Discordance of renal drug dosing using estimated creatinine clearance and measured urine creatinine clearance in hospitalized adults: A retrospective cohort study

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ABSTRACT

Background: Assessment of kidney function is fundamental to optimize drug dosing. The Cockcroft–Gault (CG) equation is widely used but has questionable validity for females, changing renal function, and the critical ill. Eight-hour urine collections (U₈h) offer direct measurement of creatinine clearance (CrCl) but lack the data for drug dosing. The primary objective of this study was to determine if there was a difference in renal drug dosing based on the estimation of CG CrCl (CrCl(CG)) versus 8-h CrCl (CrCl₈h).

Methods: This was an observational, retrospective cohort study of adult patients admitted between March 2018 and September 2018 with a collection U₈h during hospitalization. The primary outcome was discordance of renal drug dosing defined as the percentage of U₈h for which at least one different active medication CrCl dosing cutoff would result using the CrCl(CG) versus CrCl₈h. The secondary outcomes were correlation between CrCl(CG) and CrCl₈h and percentage of CrCl(CG) values outside ± 20% of the CrCl₈h.

Results: One hundred collections drawn from 85 unique patients (50.6% male, median age 55 [41–70] years, intensive care unit 88%) were included in the analysis. Median serum creatinine was 0.76 (0.52–1.06) mg/dL and blood urea nitrogen was 20 (14–28) mg/dL at time of collection₈h. Median CrCl₈h was 86.2 (43.5–140.3) mL/min versus 99.7 (56.5–166.9) mL/min CrCl(CG) (P < 0.001) and discordance was 25%. The correlation between CrCl₈h and CrCl(CG) was 0.76 (P < 0.001). Only 31% of CrCl(CG) values were within ± 20% of the CrCl₈h value.

Conclusion: We found 25% discordance for drug dosing between CrCl₈h and CrCl(CG). Further studies are needed to determine the impact on clinical outcomes.

Key Words: Augmented renal clearance, Cockcroft–Gault equation, Creatinine clearance, renal dosing, urine collection

INTRODUCTION

The assessment of kidney function is fundamental to determine the dose adjustments of renally eliminated medications to maximize efficacy and minimize adverse effects. The Cockcroft–Gault (CG) equation was developed in a study conducted at a Veterans Hospital in the 1970s to provide a simple calculation of creatinine clearance (CrCl) to estimate a patient’s kidney function without the need for urine collection.¹ The CG study...
originally planned to use 505 urine collections, but only 249 were reproducible and arbitrarily determined to be good approximations of actual clearance. Furthermore, 96% of the study participants were male; patients with variable serum creatinine (Scr) values were excluded; and the patients were mainly located in medical wards. Therefore, the validity of the CG equation in patients who are female, have fluctuating Scr values, and/or are critically ill is unknown.\[1\]

The Food and Drug Administration (FDA) recommended the use of the CG equation for developing drug dosing guidelines and pharmacokinetic studies in 1998.\[2\] More recently, the FDA draft guidance in 2010 recommended using both the CG-estimated CrCl (CrCl\textsubscript{CG}) and the Modification of Diet and Renal Disease estimation of glomerular filtration rate (eGFR) for study design in patients with impaired renal function.\[3\] In 2017, meropenem/vaborbactam became the first drug in the United States labeled for dosing adjustment based on eGFR.\[4\] Dosage adjustments based on kidney function are essential to appropriate drug therapy, but limited data assessing the various estimates of CrCl and potentially different drug dosing exist.\[5,6\]

As an alternative to estimating CrCl, urine collections provide a method to directly measure CrCl.\[7\] Twenty-four hour urine collections have been used to assess kidney function, and the CG equation was originally validated using this method.\[1\] More recently, the use of the 8-h urine collection (U\textsubscript{8h}) has evolved due to faster results, decreased workload, and decreased potential for collection errors. The comparison of 8-h urine CrCl (CrCl\textsubscript{8h}) with 24-hour urine CrCl (CrCl\textsubscript{24h}) has shown a good correlation in the surgical intensive care unit (ICU), trauma, and hospitalized elderly patients.\[8,9\] However, U\textsubscript{8h} has limited studies addressing the use for drug dosing in comparison with the CG equation.

At our institution, U\textsubscript{8h} is a relatively new method used to assess a patient’s renal function in addition to CG estimates. The primary aim of this study was to determine if there was a difference in renal drug dosing for selected renally eliminated drugs based on the estimation of CrCl\textsubscript{CG} versus CrCl\textsubscript{8h} in adult hospitalized patients.

### METHODS

**Design**

This study was a single-center, observational, retrospective cohort design.

**Participants and setting**

The University Medical Center is a 1506 bed academic medical center consisting of seven hospitals. Patients hospitalized between March 1, 2018, and September 30, 2018, were evaluated. Patients were included if they were 18 years of age or older and had a U\textsubscript{8h} during their hospital admission. Patients were excluded for the following: pregnancy/lactation, incarceration, renal replacement therapy within 72 h before collection, diuretic administration within 8 h before or during the collection, past medical history (PMH) of renal transplant or admission for renal transplant, presence of ileal conduit, factors that do not allow for CG calculation (Scr below lower limit of detection of 0.2 mg/dL, height < 60”, Scr not collected within 24 h of collection, height and weight not recorded), and no active orders to select renally adjusted medications [Table 1]. These medications were chosen because of common use in the settings where U\textsubscript{8h} are utilized at our institution. This study was approved by our university institutional review board in accordance with the ethical standards set forth in the Helsinki Declaration in 1975 (IRB Number 2018E0698).

Data retrospectively collected from the electronic medical records (EMR, EPIC, Madison, Wisconsin, USA) included age, sex, race, height, actual body weight, PMH of chronic kidney disease, patient location, date/time of U\textsubscript{8h}, Scr, and corresponding blood urea nitrogen (BUN) within 24 h before urine collection, urine volume, CrCl\textsubscript{8h} calculated by the EMR, and active medication orders [Table 1] on the day of urine collection. Medications were placed within CrCl cutoffs originating from our institution’s adult dosing guideline using the CrCl\textsubscript{8h} compared to the CrCl\textsubscript{CG}. If a medication was not included in our institution’s guideline, the package insert or societal guideline was used.\[10-12\] The study data were collected and managed using Research Electronic Data Capture.\[13\]

The EMR automatically calculates the CrCl\textsubscript{CG} utilizing the actual body weight (Wt\textsubscript{Actual}) if Wt\textsubscript{Actual} is less than the ideal body weight (IBM). If the Wt\textsubscript{Actual} is ≥ 120% of the IBW, then adjusted body weight (Wt\textsubscript{adjusted}) is used. All other situations use IBW. The Scr drawn closest to the time of urine collection within the previous 24 h was used in the CG calculation and is referred to as the reference Scr. The following equations were used for calculating CrCl\textsubscript{CG}:

\[
\text{CG calculation: } \text{Scr} = \frac{\text{Wt} \times \text{IBW} - \text{Scr}}{\text{IBW}}
\]

\[
\text{Actual body weight (Wt)} = \text{IBW} \times \frac{\text{IBW}}{(1 + 0.1 \times (\text{Wt} - \text{IBW}))}
\]

\[
\text{Adjusted body weight (Wt}\_\text{adjusted}) = \text{IBW} \times \frac{\text{IBW}}{(1 + 0.2 \times (\text{Wt} - \text{IBW}))}
\]

\[
\text{CrCl} = \frac{\text{Wt} \times \text{Scr}}{\text{Wt} - \text{Scr}}
\]

\[
\text{CrCl} = \frac{\text{Wt}\_\text{adjusted} \times \text{Scr}}{\text{Wt}\_\text{adjusted} - \text{Scr}}
\]

| Medication                | CrCl Dosing Breakpoints (mL/min) |
|--------------------------|----------------------------------|
| Aminoglycosides          | ≥ 60 40-59 20-39 < 20            |
| Ampicillin/sulbactam     | ≥ 50 30-49 15-29 < 15            |
| Cefazolin                | ≥ 30 10-29 < 10                  |
| Cefepime                 | ≥ 30 30-59 < 30                  |
| Ceftazolin               | ≥ 50 30-49 15-29 < 15            |
| Ceftolozane/tazobactam   | ≥ 50 30-49 < 30                  |
| Daptomycin               | ≥ 30 < 30                        |
| Enoxaparin               | ≥ 30 < 30                        |
| Lacosamide               | ≥ 30 < 30                        |
| Levetiracetam            | > 80 50-80 30-49 < 30            |
| Levofloxacin             | > 50 20-50 < 20                  |
| Meropenem                | ≥ 80 24-69 10-25 < 10            |
| Piperacillin/tazobactam  | > 20 < 20                        |
| Rivaroxaban (atrial fibrillation) | > 50 15-50 < 15                |
| Vancomycin               | ≥ 60 30-59 < 30                  |
Male IBW (kg) = 50+ (2.3 × inches over 5 feet)
Female IBW (kg) = 45.5+ (2.3 × inches over 5 feet)

\[ W_{\text{Adjusted}} = [(W_{\text{actual}} - \text{IBW}) \times 0.4] + \text{IBW} \]

\[ \text{CrCl}_{\text{CG}} = \left( \frac{140 \text{− age}}{\text{weight (kg)}} \right) \times \frac{72 \times \text{SCr (mg/dL)}}{0.85} \]

The EMR also displays the calculated urine CrCl for the \( U_{8h} \) using the following equation:

\[ \text{CrCl}_{8h} = \frac{\text{Urine Volume (mL)} \times \text{Urine Creatinine (mg/dL)}}{480 \text{minutes} \times \text{SCr (mg/dL)}} \]

Outcomes
The primary outcome was the discordance rate of renal drug dosing, defined as the number of urine collections for which at least one different medication CrCl dosing breakpoint would result using the CrCl_{CG} versus CrCl_{8h} divided by the total number of collections multiplied by 100. The secondary outcomes were the correlation of the CrCl_{CG} and CrCl_{8h} and percentage of CrCl_{CG} values outside ± 20% of the CrCl_{8h}. Augmented renal clearance (ARC) was defined as a CrCl_{8h} ≥ 130 mL/min.[14]

Statistical analysis
The sample size was not calculated as there was a paucity of data comparing drug dosing using CrCl_{8h} to CrCl_{CG}. Data were reported using the descriptive statistics. Dichotomous variables were analyzed using Fisher’s exact test or the Chi-squared test as appropriate. Normally distributed continuous variables were presented as mean (± standard deviation) and analyzed using the Mann-Whitney U test. Data were analyzed using the Statistical Package for the Social Sciences software version 24.0 (SPSS®, Inc. (Chicago, IL, USA).

RESULTS
A total of 150 \( U_{8h} \) were completed between March 2018 and September 2018. Fifty collections were excluded [Figure 1], leaving 100 collections drawn from 85 unique patients, with a median age of 55 (41–70) years. A little more than half of the patients were male (50.6%), and a majority (75.3%) were Caucasian. At the time of urine collection, 88% were in an ICU, but the median SCr and BUN were 0.76 (0.52–1.06) mg/dL and 20 (14–28) mg/dL, respectively. The median CrCl_{8h} was 86.2 (43.5–140.3) mL/min versus 99.7 (56.5–166.9) mL/min CrCl_{CG}, \( P < 0.001 \). Other patient characteristics at the time of urine collection are included in Table 2.

The most common active medication orders at the time of urine collection were vancomycin (52), cefepime (37), piperacillin/tazobactam (33), levetiracetam (22), enoxaparin (22), and meropenem (15) [Table 3]. Seventeen percent of all medications resulted in a different drug dose which was similar for the top six most common drugs, with the exception of piperacillin/tazobactam and enoxaparin which had 3% and 0% discordances, respectively. The analysis of differing drug doses by individual medication is included in Table 3. The primary outcome resulted in a 25% discordance rate, meaning 25% of the urine collections would have resulted in at least one different drug dose for active medications when using CrCl_{8h} versus CrCl_{CG}. The correlation between CrCl_{8h} and CrCl_{CG} was 0.76 (\( P < 0.001 \)), with an

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**Table 2: Patient characteristics at the time of urine collection**

| Characteristics   | Values |
|-------------------|--------|
| Height (inches)   | 67 (64–71) |
| Admission weight (kg) | 84.4 (71.7–102) |
| BMI (kg/m²)       | 28.5 (24.6–34) |
| SCr (mg/dL)       | 0.76 (0.52–1.06) |
| Increase in SCr of ≥0.3 mg/dL in previous 48 h (%) | 13 |
| BUN (mg/dL)       | 20 (14–28) |
| ICU status (%)    | 88 |
| CrCl_{8h} (mL/min) | 86.2 (43.5–140.3) |
| CrCl_{CG} (mL/min) | 99.7 (56.5–166.9) |
| ARC (%)           | 26 |

All data represented as median (25%–75% IQR) unless noted otherwise.

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**Figure 1**: Inclusion and exclusion of urine collections. †SCr undetectable, height <60 inches, undocumented height/weight. CG: Cockcroft–Gault

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[14] Brown, et al.: Discordance of renal drug dosing
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The correlation we observed (0.76) was only slightly lower than that observed in the CG study (0.83) and still represents a fair correlation.\[1\] However, looking at the distribution of the data revealed that 69% of the CrClCG values fell outside ±20% of the urine CrCl values as opposed to only 33% in the original CG study.\[0\] A few variances in our study may explain our different results. For one, 88% of our patients were in the ICU, whereas the CG study reported their patients were “mainly on medical wards” without further elaboration.\[1\] Our patients were evenly balanced between male and female patients, compared to almost an entirely male population (96%) in the CG study. Recommendations for the use of the 0.85 correction factor for females in the CG equation came from an estimate of fat and muscle differences between the sexes mentioned in the discussion of the CG study, but this proposed adjustment was not evaluated.\[1\] The use of this correction could lead to inaccuracies in the estimation of CrCl, especially for female patients, and may lead to inadequate medication adjustments.

A number of limitations need to be considered for our study. First, the CrClsh is not the established gold standard for estimating CrCl. Furthermore, our study was retrospective and conducted at a single center using a small study population. The decision to order Ush was not standardized and left to clinician discretion. Applying our exclusion criteria also removed 50 collections of the 150 records reviewed from the analysis. We collected a priori list of medications and did not record other active orders for renally adjusted medications. Furthermore, the CrClsh calculation in our EMR assumes a urine collection time interval of 8 h. The nurse does not record the actual amount of time for the collections, which could lead to over or underestimation of CrClsh. The CG study selected patients with renal function at a steady state by excluding patients with SCr values that differed by >20%. Based on our median SCr of 0.76 (0.52–1.06) and only 13% having a ≥0.3 mg/dL SCr increase in 48 h before collection, few had an acute

\[R^2 = 0.581.\] Only 31% of CrClCG values were within ±20% of the CrClsh value. Over half (51%) of CrClCG values were >120% of CrClsh, and 18% were below 80% of CrClsh [Figure 2].

### DISCUSSION

Our comparison of CrClCG and CrClsh resulted in at least one discordant renal drug dose for one in every four patients who had a Ush. Previous studies comparing CrClsh and CrClCG focused on correlation, bias, and precision or limited CrClsh use to identify ARC.\[14–17\] Our study is unique because we evaluated the effect on drug dosing at the time of urine collection.

It is not surprising that antibiotics were the most common class of renally eliminated medications at the time of urine collection, especially in a cohort of predominantly critical care patients. There are increasing data suggesting that dosing of antibiotics, especially beta-lactams, needs to be individualized in ICU patients.\[18,19\] We found that the rates of discordance for the most commonly observed active medication orders [Table 3] were similar to the overall medication discordance, except for piperacillin/tazobactam (3%) and enoxaparin (0%). Lower discordance rates with these medications are likely related to only having a single CrCl cutoff versus a medication like cefepime with three dosing adjustments based on CrCl. Regardless, the use of Ush to calculate CrClsh may be an appropriate surrogate for dose adjustments that would otherwise require therapeutic drug monitoring (for example, with beta-lactam antibiotics).

Differences between the CrClsh and the CrClCG were not readily apparent based on the correlation in our study. The correlation we observed (0.76) was only slightly lower than that observed in the CG study (0.83) and still represents a fair correlation.\[1\] However, looking at the distribution of the data revealed that 69% of the CrClCG values fell outside ±20% of the urine CrCl values as opposed to only 33% in the original CG study.\[0\] A few variances in our study may explain our different results. For one, 88% of our patients were in the ICU, whereas the CG study reported their patients were “mainly on medical wards” without further elaboration.\[1\] Our patients were evenly balanced between male and female patients, compared to almost an entirely male population (96%) in the CG study. Recommendations for the use of the 0.85 correction factor for females in the CG equation came from an estimate of fat and muscle differences between the sexes mentioned in the discussion of the CG study, but this proposed adjustment was not evaluated.\[1\] The use of this correction could lead to inaccuracies in the estimation of CrCl, especially for female patients, and may lead to inadequate medication adjustments.

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| Medication         | Number of active orders | Discordance by medication (%) |
|--------------------|--------------------------|--------------------------------|
| Vancomycin         | 52                       | 11 (21.2)                      |
| Cefepime           | 37                       | 8 (21.6)                       |
| Piperacillin/tazobactam | 33                  | 1 (3)                          |
| Levetiracetam      | 22                       | 6 (27.3)                       |
| Enoxaparin         | 22                       | 0                              |
| Meropenem          | 15                       | 4 (26.7)                       |
| Lacosamide         | 9                        | 0                              |
| Daptomycin         | 8                        | 4 (50)                         |
| Ceftazolin         | 4                        | 0                              |
| Levofloxacin       | 4                        | 0                              |
| Aminoglycosides    | 2                        | 0                              |
| Ampicillin/sulbactam | 1                      | 1 (100)                        |
| Ceftaroline        | 1                        | 0                              |
| Ceftolozane/tazobactam | 1                  | 1 (100)                        |
| Rivaroxaban        | 1                        | 0                              |
| Total              | 212                      | 36 (17%)                       |

*Discordance by medication calculated as the number of the specified medication orders with a different CrClsh divided by the total number of active orders for that medication. CrClCG: Eight-hour creatinine clearance, CrClsh: Cockcroft–Gault creatinine clearance
kidney injury.\textsuperscript{[1]} Furthermore, our study did not assess the clinical outcomes for our patients.

CONCLUSION

We determined that there was 25\% discordance in drug dosing between CrCl\textsubscript{8h} and CrCl\textsubscript{CG} in our study population. We also determined that over two-thirds of U\textsubscript{8h} resulted in CrCl\textsubscript{CG} values falling outside ± 20\% of the CrCl\textsubscript{8h}. Our findings support the need for subsequent studies comparing CrCl\textsubscript{GC} to CrCl\textsubscript{8h} for renal drug dosing and resulting clinical outcomes.

Research quality and ethics statement

The authors of this manuscript declare that this scientific work complies with reporting quality, formatting, and reproducibility guidelines set forth by the EQUATOR Network. The authors also attest that this clinical investigation was determined to require Institutional Ethics Committee, Research Cell, King George’s Medical University, Lucknow and appropriate approval (84\textsuperscript{th} ECM II-B-Thesis) was granted by the Research Cell, King George’s Medical University, Lucknow.

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Nil.

Conflicts of interest
There are no conflicts of interest.

Ethical conduct of research

This study was approved by the Institutional Review Board / Ethics Committee. The authors followed applicable EQUATOR Network (http://www.equator-network.org/) guidelines during the conduct of this research project.

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