U.PORTO

MASTER DEGREE IN MEDICINE

Correlation of estimated creatinine clearance and glomerular filtration rate in very elderly patients and antibiotic prescription errors

Manuel Alberto Rodrigues Silva

M

2019

U.PORTO
INSTITUTO DE CIÊNCIAS BIOMÉDICAS ABEL SALAZAR
UNIVERSIDADE DO PORTO

Correlation of estimated creatinine clearance and glomerular filtration rate in very elderly patients and antibiotic prescription errors

Author:
Manuel Alberto Rodrigues Silva
E-mail: manuelalbertorsilva@gmail.com
Master Degree in Medicine
Institute of Biomedical Sciences Abel Salazar, University of Porto

Thesis Advisor:
Teresa Maria da Costa Cardoso, MD, PhD
Consultant of Internal Medicine at the Polyvalent Intensive Care Unit of Hospital de Santo António, Centro Hospitalar Universitário do Porto
Associated Professor at Institute of Biomedical Sciences Abel Salazar, University of Porto

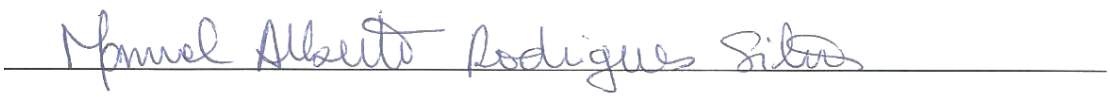
June of 2019

U.PORTO
INSTITUTO DE CIÊNCIAS BIOMÉDICAS ABEL SALAZAR
UNIVERSIDADE DO PORTO

Correlation of estimated creatinine clearance and glomerular filtration rate in very elderly patients and antibiotic prescription errors

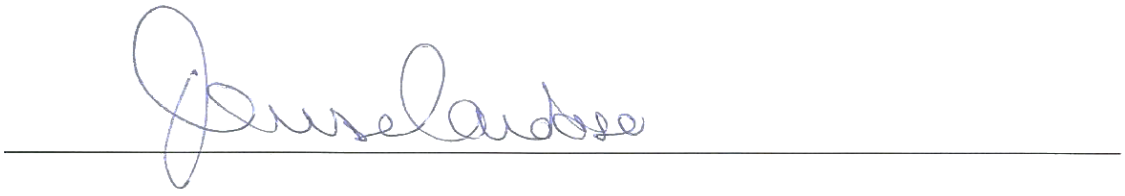
Author:

Manuel Alberto Rodrigues Silva



Thesis Advisor:

Teresa Maria da Costa Cardoso, MD, PhD



June of 2019

Para ser grande, sê inteiro: nada

Para ser grande, sê inteiro: nada
Teu exagera ou exclui.
Sê todo em cada coisa. Põe quanto és
No mínimo que fazes.
Assim em cada lago a lua toda
Brilha, porque alta vive.

Odes de Ricardo Reis. Fernando Pessoa.

ACKNOWLEDGMENTS

To Professor Teresa Cardoso – it was a privilege and a pleasure to work under your guidance. Thank you for being the doctor I aspire to be.

To Ana Luísa, Rita, Carolina, Bárbara and António – the best group of friends one could ever ask for – thank you for making this journey with me.

To my Family for all their support during this six years – I could not have done it without you.

ABSTRACT

Introduction: Determination of the renal function is particularly important when prescribing antibiotics to elderly patients. The aim of this study is to determine the correlation between estimated creatinine clearance with estimated glomerular filtration rate (GFR), for a hospitalized population of very elderly patients, and to audit antibiotic prescription errors, namely adjustment to renal function.

Material and Methods: Retrospective cohort study of all adult patients aged 80 years and older to whom antibiotic therapy was prescribed. Creatinine clearance was calculated using Cockcroft-Gault (CG) equation, and estimated GFR by using Modification of Diet in Renal Disease (MDRD) Study equation and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Dosing errors were determined through adjustment of daily define dose (DDD) to renal function.

Results: The study included 589 patients. The correlation of CG with MDRD and CKD-EPI was $r = 0.98$ and 0.96 for the minimum serum creatinine (mSCr), and 0.97 and 0.93 for the maximum serum creatinine (MxSCr). Based on the CG equation, there were errors in DDD in 45% in the mSCr, and 52% in the MxSCr day. There was a discrepancy in the error registry between 14 to 16% when CG was compared with MDRD and CKD-EPI.

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; nevertheless, the use of MDRD or CKD-EPI equations interchangeably with the CG equation in drug dosing cannot be advocated, because they estimate different things. There was a high rate of antibiotic dosing errors documented in this population of very elderly patients.

Conclusion: This study supports the use of CG equation for drug dosing in the very old population. Further studies are needed to investigate underlying causes of prescribing errors.

Keywords: creatinine clearance; glomerular filtration rate; very elderly patients; antibiotic prescription errors.

RESUMO

Introdução: A determinação da função renal é particularmente importante na prescrição de antibióticos em doentes idosos. O objetivo deste estudo é determinar a correlação entre a *clearance* de creatinina estimada com a taxa de filtração glomerular (TFG) estimada, numa população hospitalizada de doentes muito idosos, e auditar os erros de prescrição antibiótica, nomeadamente o ajuste à função renal.

Material e Métodos: Estudo de coorte retrospetivo de todos os doentes adultos com 80 ou mais anos a quem foi prescrita antibioterapia. A *clearance* da creatinina foi calculada através da equação de Cockcroft-Gault (CG), e a TFG estimada através da equação *Modification of Diet in Renal Disease* (MDRD) e da equação *Chronic Kidney Disease Epidemiology Collaboration* (CKD-EPI). Os erros de prescrição foram determinados pelo ajuste da dose diária definida (DDD) à função renal.

Resultados: O estudo incluiu 589 pacientes. A correlação da CG com MDRD e CKD-EPI foi r = 0,98 e 0,96 para a creatinina sérica mínima (mSCr), e 0,97 e 0,93 para a creatinina sérica máxima (MxSCr). Com base na equação de CG, houve erros na DDD em 45% no dia da mSCr e 52% no dia da MxSCr. Houve uma discrepância no registo de erros entre 14 a 16% quando a CG foi comparada com a MDRD e a CKD-EPI.

Discussão: Nesta população de doentes muito idosos houve uma excelente correlação da CG com a MDRD e CKD-EPI para diferentes níveis de função renal; no entanto, o uso das equações MDRD ou CKD-EPI em vez da CG não pode ser feito indiscriminadamente porque estimam coisas diferentes. Foi documentada uma elevada taxa de erros na dose de antibióticos prescrita nesta população de doentes muito idosos.

Conclusão: Este estudo reforça o uso da equação de CG 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: *clearance* da creatinina; taxa de filtração glomerular; doentes muito idosos; erros de prescrição dos antibióticos.

ABBREVIATIONS

ABW	Adjusted body weight
BMI	Body mass index
BSA	Body surface area
CCI	Charlson Comorbidity Index score
CG	Cockcroft-Gault
$CI_{95\%}$	95% Confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
Cr	Creatinine
DDD	Daily defined dose
GFR	Glomerular filtration rate
HSA-CHUP	Hospital de Santo António, Centro Hospitalar Universitário do Porto
IBW	Ideal body weight
IQR	Interquartile range
KPS	Karnofsky Performance Status scale
MDRD	Modification of Diet in Renal Disease study
OR	Odds ratio
SCr	Serum creatinine
SD	Standard deviation
SPSS	Statistical Package for the Social Sciences

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

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. After the age of 50, the number of nephrons progressively declines from approximately more than 1 million to less than 500 thousand. In addition, up to 35% of nephrons show clinically important evidence of sclerosis.[1] Because of these morphologic changes, both glomerular filtration rate (GFR) and renal plasma flow decline with aging, beginning at the third decade of life.[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 at this age.[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. A useful method of assessing renal function is to estimate the GFR. Several equations have been studied and validated as estimations of GFR using serum creatinine level as a marker for renal clearance. The most widely used equation for determining the creatinine clearance is the equation of Cockcroft-Gault (CG). However, this equation is inaccurate in the elderly, since the production and elimination of creatinine decrease with age, overestimating the renal function. Additionally, because of the inclusion of a term for weight in the numerator, this formula systematically overestimates creatinine clearance in patients who are edematous or obese. More recently, two other equations have been developed using larger populations for more accurate assessment of estimated GFR, 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] At higher GFR (GFR > 60 mL/min/1.73 m^2), CKD-EPI outperforms MDRD;[8] however, in the elderly with lower GFR, MDRD and CKD-EPI are not statistically different.[9] Despite improvements in accurate assessment of renal function, serum creatinine level is still an imperfect marker of kidney function, particularly in the elderly. Concomitant medications may falsely increase serum creatinine by interfering with secretion, whereas others may increase metabolic load by increasing creatinine production. Low muscle mass or malnutrition, common among the elderly population, may also affect serum creatinine and thus assessment of GFR.[1,6]

The determination of GFR is particularly important in the presence of renal impairment not only for the correct choice of medication but also for dose adjustments, in order to achieve the maximum therapeutic goal while avoiding toxicity. This is of the utmost relevance in antibiotic prescription.

To achieve safe antibiotic prescription in the elderly it is necessary to accurately determine both the loading dose and the daily defined dose (DDD). The loading dose is given to rapidly establish serum levels of the drug and an acute decrease in the bacterial burden, which is why the loading dose is not adjusted regardless of the presence of renal failure. Unlike the loading dose, the DDD of antibiotics that are primarily eliminated unchanged through the kidneys often require dose adjustment in renal dysfunction. Dosage modification can be accomplished by dose reduction, dosing interval prolongation, or both methods. In general, for most drugs, a combined approach is often used. This method provides a constant plasma drug concentration above the minimum inhibitory concentration without increasing the risk of toxicity from high peak or trough levels.[1,6]

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 adult 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 months' 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 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 topic antibiotics or antibiotics with a prophylactic intent or those in whom the therapy lasted ≤ 48 hours were excluded.

Patients' age, gender, race, body weight and height were obtained from the clinical records. Patients' comorbidities were determined using the Charlson Comorbidity Index (CCI) score.[10] The degree of functional impairment was determined according to the Karnofsky Performance Status Scale (KPS).[11] 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 electronic program used for inpatients drug prescription was also visited to verify if the patients' weight and creatinine were registered for automatic creatinine clearance calculus.

Renal function calculation equations

For each patient, renal function was estimated using three creatinine-based equations. The first equation used was the CG equation. It estimates creatinine clearance from age, gender, and body weight in addition to serum creatinine through the following formula: creatinine clearance (mL/min) = [(140 – age) × weight] / (72 × SCr) × 0.85 [if female], where *SCr* is serum creatinine.[12] Based on several studies and expert opinions, further adjustments to the CG equation based on body weight and body mass index (BMI) should be made, since the CG equation appears to become less accurate in weight extremes (underweight and particularly overweight and obesity). Therefore, in underweight patients (BMI < 18.5 kg/m^2), real body weight was used; in patients with normal weight (BMI between 18.5 and 24.9 kg/m^2), the ideal body weight (IBW) was preferred; and in overweight or obese patients (BMI ≥ 25 kg/m^2), adjusted body weight (ABW) was selected. The formula for IBW is: IBW (kg) = 50.0 kg + 2.3 kg

for every 2.5 cm over 152 cm [if male], and IBW (kg) = 45.5 kg + 2.3 kg for every 2.5 cm over 152 cm [if female]. The ABW can be calculated by: ABW (kg) = IBW + 0.4 × (real body weight – IBW).[13]

The second equation used was the 4-variable MDRD Study equation, whose formula is: GFR (mL/min/1.73 m^2) = 175 × $SCr^{-1.154}$ × $age^{-0.203}$ × 0.742 [if female] × 1.210 [if black], where *SCr* is serum creatinine. The 4-variable was chosen over the 6-variable MDRD equation, because it is simpler to use since it does not require inclusion of serum urea nitrogen and serum albumin concentration, not routinely obtained by all patients. Exclusion of these variables also makes the equation less susceptible to error in conditions in which serum urea nitrogen or albumin are strongly influenced by other factors than GFR.[14]

The third equation used on this study was the CKD-EPI equation calculated using the following formula: GFR (mL/min/1.73 m^2) = 141 × min (SCr / **κ**, 1)$^{\alpha}$ × max (SCr / **κ**, 1) $^{-1.209}$ × 0.993^{Age} × 1.018 [if female] × 1.159 [if black], where: *SCr* is serum creatinine, ***κ*** is 0.7 for females and 0.9 for males, ***α*** is -0.329 for females and - 0.411 for males, *min* indicates the minimum of S_{cr} /**κ** or 1, and *max* indicates the maximum of S_{cr} /**κ** or 1.[15] 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 so that all were expressed in units of mL/min, the units of GFR that are expressed in the majority of drug dosing labels. Actual GFR can be calculated from the following equation: actual GFR (mL/min) = estimated GFR × BSA/1.73, where BSA (m^2) = $weight^{0.425}$ × $height^{0.725}$ × 0.007184.[16]

Antibiotic prescription 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,*[17] 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 electronic prescription program were also examined.

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.

Covariance was studied with Pearson correlation coefficient. Association between the dependent variable (antibiotic prescription error) and the other variables was studied through univariate logistic regression. The results are expressed as odds ratio (OR) and p-values.

Level of significance was set 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 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 (Figure 1): 12 (1.3%) had end-stage renal disease undergoing hemodialysis, peritoneal dialysis or kidney transplantation; 7 (0.8%) were on topic antibiotics; 89 (9.6%) had antibiotic prophylaxis; 104 (11.2%) had antibiotic therapy for ≤ 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 registries in the clinical records.

Clinical characteristics of the 589 patients included in the study population are listed in Table I. Mean age of the cohort was 87 ± 4 years. Male gender accounted for 42% of patients. Only 1 patient of this population was black. Regarding the KPS, 37% of patients were independent in activity daily living (Karnofsky score ≥ 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 Figure 2A and with CKD-EPI ($r = 0.96$, $p < 0.001$) in Figure 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 $r = 0.93$ ($p < 0.001$).

Antibiotic prescription 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 II. Errors rate varied from 46.7% to 52.0%, in the day of the minimum creatinine, and 40.1% to 53.7%, in the day of maximum creatinine.

Table III 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 CG equation for creatinine clearance for minimum creatinine and 98 (16.6%) for maximum creatinine. Using 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 IV.

Prescribed antibiotics were modified in 154 cases (26.1%) and only in 5 patients it was due to side effects. Of these 5 patients, and according to the CG equation, 4 presented excess dosing either in the minimum creatinine day, maximum creatinine day or in the loading dose, and only 1 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. These results support the use of CG equation for drug dosing in the very old population.

In the elderly, MDRD and CKD-EPI have been shown to more accurately estimate GFR when compared with CG.[6] However, pharmacokinetic studies over the last several years have used the CG equation to determine level of renal function for dosage adjustment in drug labels. As a result, it has become a common practice for drug dosing. Furthermore, the information on dosage adjustments in renal impairment given in the majority of published information available 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 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%.[18] Although these studies considered drugs other than antibiotics, the majority of 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.[19]

Dosing errors reported on 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 5 patients in whom the initial antibiotic was changed due to side effects, there was over dosing of the prescribed antibiotic in 4. Conversely, under dosing may result in compromised therapeutic efficacy, resistance development and poor prognosis.

When comparing CG with MDRD and CKD-EPI for the calculus of antibiotic dosing, there was a discrepancy in 14 to 16% of the 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 MDRD and CKD-EPI equations overestimate creatinine clearance.[19-24] 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.[25] Also, new creatinine-based GFR estimating equations have been reported. A recent study, in a group of patients 65 years and older, compared 4 equations – including the CKD-EPI equation – with the reference inulin-measuring method. The authors found that none of the equations had a superior diagnostic performance and that each equation had limitations regarding accuracy.[26] Thus, for patients with extreme characteristics, like those with morbid obesity, one may opt for a specific equation for an optimum result,

while for the common patients, the CG equation is more practical because it is already established in clinical practice with good results.

This study also focused on risk factors for antibiotic prescription errors for which it was not found any systematic risk factor.

This study has some limitations. In order to audit antibiotic prescription 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, side effects should have been searched in every patient and not only in situations of antibiotic modification. Thus, it is possible that adverse drug events related to prescription 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. Also, 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.

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 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.

APPENDIX I – TABLES

Table I. 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	65.1 ± 14.1
Ideal body weight (kg), mean ± SD	56.0 ± 10.0
Adjusted body weight (kg), mean ± SD	59.6 ± 10.0
Height (cm), mean ± SD	161.4 ± 9.1
BMI (kg/m^2), mean ± SD	24.99 ± 5.17
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)

Abbreviations: 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.

Table II. 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.

Abbreviations: Cr, creatinine; CG, Cockcroft-Gault equation; MDRD, Modification of Diet in Renal Disease Study equation; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation.

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

			CG					
			Minimum Cr			Maximum Cr		
Equations	Dosing errors		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.

Abbreviations: CG, Cockcroft-Gault equation; MDRD, Modification of Diet in Renal Disease Study equation; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation.

Table IV. 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

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

APPENDIX II – FIGURES

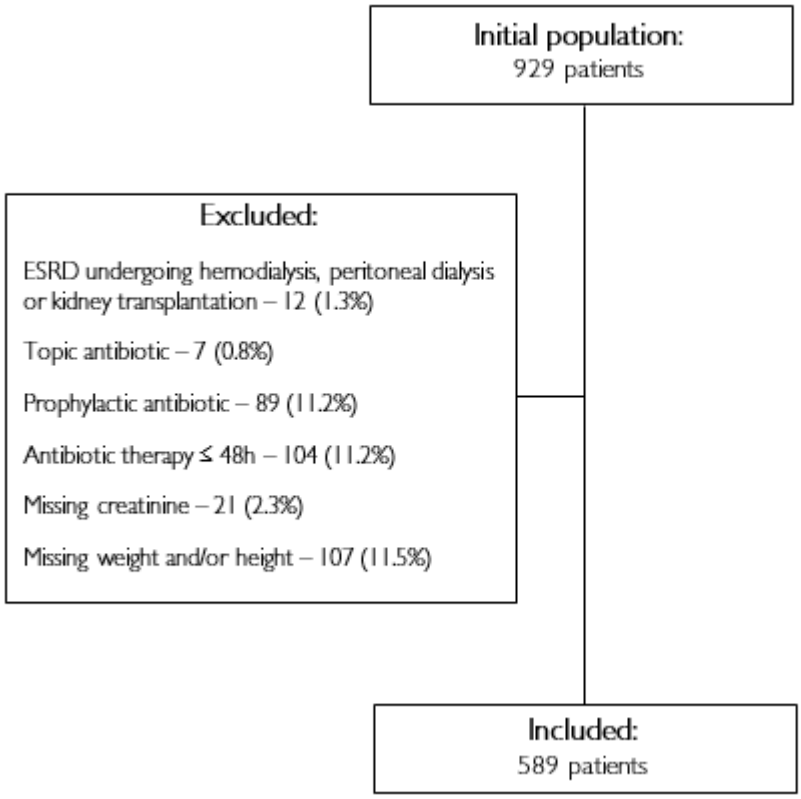


Figure 1. Flow diagram of included patients.

Abbreviations: ESRD, end-stage renal disease.

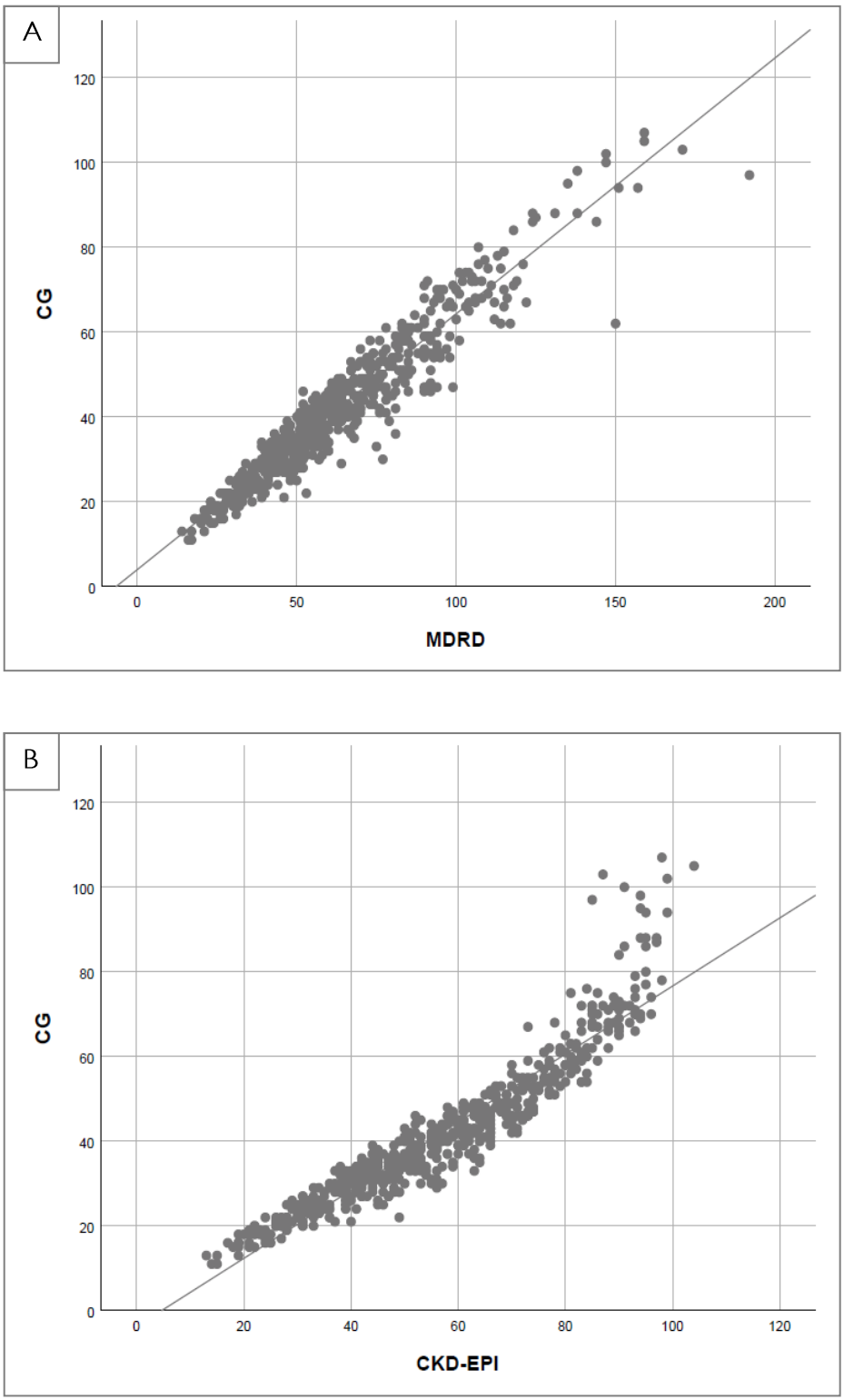


Figure 2. A. Correlation between baseline estimated CG and estimated GFR by MDRD equation (mL/min). B. Correlation between baseline estimated CG and estimated GFR by CKD-EPI equation (mL/min).

Abbreviations: CG, Cockcroft-Gault equation; MDRD, Modification of Diet in Renal Disease Study equation; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation.

APPENDIX III – CASE REPORT FORM

Case Report Form used for the collection of data from clinical records of all patients in this study.

INCLUSION CRITERIA
All adult patients aged 80 years and older admitted to Hospital de Santo António, Centro Hospitalar Universitário do Porto (HSA-CHUP), over a three months' period (between 1st January 2017 and 31th March 2017).

EXCLUSION CRITERIA
Patients with end-stage renal disease undergoing hemodialysis, peritoneal dialysis, or kidney transplantation; those prescribed with topic antibiotics; or antibiotics with a prophylactic intent; or those in whom the therapy lasted ≤ 48 hours.

STUDY VARIABLES – Definitions and instructions	
General instructions	Complete all the information by selecting the appropriate box and entering the required data for each field as indicated.
Age	Enter the age of the patient in years (patients must be aged 80 years and older).
Sex	Select the patient sex (male or female).
Race	Choose the patient race (caucasian, black or other).
Weight	Enter the weight of the patient in kg.
Height	Enter the height of the patient in cm.
Comorbidities	Select the comorbidities from the list.
Charlson Comorbidity Index	Charlson Comorbidity Index Score – Condition 1 – Myocardial infarction (history, not ECG changes only) Congestive heart failure Peripheral vascular disease (includes aortic aneurysm ≥ 6 cm) Cerebrovascular disease: CVA with mild or no residua or TIA Dementia Chronic obstructive pulmonary disease Connective tissue disease Peptic ulcer disease Mild liver disease (without portal hypertension, includes chronic hepatitis) Diabetes without end-organ damage (excludes diet-controlled alone) 2 – Hemiplegia Moderate or severe renal disease Diabetes with end-organ damage (retinopathy, neuropathy, nephropathy, or brittle diabetes) Solid tumor without metastases (exclude if > 5 yr. from diagnosis) Leukemia (acute or chronic) Malignant lymphoma 3 – Moderate or severe liver disease 6 – Metastatic solid tumor AIDS (not just HIV positive) **Note**: For each decade > 40 years of age, a score of 1 is added to the above score. **Abbreviations:** ECG, electrocardiogram; CVA, cerebral vascular accident; TIA, transient ischemic accident; AIDS, acquired immune deficiency syndrome; HIV, human immunodeficiency virus. Record the calculated score.

<table>
<tr><td>Karnofsky Performance Status Scale</td><td>Karnofsky Performance Status Scale<table><tr><th>Score (category)</th><th>Karnofsky</th></tr><tr><td>100</td><td>Normal; no complaints; no evidence of disease.</td></tr><tr><td>90</td><td>Able to carry on normal activity; minor signs or symptoms.</td></tr><tr><td>80</td><td>Normal activity with effort; some signs or symptoms of disease.</td></tr><tr><td>70</td><td>Care for self; unable to carry on normal activity or to do active work.</td></tr><tr><td>60</td><td>Requires occasional assistance but is able to care form most of his needs.</td></tr><tr><td>50</td><td>Requires considerable assistance and frequent medical care.</td></tr><tr><td>40</td><td>Disabled; requires special care and assistance.</td></tr><tr><td>30</td><td>Severely disabled; hospitalization necessary; active supportive treatment is necessary.</td></tr><tr><td>20</td><td>Very sick; hospitalization necessary; active supportive treatment is necessary.</td></tr><tr><td>10</td><td>Moribund; fatal processes progressing rapidly.</td></tr><tr><td>0</td><td>Dead.</td></tr></table>
Record the calculated score.</td></tr>
<tr><td>Baseline creatinine and date of measurement</td><td>Enter last serum creatinine levels (in mg/dL) measured before hospital admission. Enter the date of measurement.</td></tr>
<tr><td>Minimum creatinine and date of measurement</td><td>Enter minimum serum creatinine levels (in mg/dL) observed in the period of antibiotic treatment. Enter the date of measurement.</td></tr>
<tr><td>Maximum creatinine and date of measurement</td><td>Enter maximum serum creatinine levels (in mg/dL) observed in the period of antibiotic treatment. Enter the date of measurement.</td></tr>
<tr><td>Prescribed antibiotic(s)</td><td>Enter the antibiotic(s) prescribed in the first cycle of treatment in each hospitalization.</td></tr>
<tr><td>Loading dose</td><td>Enter the loading dose(s) of the selected antibiotic(s).</td></tr>
<tr><td>Daily defined dose(s) in the day of minimum creatinine</td><td>Enter the daily defined dose(s) of the selected antibiotic(s), in the day of minimum creatinine.</td></tr>
<tr><td>Daily defined dose(s) in the day of maximum creatinine</td><td>Enter the daily defined dose(s) of the selected antibiotic(s), in the day of maximum creatinine.</td></tr>
<tr><td>Modifications in prescribed antibiotic(s)</td><td>Select “yes” if there is a modification in the prescribed antibiotic(s); select “no” if there is not a modification in the prescribed antibiotic(s).</td></tr>
<tr><td>Reasons for modifications in prescribed antibiotic(s)</td><td>Select from the list the reason (according to the clinical registry) why the prescribed antibiotic(s) was (were) changed.</td></tr>
<tr><td>Total period of antibiotic therapy</td><td>Enter the total period of antibiotic therapy in days.</td></tr>
<tr><td>Weight registry in the electronic prescription program</td><td>Select “yes” if weight was registered in the electronic prescription program used for inpatients drug prescription. Select “no” if weight was not registered in the electronic prescription program used for inpatients drug prescription.</td></tr>
<tr><td>Creatinine registry in the electronic prescription program</td><td>Select “yes” if serum creatinine was registered in the electronic prescription program used for inpatients drug prescription. Select “no” if serum creatinine was not registered in the electronic prescription program used for inpatients drug prescription.</td></tr>
</table>

STUDY VARIABLES – Form	
Age (years)	☐☐☐
Sex	☐1. Male ☐2. Female
Race	☐1. Caucasian ☐2. Black ☐3. Other
Weight (kg)	☐☐☐
Height (cm)	☐☐☐
Comorbidities	☐1. Myocardial infarction (history, not ECG changes only). ☐2. Congestive heart failure ☐3. Peripheral vascular disease (includes aortic aneurysm ≥ 6 cm) ☐4. Cerebrovascular disease: CVA with mild or no residua or TIA ☐5. Dementia ☐6. Chronic obstructive pulmonary disease ☐7. Connective tissue disease ☐8. Peptic ulcer disease ☐9. Mild liver disease (without portal hypertension, includes chronic hepatitis) ☐10. Moderate or severe liver disease ☐11. Diabetes without end-organ damage (excludes diet-controlled alone) ☐12. Diabetes with end-organ damage (retinopathy, neuropathy, nephropathy, or brittle diabetes) ☐13. Hemiplegia ☐14. Moderate or severe renal disease ☐15. Solid tumor without metastases (exclude if > 5 yr. from diagnosis) ☐16. Metastatic solid tumor ☐17. Leukemia (acute or chronic) ☐18. Malignant lymphoma ☐19. AIDS (not just HIV positive) **Note:** items 9 and 10; 11 and 12; and 15 and 16 are mutually exclusive. **Abbreviations:** ECG, electrocardiogram; CVA, cerebral vascular accident; TIA, transient ischemic accident; AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.
Charlson Comorbidity Index	☐☐
Karnofsky Performance Status Scale	☐☐☐
Baseline creatinine (mg/dL) and date of measurement	☐☐.☐☐ D D M M M Y Y Y Y

Minimum creatinine (mg/dL) and date of measurement	☐☐ . ☐☐ D D M M M Y Y Y Y
Maximum creatinine (mg/dL) and date of measurement	☐☐ . ☐☐ D D M M M Y Y Y Y
Prescribed antibiotic(s)	
Loading dose(s)	
Daily defined dose(s) in the day of minimum creatinine	
Daily defined dose(s) in the day of maximum creatinine	
Modifications in prescribed antibiotic(s)	☐1. Yes ☐2. No
Reasons for modifications in prescribed antibiotic(s)	☐1. No response / clinical worsening ☐2. Microbiological indication ☐3. No infection ☐4. Side effects ☐5. Other _____
Total period of antibiotic therapy (days)	☐☐
Weight registry in the electronic prescription program	☐1. Yes ☐2. No
Creatinine registry in the electronic prescription program	☐1. Yes ☐2. No

BIBLIOGRAPHY

1. Olyaei AJ, Bennett WM. Chapter 9: Drug Dosing and Renal Toxicity in the Elderly Patient. *Geriatric Nephrology Curriculum, American Society of Nephrology* 2009; https://www.asn-online.org/education/distancelearning/curricula/geriatrics/Chapter9.pdf. Accessed September, 2018.
2. Glassock RJ, Rule AD. Aging and the Kidneys: Anatomy, Physiology and Consequences for Defining Chronic Kidney Disease. *Nephron.* 2016;134(1):25-29.
3. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA.* 1998;279(15):1200-1205.
4. Pretorius RW, Gataric G, Swedlund SK, Miller JR. Reducing the risk of adverse drug events in older adults. *Am Fam Physician.* 2013;87(5):331-336.
5. Gurwitz JH, Field TS, Harrold LR, et al. Incidence and preventability of adverse drug events among older persons in the ambulatory setting. *JAMA.* 2003;289(9):1107-1116.
6. Lassiter J, Bennett WM, Olyaei AJ. Drug dosing in elderly patients with chronic kidney disease. *Clin Geriatr Med.* 2013;29(3):657-705.
7. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med.* 1999;130(6):461-470.
8. Stevens LA, Schmid CH, Greene T, et al. Comparative Performance of the CKD Epidemiology Collaboration (CKD-EPI) and the Modification of Diet in Renal Disease (MDRD) Study Equations for Estimating GFR Levels Above 60 mL/min/1.73 m^2. *American Journal of Kidney Diseases.* 2010;56(3):486-495.
9. Carter JL, Stevens PE, Irving JE, Lamb EJ. Estimating glomerular filtration rate: comparison of the CKD-EPI and MDRD equations in a large UK cohort with particular emphasis on the effect of age. *QJM: An International Journal of Medicine.* 2011;104(10):839-847.
10. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis.* 1987;40(5):373-383.
11. Karnofsky D, Burchenal J. *The Clinical Evaluation of Chemotherapeutic Agents in Cancer.* MacLeod CM (Ed), Evaluation of Chemotherapeutic Agents. Columbia Univ Press; 1949.
12. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron.* 1976;16(1):31-41.
13. Winter MA, Guhr KN, Berg GM. Impact of various body weights and serum creatinine concentrations on the bias and accuracy of the Cockcroft-Gault equation. *Pharmacotherapy.* 2012;32(7):604-612.
14. Levey AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Annals of Internal Medicine.* 2006;145(4):247-254.

15. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Annals of Internal Medicine.* 2009;150(9):604-612.
16. Dubois D, Dubois E. A formula to estimate the approximate surface area if height and weight be known. *Arch Intern Med.* 1916;17:863-871.
17. Gilbert DN, Chambers HF, Eliopoulos GM, Saag MS, Pavia AT. *The Sanford Guide to Antimicrobial Therapy.* 48th Edition ed: Sperryville, VA, USA : Antimicrobial Therapy, Inc.; 2018.
18. Long CL, Raebel MA, Price DW, Magid DJ. Compliance with dosing guidelines in patients with chronic kidney disease. *Ann Pharmacother.* 2004;38(5):853-858.
19. Cartet-Farnier E, Goutelle-Audibert L, Maire P, De la Gastine B, Goutelle S. Implications of using the MDRD or CKD-EPI equation instead of the Cockcroft-Gault equation for estimating renal function and drug dosage adjustment in elderly patients. *Fundamental & clinical pharmacology.* 2017;31(1):110-119.
20. Wargo KA, Eiland EH, 3rd, Hamm W, English TM, Phillippe HM. Comparison of the modification of diet in renal disease and Cockcroft-Gault equations for antimicrobial dosage adjustments. *Ann Pharmacother.* 2006;40(7-8):1248-1253.
21. Gill J, Malyuk R, Djurdjev O, Levin A. Use of GFR equations to adjust drug doses in an elderly multi-ethnic group--a cautionary tale. *Nephrol Dial Transplant.* 2007;22(10):2894-2899.
22. Golik MV, Lawrence KR. Comparison of dosing recommendations for antimicrobial drugs based on two methods for assessing kidney function: cockcroft-gault and modification of diet in renal disease. *Pharmacotherapy.* 2008;28(9):1125-1132.
23. Hermsen ED, Maiefski M, Florescu MC, Qiu F, Rupp ME. Comparison of the Modification of Diet in Renal Disease and Cockcroft-Gault equations for dosing antimicrobials. *Pharmacotherapy.* 2009;29(6):649-655.
24. Dowling TC, Wang ES, Ferrucci L, Sorkin JD. Glomerular filtration rate equations overestimate creatinine clearance in older individuals enrolled in the Baltimore Longitudinal Study on Aging: impact on renal drug dosing. *Pharmacotherapy.* 2013;33(9):912-921.
25. Delanaye P, Guerber F, Scheen A, et al. Discrepancies between the Cockcroft-Gault and Chronic Kidney Disease Epidemiology (CKD-EPI) Equations: Implications for Refining Drug Dosage Adjustment Strategies. *Clinical pharmacokinetics.* 2017;56(2):193-205.
26. da Silva Selistre L, Rech DL, de Souza V, Iwaz J, Lemoine S, Dubourg L. Diagnostic Performance of Creatinine-Based Equations for Estimating Glomerular Filtration Rate in Adults 65 Years and Older. *JAMA Intern Med.* 2019.

Correlation of the estimated creatinine clearance and glomerular filtration rate in very elderly patients and antibiotic prescription errors

Manuel Alberto Rodrigues Silva

INSTITUTO DE CIÊNCIAS BIOMÉDICAS ABEL SALAZAR