Correlation of Estimated Creatinine Clearance and Glomerular Filtration Rate in Very Elderly Patients and Antibiotic Prescribing Errors: A Cohort Study

Correlação entre a Clearance da Creatinina Estimada e a Taxa de Filtração Glomerular Estimada nos Doentes Muito Idosos e Erros de Prescrição dos Antibióticos: Um Estudo de Coorte

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ABSTRACT

Introduction: Determination of renal function is particularly important when prescribing antibiotics to elderly patients. This study aims to determine the correlation between estimated creatinine clearance and the estimated glomerular filtration rate, for a hospitalized population of very elderly patients, and to audit antibiotic prescribing errors.

Material and Methods: Retrospective cohort study of all patients ≥ 80 years hospitalized with antibiotic. Creatinine clearance was calculated using Cockcroft-Gault equation and estimated glomerular filtration rate by Modification of Diet in Renal Disease Study and Chronic Kidney Disease Epidemiology Collaboration equations. Dosing errors were determined through adjustment of daily define dose to renal function.

Results: The study included 589 patients. The correlation of Cockcroft-Gault with Modification of Diet in Renal Disease and Chronic Kidney Disease Epidemiology Collaboration was *r* = 0.98 and 0.96 for the minimum serum creatinine, and 0.97 and 0.93 for the maximum serum creatinine. Based on Cockcroft-Gault, there were errors in the daily defined dose in 45% in the minimum serum creatinine, and 52% in the maximum serum creatinine day. There was a discrepancy in the recording of errors of 14% to 16% when Cockcroft-Gault was compared with Modification of Diet in Renal Disease and Chronic Kidney Disease Epidemiology Collaboration.

Discussion: There was a good correlation of Cockcroft-Gault with the estimated glomerular filtration rate by Modification of Diet in Renal Disease or Chronic Kidney Disease Epidemiology Collaboration. Regardless of the equation used to estimate renal function there was a high rate of antibiotic dosing errors documented in this population.

Conclusion: This study supports the maintenance of the Cockcroft-Gault equation for drug dosing in the very elderly population. Further studies are needed to investigate underlying causes of prescribing errors.

Keywords: Aged, 80 and over; Aging; Anti-Bacterial Agents; Creatinine; Glomerular Filtration Rate; Medication Errors

RESUMO

Introdução: A determinação da função renal é particularmente importante na prescrição de antibióticos em doentes idosos. O objetivo deste estudo é correlacionar a *clearance* de creatinina com a taxa de filtração glomerular estimada, numa população hospitalizada de doentes muito idosos, e auditar os erros de prescrição antibiótica.

Material e Métodos: Coorte retrospetivo de todos os doentes ≥ 80 anos hospitalizados com antibioterapia prescrita. A *clearance* de creatinina foi calculada através da equação Cockcroft-Gault, e a filtração glomerular estimada através das equações *Modification of Diet in Renal Disease* e *Chronic Kidney Disease Epidemiology Collaboration*. Os erros de prescrição foram determinados pelo ajuste da dose diária definida à função renal.

Resultados: Foram incluídos 589 doentes. A correlação da Cockcroft-Gault com *Modification of Diet in Renal Disease* e *Chronic Kidney Disease Epidemiology Collaboration* foi *r* = 0,98 e 0,96 para a creatinina sérica mínima, e 0,97 e 0,93 para a creatinina sérica máxima. Com base na Cockcroft-Gault, a taxa de erro na dose diária definida foi 45% no dia da creatinina sérica mínima e 52% no dia da creatinina sérica máxima. Quando a Cockcroft-Gault foi comparada com a *Modification of Diet in Renal Disease* e a *Chronic Kidney Disease Epidemiology Collaboration* houve uma discrepância no registo de erros de 14% a 16%, respetivamente.

Discussão: Verificou-se uma boa correlação entre a Cockcroft-Gault e as equações que calculam a filtração glomerular: *Modification of Diet in Renal Disease* ou *Chronic Kidney Disease Epidemiology Collaboration*. Independentemente da equação utilizada para estimar a função renal, foi documentada uma taxa elevada de erros na dose de antibióticos prescrita nesta população.

Conclusão: Este estudo reforça a manutenção do uso da equação de Cockcroft-Gault para calcular a dose adequada de antibióticos na população muito idosa. Mais estudos são necessários para investigar as causas subjacentes aos erros de prescrição.

Palavras-chave: Antibacterianos; Creatinina; Envelhecimento; Erros de Medicação; Idoso de 80 Anos ou mais; Taxa de Filtração Glomerular

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INTRODUCTION

Most drugs and their metabolites are excreted by the kidney through glomerular filtration. The overall size, mass and effective area of filtration decrease with increasing age.[1,2]

Therefore, there is an increased risk of drug and active metabolite accumulation in older patients, which accounts for the greater incidence of adverse drug reactions in this age group.[1]

Adverse drug events are between the fourth and sixth leading cause of death in the United States[3] and are responsible for one in six hospital admissions of older adults.[4]

Antibiotics are the second most common cause of adverse drug events in the ambulatory setting among seniors.[5]

Most guidelines recommend drug dosing adjustments in older adults with or without renal disease. The focus should be placed on reaching the optimal balance between improved outcomes while minimizing potential for drug toxicity. Therefore, the evaluation of renal function is of the essence. In order to determine renal function, several equations have been studied and validated using serum creatinine level as a marker for renal clearance. The Cockcroft-Gault (CG) equation, despite inaccurate in the elderly, remains the most widely used equation for determining the creatinine clearance. For more accurate assessment of estimated glomerular filtration rate (GFR), two other equations have been developed using larger populations: the Modification of Diet in Renal Disease (MDRD) Study equation and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[1,6]

In comparisons between the CG, MDRD and CKD-EPI in the elderly, MDRD and CKD-EPI have been shown to more accurately assess estimated GFR than CG[6]; however, the MDRD Study equation has not been validated in elderly persons (> 70 years of age).[7]

The aim of this study is to determine the correlation between estimated creatinine clearance by CG equation with estimated GFR by MDRD and CKD-EPI equations, for a hospitalized population of very elderly patients (aged 80 years and older), and to audit antibiotic prescription, namely adjustment to renal function.

MATERIAL AND METHODS

Retrospective cohort study of all patients aged 80 years and older, admitted to Hospital de Santo António, Centro Hospitalar Universitário do Porto (HSA-CHUP), to whom antibiotic therapy was prescribed with intention to treat (antibiotic prophylaxis was not included). It was conducted over a three- month period, between 1st January 2017 and 31th March 2017. Ethical approval was obtained from the Ethical Committee for Health of HSA-CHUP, on March 2019 – N/REF.ª 2018.224(194-DEFI/193-CES).

Clinical characterization and approach

In the study period, prescribed antibiotic regimens, the loading doses, the daily defined doses (DDD) – in the day of maximum and minimum serum creatinine – and the total period of antibiotic therapy were obtained from the clinical records. In every patient, only the first cycle of antibiotic treatment in each hospitalization was considered. If modifications were made to the prescribed antibiotics, the reasons stated in the clinical records were also obtained. Patients with end-stage renal disease undergoing hemodialysis, peritoneal dialysis, or kidney transplantation, those prescribed with topical antibiotics or antibiotics with a prophylactic intent or those in whom the treatment lasted less than 48 hours were excluded.

Patients' age, gender, race, body weight and height were obtained from the clinical records. Patients' comorbidities were determined and used to obtain the Charlson Comorbidity Index (CCI) score.[8] The degree of functional impairment was determined according to the Karnofsky Performance Status Scale (KPS), using the information provided by clinical records.[9] This variable was then categorized in two groups: a group of patients with preserved autonomy in activities of daily living (score ≥ 70%) and a group of patients with some degree of dependence (score < 70%). The prescribing software used for inpatients was also used to assess if the patients' weight and creatinine were registered for automatic calculation of creatinine clearance.

Renal function calculation equations

For each patient, renal function was estimated using three creatinine-based equations: the CG equation,[10] which was further adjusted based on body weight and body mass index (BMI), since this equation appears to become less accurate in weight extremes (underweight and particularly overweight and obesity)[11]; the 4-variable MDRD Study equation[12]; and the CKD-EPI equation.[13] The MDRD Study and CKD-EPI equations calculate the estimated GFR normalized to a standard body surface area (BSA) of 1.73 m^2 and generally are reported in mL/min/1.73 m^2. These BSA-adjusted values were converted through the Dubois formula,[14] so that all were expressed in units of mL/min, the units of GFR that are expressed in the majority of drug dosing labels.

Antibiotic prescribing errors

A prescription was classified as a dosing error if it did not follow the recommended guidelines for drug adjustment to the renal function, according to The Sanford Guide to Antimicrobial Therapy,[15] whether it was by exceeding the maximum DDD – excess dosing – or by giving a lower dose than recommended – under dosing. An incorrect loading dose was also classified as a dosing error. In the case that more than one antibiotic was prescribed simultaneously, and only one presented a dosing error, that error prevailed upon the correct dosing; if both presented different types of dosing errors (e.g.: under and excess dosing), under dosing was prioritized. As three different equations for estimating renal function were used, the impact that using different formulas to estimate renal function had on the number of dosing errors was also compared. The association of dosing errors

with patient age, gender, race, comorbidities, functional status, body weight (real, ideal, adjusted), height, BMI, weight and/or creatinine registry in the prescribing software were also examined. All dosing errors were based on the same day creatinine.

Statistical analysis

Categorical variables were described as proportions and compared using chi-square or Fisher's exact test. Continuous variables were described by mean and standard deviation. Comparisons of continuous variables were performed using student *t*-test, after confirming its normal distribution through histogram.

Correlation was studied with Pearson correlation coefficient.

The association between the dependent variable (antibiotic prescribing error) and the other variables was studied through univariate logistic regression. Those with a clear association in the univariate analysis (p-value < 0.1) were selected for the multivariable analysis. The results of the multivariable models are expressed as odds ratio (OR) with 95% confidence interval ($CI_{95\%}$) and p-values. The calibration was tested using the Hosmer-Lemeshow goodness-of-fit test. The significance level was defined as $p < 0.05$.

The statistical analysis was performed in IBM SPSS (Statistical Package for the Social Sciences)® 25 (SPSS Inc., Chicago IL).

RESULTS

Clinical characterization and correlation between estimated CG and estimated GFR

During the study period, 929 patients aged 80 years or older undergoing antibiotic therapy were admitted to HSA-CHUP. Of these, a total of 340 patients (36.6%) were excluded from this study (Fig. 1): 12 (1.3%) had end-stage renal disease undergoing hemodialysis, peritoneal dialysis or kidney transplantation; 7 (0.8%) were on topical antibiotics; 89 (9.6%) had antibiotic prophylaxis; 104 (11.2%) had antibiotic therapy for less than 48 hours; 21 (2.3%) did not have serum creatinine values available in the clinical records during the antibiotic therapy period; and 107 (11.5%) did not have weight and/or height data available in the clinical records.

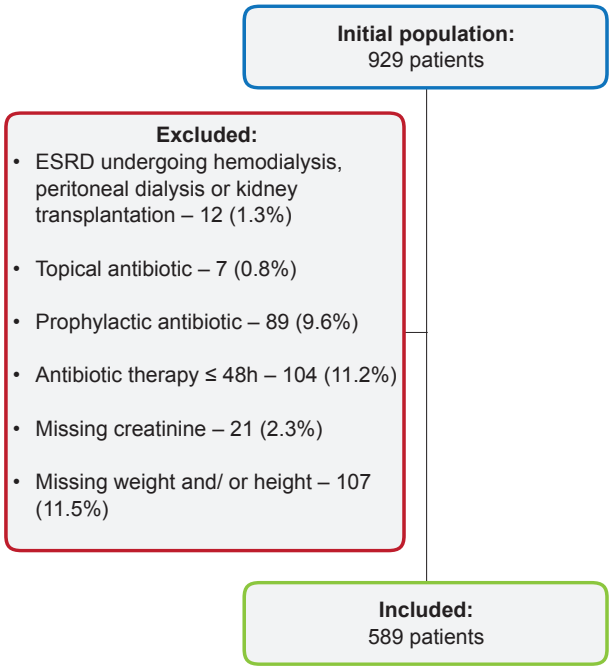

Figure 1 – Flow diagram of included patients
ESRD: end-stage renal disease

The clinical characteristics of the 589 patients included in the study population are listed in Table 1. The mean age of the cohort was 87 ± 4 years. The male gender accounted for 42% of patients. Only one patient of this population was black. Regarding the KPS, 37% of patients were independent in activities of daily living (Karnofsky score above 70%).

Considering the baseline serum creatinine, mean creatinine clearance estimated with CG equation was 42 ± 17 mL/min and mean estimated GFR with MDRD Study and CKD-EPI equations were 63 ± 27 and 57 ± 20 mL/min, respectively ($p < 0.001$). The correlation of CG equation with MRDR ($r = 0.95$, $p < 0.001$) is shown in Fig. 2A and with CKD-EPI ($r = 0.96$, $p < 0.001$) in Fig. 2B.

Considering the minimum serum creatinine, mean creatinine clearance from CG equation was 36 ± 19 mL/min and mean estimated GFR from MDRD Study and CKD-EPI equations were 54 ± 31 and 49 ± 24 mL/min, respectively ($p = 0.002$). The correlation of CG equation with MRDR obtained an $r = 0.98$ ($p < 0.001$) and with CKD-EPI an $r = 0.96$ ($p < 0.001$).

Considering the maximum baseline serum creatinine, mean creatinine clearance from CG equation was 46 ± 22 mL/min and mean estimated GFR from MDRD Study and CKD-EPI equations were 70 ± 38 and 59 ± 24 mL/min, respectively ($p < 0.001$). The correlation of CG equation with MRDR obtained an $r = 0.97$ ($p < 0.001$) and with CKD-EPI an $r = 0.93$ ($p < 0.001$).

Table 1 – Clinical characteristics

Characteristic	
Age (years), mean ± SD	87 ± 4
Male gender, n (%)	246 (42)
KPS scale ≥ 70, n (%)	216 (37)
CCI score, mean ± SD	7 ± 2
Weight (kg), mean ± SD	65 ± 14
Ideal body weight (kg), mean ± SD	56 ± 10
Adjusted body weight (kg), mean ± SD	60 ± 10
Height (cm), mean ± SD	161 ± 9
BMI (kg/m^2), mean ± SD	30 ± 5
CG (mL/min), mean ± SD	42 ± 17
MDRD (mL/min), mean ± SD	63 ± 27
CKD-EPI (mL/min), mean ± SD	57 ± 20
Antibiotic therapy period (days), median (IQR)	8 (6 – 10)

SD: standard deviation; KPS: Karnofsky Performance Status scale; CCI: Charlson Comorbidity index; BMI: body mass index; CG: Cockcroft-Gault equation; MDRD: Modification of Diet in Renal Disease Study equation; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration equation; IQR: interquartile range

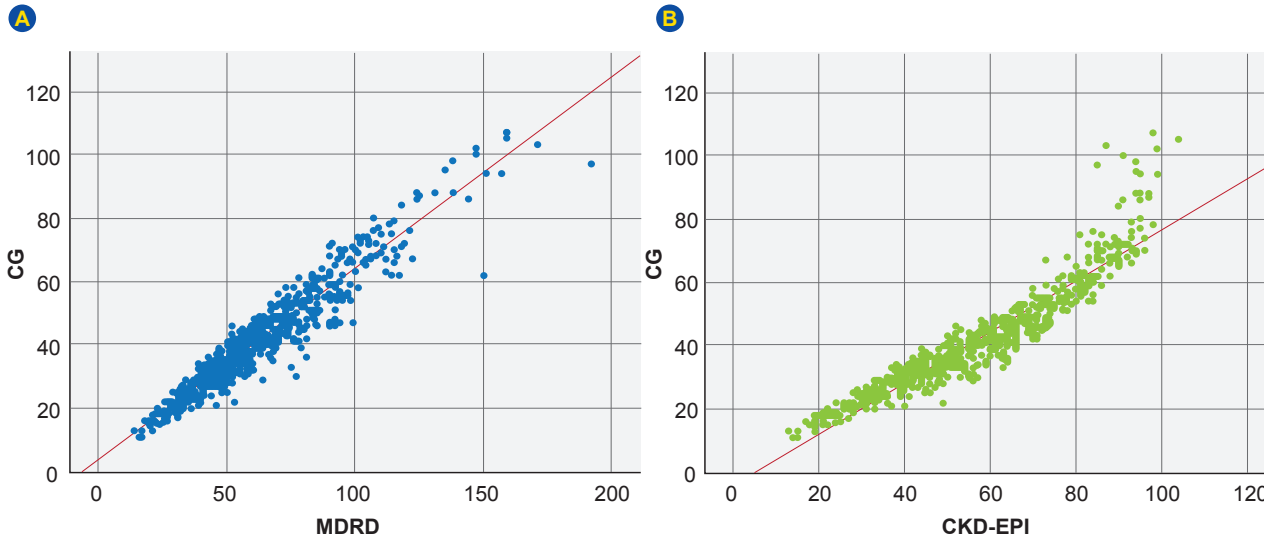

Figure 2 – (A) Correlation between baseline estimated CG and estimated GFR by MDRD equation (mL/min); (B) Correlation between baseline estimated CG and estimated GFR by CKD-EPI equation (mL/min).
CG: Cockcroft-Gault equation; MDRD: Modification of Diet in Renal Disease Study equation; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration equation

Antibiotic prescribing errors

Dosing errors in the loading dose were observed in 264 patients (44.8%): 226 (38.4%) in excess and 38 (6.5%) in under dosing.

Considering the CG equation, there were errors in DDD in 52.0% of the patients in the minimum creatinine day and 47.7% of the patients in the maximum creatinine day. Errors in the DDD according to the different renal function calculation equations are presented in Table 2. Error rates varied from 46.7% to 52.0%, in the day of minimum creatinine, and 40.1% to 53.7%, in the day of maximum creatinine.

Table 3 compares dosing errors obtained according to the MDRD and CKD-EPI equations compared to the CG equation. Using MDRD to calculate GFR, there were 85 patients (14.4%) in whom dosing errors were classified differently from the CG equation for creatinine clearance for minimum creatinine and 98 (16.6%) for maximum creatinine. Using the CKD-EPI equation, there were 83 patients (14.1%) classified differently when compared to the classification based on the CG equation for the minimum serum creatinine and 92 (15.6%) for the maximum serum creatinine.

The study of risk factors associated with error in DDD is presented in Table 4. The final multivariate logistic model retained, with an adjusted OR ($CI_{95\%}$), without available data on weight = 1.571 (1.123 - 2.197), for the minimum creatinine day, and ideal body weight = 0.982 (0.966 - 0.998) per kg for the maximum creatinine day. The Hosmer and Lemeshow test did not show evidence of lack of fit.

Prescribed antibiotics were modified in 154 cases (26.1%) and only in five patients it was due to side effects. Of these five patients, and according to the CG equation, four presented excess dosing either in the minimum creatinine day, maximum creatinine day or in the loading dose, and only one did not present any dosing errors at all.

DISCUSSION

In this population of very old patients there was an excellent correlation of CG with MDRD and CKD-EPI for different levels of renal impairment. Regardless of the equation used to estimate renal function there was a high rate of antibiotic dosing errors documented in this population.

In the elderly, MDRD and CKD-EPI have been shown to more accurately estimate GFR when compared with CG.[6]

Table 2 – Dosing errors in the daily defined dose of antibiotic therapy according to the different renal function calculation equations in the day of minimum and maximum serum creatinine

Errors in daily defined dose, n (%)	CG	MDRD	CKD-EPI
Minimum Cr			
Under	157 (26.7)	186 (31.6)	193 (32.8)
Excess	149 (25.3)	89 (15.1)	90 (15.3)
Total	306 (52.0)	275 (46.7)	283 (48.0)
Maximum Cr			
Under	89 (15.1)	117 (19.9)	192 (32.6)
Excess	192 (32.6)	119 (20.2)	124 (21.1)
Total	281 (47.7)	236 (40.1)	316 (53.7)

Note: 'Under' refers to dosing errors in which lower daily doses than recommended were given; 'excess' refers to dosing errors in which the maximum daily dose was exceeded.
Cr: creatinine; CG: Cockcroft-Gault equation; MDRD: Modification of Diet in Renal Disease Study equation; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration equation

Table 3 – Comparison of dosing errors using MDRD and CKD-EPI formulas compared with the CG equation

Equations	Dosing errors		CG					
			Minimum Cr			Maximum Cr		
			Under	Correct	Excess	Under	Correct	Excess
MDRD	**Under**	Count	157	25	4	89	25	3
		% within total	26.7	4.2	0.7	15.1	4.2	0.5
	Correct	Count	0	258	56	0	283	70
		% within total	0	43.8	9.5	0	48.0	11.9
	Excess	Count	0	0	89	0	0	119
		% within total	0	0	15.1	0	0	20.2
CKD-EPI	**Under**	Count	157	24	12	89	22	4
		% within total	26.7	4.1	2.0	15.1	3.7	0.7
	Correct	Count	0	259	47	0	286	66
		% within total	0	44.0	8.0	0	49.1	11.2
	Excess	Count	0	0	90	0	0	122
		% within total	0	0	15.3	0	0	20.7

Note: 'Under' refers to dosing errors in which lower DDD than recommended were given; 'correct' refers to the lack of dosing errors; and 'excess' refers to dosing errors in which the maximum doses were exceeded. The blue-colored cells refer to dosing errors classified in the same way by both equations; and the yellow-colored cells refer to dosing errors classified differently by both equations.
CG: Cockcroft-Gault equation; MDRD: Modification of Diet in Renal Disease Study equation; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration equation.

However, pharmacokinetic studies over the last few years have used the CG equation to determine the level of renal function for dosage adjustment in drug labels. As a result, it has become a common practice for drug dosing. Furthermore, most of the published information on dosage adjustments in renal impairment is based on creatinine clearance estimated from the CG equation.

Based on the CG equation, there were errors in DDD in approximately half of the study population; this value is within the range described by Long *et al*, a review that included 4 studies conducted in inpatient settings that describes renal dosing guideline noncompliance rates between 19% and 67%.[16] Although these studies considered drugs other than antibiotics, most of the medications prescribed at unadjusted doses were antibiotics. A recent retrospective observational study performed in two geriatric hospitals found that 20% of inpatients were prescribed a drug with incorrect adjustment for renal function based on the CG equation.[17]

Dosing errors reported in this study were due to both under and excess dosing. In the loading dose, excess dosing was more frequent; in the DDD, under dosing was slightly more frequent in the minimum creatinine day, whereas over-dosing was more frequent in the maximum creatinine day. Any form of dosing error can be harmful. Over-dosing a drug may lead to administration of inappropriately large doses and possible toxicity. Among the five patients in whom the initial antibiotic was changed due to side effects, there was over-dosing of the prescribed antibiotic in four. Conversely, under dosing may result in compromised therapeutic efficacy, resistance development and poor prognosis.

Table 4 – Factors associated with error in daily defined dose

	DDD error in the minimum creatinine day (n = 306)			**DDD error in the maximum creatinine day** (n = 281)		
Risk factor		Crude OR	*p* value		Crude OR	*p* value
Age (years), mean ± SD	87 ± 4	1.020 per year	0.300	87 ± 5	1.017 per year	0.359
Male gender, n (%)	123 (40)	0.874	0.422	107 (38)	0.748	0.083
KPS scale ≥ 70, n (%)	111 (36)	0.965	0.835	93 (33)	0.744	0.086
CCI, mean ± SD	7 ± 2	1.044 per point	0.311	7 ± 2	0.992 per point	0.843
Real body weight (kg), mean ± SD	65 ± 15	1.003 per kg	0.643	65 ± 15	1.001 per kg	0.849
Ideal body weight (kg), mean ± SD	56 ± 10	0.995 per kg	0.546	55 ± 10	0.982 per kg	**0.032**
Adjusted body weight (kg), mean ± SD	60 ± 10	0.999 per kg	0.917	59 ± 10	0.989 per kg	0.217
Height (cm), mean ± SD	161 ± 9	0.995 per cm	0.612	161 ± 9	0.981 per cm	**0.035**
BMI (kg/m^2), mean ± SD	25 ± 6	1.014 per kg/m^2	0.393	25 ± 5	1.021 per kg/m^2	0.193
Baseline serum creatinine (mg/dL), mean ± SD	1.1 ± 0.4	1.401 per mg/dL	0.077	1.1 ± 0.4	1.012 per mg/dL	0.948
Electronic weight registry absent, n (%)	173 (57)	0.637	**0.008**	176 (63)	1.085	0.632

DDD: daily defined dose; OR: odds ratio; SD: standard deviation; KPS: Karnofsky Performance Status; CCI: Charlson Comorbidity Index; BMI: body mass index

When comparing CG with MDRD and CKD-EPI for the calculation of antibiotic dosing, there was a discrepancy in 14% to 16% of patients. In all these patients, if the antibiotic dosing was based on MDRD or CKD-EPI, a higher dose of antibiotic would have been recommended, because the MDRD and CKD-EPI equations overestimate creatinine clearance.[17-22] However, according to the study by Delanaye *et al*, the assertion that CG must be favored because it gives systematically lower results, and thus prevents over-dosing is an oversimplification. The authors found that CKD-EPI did not always overestimate creatinine clearance since this was not true in obese geriatric patients.[23] Also, new creatinine-based GFR estimating equations have been reported. A recent study, in a group of patients 65 years and older, compared four equations – including the CKD-EPI equation – with the reference inulin-measuring method. The authors found that none of the equations had a better diagnostic performance and that each equation had limitations regarding accuracy.[24] Thus, for patients with extreme characteristics, like those with morbid obesity, one may opt for a specific equation for an optimum result, while for common patients, the CG equation is more practical because it is already established in clinical practice with good results and there is no compelling evidence supporting change (either clinical benefits or pharmacokinetic evidence). In light of these findings, the use of the MDRD or CKD-EPI equations interchangeably with the CG equation in drug dosing cannot be advocated.[17-22]

This study also focused on risk factors for antibiotic prescribing errors for which no systematic risk factors were found.

This study has some limitations. In order to audit antibiotic prescribing and its adequacy to renal function, dosages that did not follow the recommended guidelines were determined. However, it would have been important to assess the consequences of dosing errors in clinical practice. Concerning excess dosing, antibiotic modifications motivated by side effects were determined. However, the presence of side effects should have been assessed in every patient and not only in situations of antibiotic switch. Therefore, it is possible that adverse drug events related to prescribing errors were missed. Moreover, side effects should have been further characterized. In the case of under dosing, indices of therapeutic failure should have been searched.

Another important limitation was that neither the glomerular filtration rate nor the antibiotic serum concentration were measured, which would have been the gold standard, but being a retrospective study, this was not possible to obtain and, at the moment, only the serum levels of aminoglycosides and vancomycin can be assessed in our hospital.

As GFR was not directly measured, it was not possible to assess which equation was more accurate in estimating renal function in this group of very elderly patients. Thus, the present analysis was based solely on the comparison of estimated values.

Patients with acute illness frequently present altered pharmacokinetics either in absorption, distribution, metabolism and/or elimination, meaning that antibiotic dosing is challenging in this population and should be individualized. Since assessment of serum antibiotic levels for most antibiotics are not available, clinicians have to resort to other methods. The recommendation in acute kidney injury (AKI) is to use the trend in serum creatinine over several measurements – that is difficult to operate in a common ward and more feasible in high dependency or intensive care units, where the standard is the measure of creatinine clearance using its serum and urinary concentration, which is not possible for all hospitalized patients under antibiotic therapy and AKI. Therefore, dosage adjustments should be cautious and adjusted to the clinical scenario.

This study has a number of strengths. It included only very elderly patients, a particularly vulnerable segment of the population, in which adverse drug events are extremely common. Official dosing guidelines for renal impairment often disregard elderly patients as, in general, their inclusion in clinical studies is limited. Furthermore, this study only included antibiotics, a class of drugs widely used in clinical practice, associated with a high rate of adverse drug events. Finally, in order to ensure data was consistent, a large group of patients was studied.

CONCLUSION

In this population of very old patients there was an excellent correlation of CG with MDRD and CKD-EPI for different levels of renal impairment. The GFR calculated by MDRD and CKD-EPI equations overestimates creatinine clearance calculated by CG equation, and they estimate different things. Therefore, the use of the MDRD or CKD-EPI equations interchangeably with the CG equation in drug dosing cannot be advocated. Using the CG equation for drug dosing may be a safer and easier practice, especially in the very elderly. Also, given the high rate of antibiotic dosing errors documented, further studies should be conducted to investigate underlying causes of prescribing errors.

PROTECTION OF HUMAN AND ANIMAL SUBJECTS

The authors declare that the research procedures were performed according to the regulations of the institution's ethics committee and the Code of Ethics of the World Medical Association (Declaration of Helsinki).

PROTECTION OF HUMAN AND ANIMAL SUBJECTS CONFIDENTIALITY OF DATA

The authors declare that they have followed the protocols of their work center regarding the publication of data from patients.

CONFLICT OF INTEREST

No conflict of interest has been declared by any author.

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