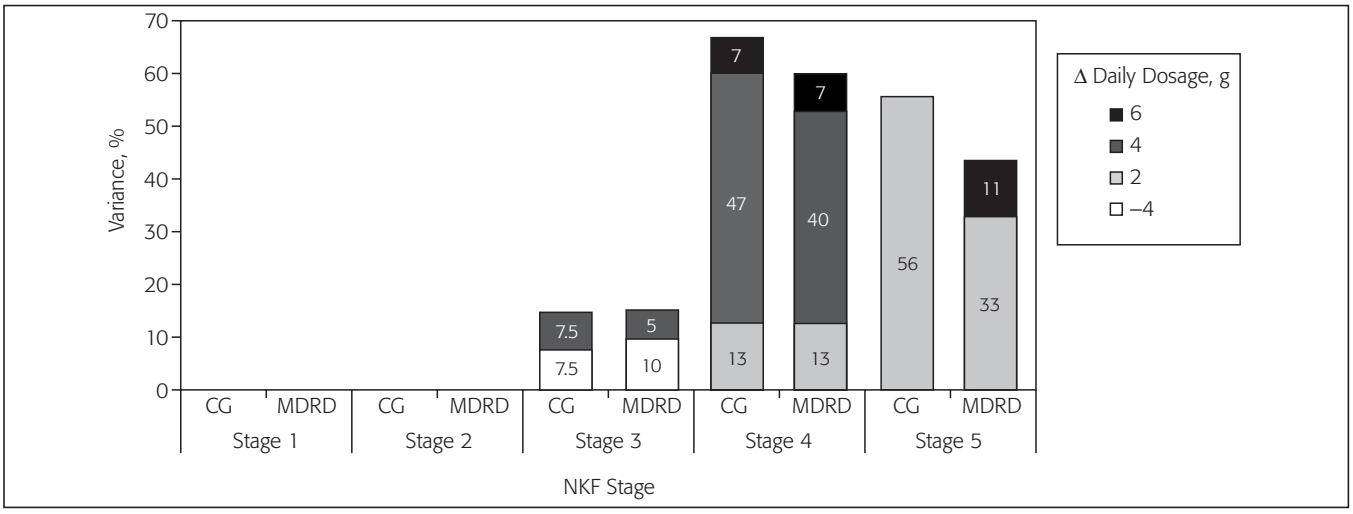

Figure 3. *Percentage of variance of piperacillin/tazobactam according to NKF stage and dosage difference (g) (dosage of Drug Information Handbook): Cockcroft-Gault (CG) compared with Modification of Diet in Renal Disease (MDRD).*

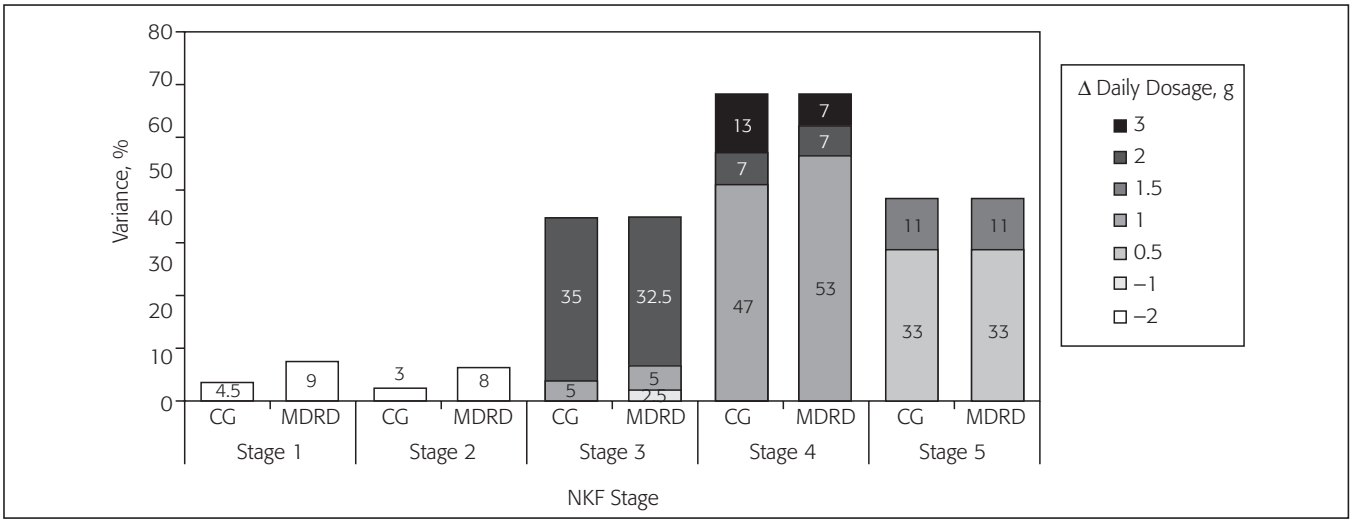

Figure 4. *Percentage of variance of cefepime according to NKF stage and dosage difference (g): Cockcroft-Gault (CG) compared with Modification of Diet in Renal Disease (MDRD).*

Cefepime

Within-subject statistical analysis of cefepime of the 2 formulas compared, CG and MDRD with respect to $CrCl_{24h}$, shows a good degree of concordance without statistically significant differences (Table 2).

Deviations of overall dosage are slightly surpassed by creatinine clearance estimation by MDRD, and these occur with the 2 estimation methods in all stages, without achieving statistical significance in any case.

In the cefepime figure, it is demonstrated that in stages 1 and 2 discrepancies of dosage are due to underdosing. In stage 3, the risk of overdosing is very similar in both methods; however, in MDRD there is a small risk of underdosing (2.5%) of Δ = (–1 g/day) which is not observed in CG. In the entirety of discrepancies detected with MDRD in stages 4 and 5 occur due to overdosing, while in stage 4, the MDRD formula is safer regarding less risk of overdosing of Δ = (+3 g/day) (Figure 4).

DISCUSSION

In view of the previous results, statistically significant differences have not been observed between the 2 estimation methods of aGFR in any of the beta-lactamase antibiotics studied, considering that either of the 2 formulas (CG and MDRD) may be employed for the dosage of these antibiotics in critically ill patients with different degrees of renal functionality.

In the case of meropenem, the use of the CG formula could be recommendable for patients with renal function in NKF stages 1 and 2 (GFR >60 mL/min · 1.73 m^2) for avoiding the risk of therapeutic ineffectiveness (underdosing of 1 g daily) which could be produced when dosing based on eGFR by MDRD (Figure 1). Nevertheless, in stage 3, the differences between both glomerular estimation formulas are reduced and imply less failure with CG, and in NKF stage 4, less risk of overdosing is observed with the MDRD formula, although this result should be interpreted cautiously given the small sampling (n_4=15). Finally, even though the size of the NKF stage 5 sampling is very small (n_5=9), it seems that MDRD is safer considering that the risk of overdosing of Δ = (+1.5 g/day) is less. It is apparent that, as the stage of renal dysfunction advances, the CG formula worsens in regard to the estimation of glomerular filtration, therefore the use of MDRD is recommended, mainly from stage 4 onward. These data are consistent with previous studies on patients which conclude that: *a)* MDRD compared with CG shows improved exactness and precision of the estimation[12] of aGFR of ^{125}I-iothalamalate in chronically ill patients with a GFR <60 mL/min · 1.73 m^2, *b)* MDRD systematically underestimates the aGFR's of ^{125}I-iothalamalate[7,12,24] or ^{51}Cr-EDTA[25] in healthy kidney donors; and *c)* CG overestimates the aGFR's of ^{125}I-iothalamalate[12,13,24] or ^{51}Cr-EDTA[25] in chronically ill kidney patients. Regarding the CG formula, in some studies carried out on healthy individuals, an underestimation is shown[7,24] and in others, an overestimation[12,25] of aGFR. In another study carried out on 26 patients with end-stage renal disease (ESRD) the low precision of MDRD and CG compared with inulin and $CrCl_{24h}$ in an interval of inulin clearance values of 2.21 to 18.85 mL/min and $CrCl_{24h}$ from 5.11 to 23.33 mL/min has been confirmed, although MDRD shows greater predictive value than CG in these circumstances.[26]

In reference to piperacillin/tazobactam, the use of the CG formula is estimated to be more convenient, independently from the NKF stage. This is especially applicable for NKF stage 5, with an 11% risk of serious overdosing (6.25 g/day, Micromedex, or 6g/day, Drug Information Handbook) with MDRD, and it has an important clinical relevance if we consider that patients experiencing the mentioned stage present with a serious deterioration of renal function which supposes reduced elimination of the medicine through the kidneys, with the subsequent risk of adverse events due to accumulated toxicity of the medicine. Therefore, although we should cautiously interpret these results due to the small population studied (n_5=9). It is more acceptable, regarding the benefit/risk, to assume the risk of overdosing from 2.25 g/day in 56% of patients with CG applied than accepting the risk of serious overdosing from 6.25 g/day, or from 6 g/day with MDRD (11%). On the other hand, it is fitting to remember that the CG equation only integrates variables of age, weight, and serum creatinine value, while MDRD considers serum creatinine variables, NUB, albumin, age, sex, and race.

Deviations of cefepime dosage are evident with 2 methods of glomerular filtration estimation in all stages of NKF, committing smaller percentage errors with CG in patients with $CrCl_{24h}$ >60 mL/min · 1.73 m^2 due to the fact that underestimation of aGFR is even greater with MDRD.[12] Nevertheless, in stage 4 a greater risk is observed (in daily quantity) of overdosing using CG, although more studies are necessary with a broader population to confirm these results and their actual clinical relevance. Until otherwise demonstrated, it seems advisable to use the CG method to allow for greater simplicity in its use in medical practice, due to the simplicity of calculation offered by the CG formula.

A high number of beta-lactamase antibiotics are characterized by their renal elimination. Cefepime shows almost exclusive renal elimination and mainly by glomerular filtration, demonstrating a urinary recovery of more than 80%[27] of the total dosage of unaltered medicine, along with an absence of biliary excretion. Renal excretion reaches 70%, 69%, and 50%-60% for meropenem,[28] piperacillin,[29] and tazobactam[20] (when it is co-administered with piperacillin, given that the last one decreases the elimination of tazobactam), respectively. The differences, especially of underdosing in NKF stages 1 and 2, seem to depend on the percentage of renal elimination of each one of the beta-lactamase antibiotics, with cefepime being more sensitive to prediction errors with CG and MDRD when being almost totally excreted by the kidneys, and concretely, by glomerular filtration. Following cefepime, second is meropenem, and lastly piperacillin/tazobactam, this being the least affected medicine.

On the other hand, the cut-off point of meropenem for dosage adjustment in these stages is more restrictive than that of piperacillin/tazobactam: a CrCl of 50 mL/min of the first compared with the CrCl of 40 mL/min of the last. In general, healthy individuals tend to have values of $CrCl_{24h}$ ≥60 mL/min · 1.73 m^2, and the repercussion of differences between eGFR and aGFR in the dosage of beta-lactamase antibiotics is much less than in patients with values of $CrCl_{24h}$ <60 mL/min · 1.73 m^2, due to the fact that all of the first ones remain included in the same dosage regimen without requirements of dosage adjustment in a very broad interval of $CrCl_{24h}$.

The MDRD equation was developed in a cohort study of 1628 adult non-diabetic patients with moderate chronic renal insufficiency in 1999 with a $CrCl_{24h}$ average (standard deviation [SD])[13] of 48.6 (24.5) mL/min · 1.73 m^2, and subsequently its applicability was validated in more extensive populations of patients with chronic disease.[12] Renal insufficiency generally means a reduction of GFR values, particularly below 60 mL/min · 1.73 m^2. On the other hand, the CG equation was obtained from a population of 249 adult males, from which the values of the CG formula were compared with $CrCl_{24h}$ in 236 patients with an interval of $CrCl_{24h}$ of 11 mL/min up to normal values, with an average of 72.7 (36.6) mL/min.[11] Therefore, although the results from our study indicate that the applicability of MDRD and CG improves when there is a greater approximation to population characteristics of original samples, none of the equations possesses optimal precision for ideal care of non-critical subjects,[2,7,24,25] considering that erroneous classification is believed in approximately 3 or 4 cases out of every 10 patients in the NKF category.[2,25] This coincides with our results regarding overall

percentages of deviation of cefepime. Moreover, deficiencies of CG and MDRD seem to worsen in patients with ESRD[26] and in ICU[9,10,16] because of not being specifically developed in these extreme populations.

Some of the possible limitations of this study are: *a)* the original CG[11] formula is based on actual weight, although in the discussion, the authors suggest the use of ideal weight in obesity and liquid accumulation, even though this has not been validated. In our population, according to the results indicated from another study carried out in our centre,[30] equal or even better correlation is obtained with $CrCl_{24h}$ when CG is used than with CG with ideal weight, without observing statistical significance; *b)* the reduced size of the sample corresponding to the subgroups of NKF stage 4 and 5 patients (n_4=15 and n_5=9); *c)* the lack of availability of all heights; and *d)* the variability of factors which influence creatinine production presupposes that the creatinine value could be false in multiple situations, and therefore, give place to prediction errors of aGFR with formulas based on the serum creatinine value.[1,8] In general, it is known that the predictive ability of CG and MDRD equations is suboptimal for correct and integral assistance of patients.[2,7,24,25] In addition, in ICU patients, malnutrition, postration,[10,16] or deterioration of hepatic function[10] tend to decrease serum creatinine values. There are few ICU patients who do not present with any of the situations previously discussed, because it is difficult to predict or estimate their aGFR, particularly the unstable ones.[10] Another source of variability could be the determination of serum creatinine between different laboratories of the same hospital, whether a central or an emergencies one. It seems that these differences are more pronounced in lower serum creatinine values,[12] and the sensitivity of serum creatinine is limited for detecting reductions of aGFR in its interval of values considered normal.[2]

The few publications on the comparison of equations based on serum creatinine in ICU patients corroborate our results that CG[9,10] and MDRD[10] do not provide a good approximation to $CrCl_{24h}$.

Nevertheless, our recommendation for actual clinical practice is the estimation of aGFR by CG, given its acceptable level of precision and its greater calculation simplicity.

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