

# Estimating Renal Function for Drug Dosing: Equations Matter

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ILLUSTRATION BY SCOTT ROBEILL

## Introduction

Suggestions for dose adjustment of drugs according to renal function (RF) are a significant part of the Clinical pharmacist intervention (PI). These suggestions are based on the recommendations of the SPCs and the main references in the area according to creatinine clearance (CrCl) or glomerular filtration rate (GFR) ranges.

Historically the recommended formula for estimating CrCl from adult serum Cr, which is itself an estimate of GFR, is Cockcroft-Gault (CG). This equation was developed from a study of about 200 men without chronic kidney disease (CKD) in the 1970s with a serum creatinine assay method not comparable to the current one. More recently, other equations have arisen based on studies with populations of thousands of men and women with CKD in the case of Modification of Diet in Renal Disease (MDRD) and with and without CKD of various ethnicities in Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI). The latter two, as they are a more accurate estimate of GFR, are now recommended by the main references in the area for CKD staging and to simplify are increasingly used for drug dosing, although there is not consensual in the recommendations. Any of these formulas is valid for unstable renal function and therefore should be used carefully acute care patients with fluctuating renal function.

## Purpose

To assess the impact of the differences between the two GFR estimation formulas (CG and CKD-EPI) in drug dosing recommendations.

## Methods

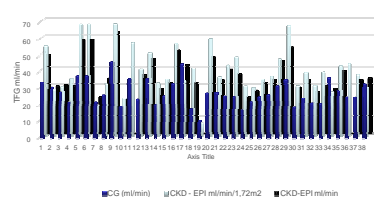
Pharmaceutical Interventions (PI) of the 1st semester of 2017 aiming drug dosing recommendations for renal impairment or renal function recover, were selected from de PI database. The information collected included drug identification and dosing recommendation made (dose reduction / increase/ drug suspension). Age, weight, height, and creatinine were added and GFR was calculated using the above two equations. Finally, we analyzed the impact of the result on the dosing suggestion made, according to the GFR cut-off value for each drug dosing recommendation.

Drug	CrCl Cut-off (ml/min)	Dosing Recommendation
Co-Amoxiclav 1,2g IV	<30	Increase administration interval
Co-Amoxiclav 875/125mg tablets	<30	Contraindicated
Meropenem 1000 mg IV	<50	Increase administration interval
Piperacillin-Tazobactam 4,5g IV	<40	Dose Reduction
Ketorolac 30mg IV	<30	Dose Reduction
Metamizole 2000 mg IV	<30	Dose Reduction
Enoxaparin SC – several dosages	<30	Dose Reduction
Dabigatran 110mg tablets	<30	Contraindicated
Rivaroxaban 20mg tablets	<50	Dose Reduction

## Results

The median difference in the GFR value was 5 ml/min ranging from 0 to 33 ml/min

TFGe CG vs CKD-EPI

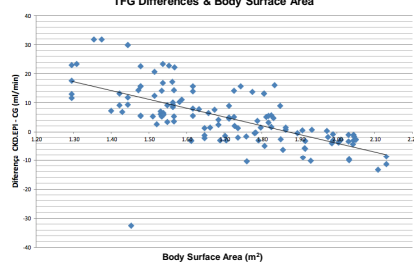


There were 149 interventions involving 115 individuals, of whom 37% had chronic kidney disease and a median age of 85 years.

The value of GFR calculated with the CKD-EPI formula was higher than the result using CG in 64% of the situations, however in 50% of the cases the difference was less than 5ml / min. When normalization of the body surface of the CKD-EPI formula is withdrawn, the values are closer to those of CG.

Larger differences appear to be associated with older age and body weight limits

TFG Differences & Body Surface Area



The relationship between the difference in the GFR result for the two formulas and the body surface area (BSA) shows a trend towards higher values with CKD-EPI for smaller BSA and higher values with CG for larger BSA. This is directly related to the fact that the results with CKD-EPI were normalized to a BSA of 1.72m<sup>2</sup> (result in ml/min / 1.72m<sup>2</sup>). On the other hand in over weighted individuals CG would probably overestimate the value of CrCl.

In 24% of cases there was a discrepancy between the recommendations to be made depending on the formula

The discrepancies were mostly seen with dose reduction recommendations and drug withdrawal, that would not have been made strictly considering the eGFR result using the CKD-EPI formula ( summarized below).

Dosing Recommendation using CG Equation	N
<b>Dose Increase</b>	1
Piperacillin-Tazobactam 4,5g IV	1
<b>Dose Reduction</b>	34
Co-Amoxiclav 1,2g IV	1
Co-Amoxiclav 875/125mg tablets	2
Enoxaparin SC – several dosages	11
Levofloxacin 500 mg IV	1
Meropenem 1000 mg IV	3
Metamizole 2000 mg IV	2
Piperacillin-Tazobactam 4,5g IV	6
Rivaroxaban 20mg tablets	2
Sitagliptin 100 mg tablets	1
<b>Contraindicated/ Use with Caution</b>	3
Dabigatran 110mg tablets	2
Parecoxib 40 mg IV	1
<b>Total</b>	<b>38</b>

The differences with greater impact will be in our perspective those related to anticoagulants because of the narrower therapeutic index in a patient population with a mean age above 80 years

## Conclusion

The choice of the GFR estimation formula can have a significant impact on the recommendations for drug dosing, especially at weight / body surface extremes. Taking into account our results and the literature review, it seems acceptable to use either CG (considering an adjusted weight in cases of overweight) or CKD-EPI (possibly removing normalization at the extremes of body surface) as estimates of the GFR. It is nevertheless fundamental to know the formulas and their limitations in order to interpret the result, thinking it as a range of probability instead of a single value, and to frame it in the global clinical context.

Beyond the dose decision, taking into account the estimated GFR and recommendations in the literature, it is necessary to define and monitor the efficacy and toxicity indicators to continuously re-evaluate the need for adjustment.

## References

- The National Kidney Disease Education Program (NKDEP). CKD and Drug Dosing: Information for Providers. Abril 2015 Disponível em: <https://www.niddk.nih.gov/health-information/health-communication-programs/nkdep/a-z/ckd-drug-dosing/Documents/ckd-drug-dosing-508.pdf>
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