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Research paper

Estimation of Renal Function for Antibiotic Dosing Decision

Adina Fésüs [1,*] Zsanett Szilágyi[1,2], Ghazal Mohammadi Khabbaz[1], Attila Vaskó[3]

[1] Department of Pharmacology, Faculty of Pharmacy, University of Debrecen, H-4032 Debrecen, Hungary
[2] Doctoral School of Medical Sciences, University of Debrecen, H-4032 Debrecen, Hungary
[3] Department of Pulmonology, Faculty of Medicine, University of Debrecen, H-4032 Debrecen, Hungary;
* Correspondence: fesus.adina@pharm.unideb.hu

Abstract

Background: Accurate renal function assessment is essential for appropriate antibiotic dosing in critically ill patients. However, different estimation equations may yield discrepant results, potentially leading to dosing errors and suboptimal clinical outcomes.

Objectives: To compare antibiotic dosing appropriateness based on renal function estimated using Cockcroft–Gault (CG), Modification of Diet in Renal Diseases (MDRD), and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations, and to evaluate associated clinical outcomes in ICU patients with pneumonia-associated sepsis.

Methods: In this single-center retrospective observational study, 229 adult intensive care unit (ICU) patients were included. Renal function was estimated using CG, MDRD, and CKD-EPI equations. Antibiotic dosing was classified as appropriate or inappropriate according to Summary of Product Characteristics (SmPC) and local guidelines. Clinical outcomes, including 30-day mortality/survival, and length of stay (LOS) were analyzed.

Results: Based on CKD-EPI and MDRD, 57.2% and 55.5% of patients received appropriate dosing, respectively. However, 7.4% of patients considered appropriately dosed by these equations were reclassified as inappropriately dosed using CG. While mean renal function values were similar across equations (~67 mL/min), median values differed by approximately 20 mL/min (CG: 74 mL/min vs. CKD-EPI/MDRD: 52 and 50 mL/min), leading to clinically relevant reclassification. Inappropriate dosing was associated with older age and higher comorbidity burden. Piperacillin/tazobactam was

most frequently underdosed, whereas clarithromycin, cefepime, and amikacin were commonly overdosed. Patients with inappropriate dosing had longer hospital LOS (median 14 vs. 11 days) and ICU-LOS (9 vs. 6 days), and showed worse survival, although 30-day mortality differences were not significant.

Conclusions: The choice of renal function equation significantly impacts antibiotic dosing decisions. CG-based assessment may better identify dosing inaccuracies, and inappropriate dosing is associated with worse clinical outcomes. Optimized, individualized dosing strategies are warranted in critically ill patients.

1. Introduction

Antibiotics (AB) have fundamentally transformed modern medicine and remain essential for both the treatment and prevention of bacterial infections, including pneumonia and sepsis. However, antibiotic misuse has become a major global health concern. Inappropriate use—including unnecessary prescriptions, incorrect dosing, and incomplete treatment courses—contributes significantly to the emergence of antimicrobial resistance (AMR), which threatens the effectiveness of current therapies and undermines clinical outcomes. A critical but often under-recognized contributor to this problem is the lack of individualized antibiotic dosing, particularly in vulnerable populations such as patients with impaired renal function.

The global burden of AMR is substantial. The World Health Organization (WHO) estimated that AMR was directly responsible for 1.27 million deaths worldwide in 2019. Between 2016 and 2023, global antibiotic consumption increased by 16.3%, reaching 34.3 billion defined daily doses (DDDs) (1). In the United States alone, more than 2.8 million antimicrobial-resistant infections occur annually, resulting in over 35,000 deaths and an estimated economic burden of approximately USD 20 billion per year (2) (3, 4). Across Europe, antibiotic consumption varies widely, ranging from 28.55 DDD per 1,000 inhabitants per day in Greece to 9.6 in the Netherlands, with reports indicating that in some regions up to one-third of the population uses antibiotics without a prescription (5). In the European Union and European Economic Area, AMR was associated with approximately 541,000 deaths in 2019, including 133,000 directly attributable to resistant infections (6). These data underscore the urgent need for

improved antibiotic stewardship, stronger regulatory policies, and optimized prescribing practices.

Appropriate antibiotic dosing is essential to ensure therapeutic efficacy while minimizing toxicity and the development of resistance. Underdosing may result in subtherapeutic drug concentrations, leading to treatment failure and promoting the selection of resistant microorganisms, whereas overdosing increases the risk of toxicity without additional clinical benefit. Achieving optimal exposure is particularly challenging in critically ill patients, where pharmacokinetics are frequently altered. In this context, multidisciplinary antimicrobial stewardship - including the active involvement of clinical pharmacists - plays a crucial role in optimizing antibiotic selection, dosing, and monitoring in routine practice.

Renal function is a key determinant of antibiotic pharmacokinetics, as many agents - including β-lactams, aminoglycosides, glycopeptides, and fluoroquinolones - are primarily eliminated via the kidneys. Impaired renal clearance may lead to drug accumulation and toxicity, while overestimation of renal function can result in subtherapeutic exposure and treatment failure. In clinical practice, renal function is commonly estimated using serum creatinine-based equations, including the Cockcroft–Gault (CG), Modification of Diet in Renal Disease (MDRD), and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formulas. However, these methods may yield substantially different results in the same patient due to differences in included variables such as age, body weight, and normalization to body surface area.

The CG equation estimates creatinine clearance (CrCl) and has traditionally been used to guide drug dosing, whereas MDRD and CKD-EPI estimate glomerular filtration rate (eGFR), which may not directly reflect drug clearance. Furthermore, serum creatinine is influenced by muscle mass, potentially leading to overestimation of renal function in elderly, malnourished, or critically ill patients. Since the CG equation incorporates body weight, it may provide a more clinically relevant estimate for drug dosing in certain populations, although it is not without limitations. These discrepancies between renal function estimation methods complicate dosing decisions and may contribute to inappropriate antibiotic therapy. In such complex clinical scenarios, pharmacists can provide essential support by interpreting renal function estimates,

identifying discrepancies between equations, and recommending dose adjustments tailored to individual patient characteristics.

This issue is particularly relevant in critically ill patients, in whom renal function is often unstable due to sepsis, hemodynamic changes, and exposure to nephrotoxic agents. Despite established recommendations in the Summary of Product Characteristics (SmPC) and clinical guidelines, inappropriate dosing remains common in practice due to uncertainties (7-11). This may result in adverse outcomes, including toxicity, prolonged hospitalization, and increased mortality. While clinical pharmacist involvement has been shown to reduce dosing errors and improve therapeutic outcomes, such services are not consistently integrated into all healthcare settings, and prescribing practices may still deviate from guideline recommendations (8, 12, 13) (14, 15) (5).

Given these challenges, it is essential to better understand how different renal function estimation methods influence antibiotic dosing decisions and their clinical consequences. Therefore, the aim of this study was to compare antibiotic dosing appropriateness based on renal function estimated using CG, MDRD, and CKD-EPI equations in ICU patients with pneumonia or sepsis. Additionally, we aimed to identify factors associated with inappropriate dosing and to evaluate their impact on clinical outcomes, including 30-day mortality, length of stay, and survival.

2. Materials and methods

2.1 Study Design

This study was conducted as a single-centre retrospective observational study in the ICU of the Pulmonology Clinic at the Clinical Centre of the University of Debrecen (Hungary). The study period spanned from June 2018 to February 2024. Ethical approval was obtained from the Regional Institutional Research Ethics Committee of the University of Debrecen (DE RKEB/IKEB: 6267-2022). The study population included adult patients (>18 years) admitted to the ICU with pneumonia or sepsis.

2.2 Data collection

Patient demographic characteristics, laboratory results, comorbidities, and antibiotic therapy data (agent selection, dosage, duration), and clinical outcomes (30-day mortality, length of stay) were retrospectively collected from the UD-MED electronic medical record system.

2.3 Equations, scores, and calculators used

Comorbidity burden was assessed using the Charlson Comorbidity Index (CCI) (16). Appropriate AB dosing was defined according to the SmPC and local clinical guidelines, taking into account patient-specific factors. Renal function was assessed using estimated glomerular filtration rate (eGFR) and creatinine clearance (CrCl), calculated using the MdCalc clinical calculator (17). Three commonly used equations were applied: Cockcroft–Gault (CG) (18), Modification of Diet in Renal Disease (MDRD) (19), and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (20):

Equation	Glomerular filtration rate (mL/min)
CG	CrCl = (140 – age) × weight × (0.85 if female) / (72 × Scr)
MDRD	GFR = 175 x $Scr^{-1.154}$ x $age^{-0.203}$ x 1.212 (if patient is black) 0.742 (if female)
CKD-EPI	GFR = 142 × $(Scr/A)^{B}$ × 0.9938^{age} × (1.012 if female)

age (years), weight (kg), Scr: serum creatinine (mg/dl); Female: A = 0.7 ; B = - 0.241 (Scr ≤ 0.7); B = -1.2 (Scr ≥ 0.7); Male: A = 0.9 ; B = - 0.302 (Scr ≤ 0.9); B = - 1.2 (Scr ≥ 0.9).

The CG equation estimates creatinine clearance based on serum creatinine, age, body weight, and sex, and is commonly used for drug dose adjustment. In contrast, MDRD and CKD-EPI estimate eGFR using serum creatinine, age, sex, and race, and are primarily applied for chronic kidney function assessment and staging.

2.4 Statistical analysis

Data processing and visualization were performed using Microsoft Excel and GraphPad Prism version 10.3.1. Statistical analyses included Fisher's exact test, t-test, two-way ANOVA, and Kaplan Meier survival analysis to evaluate differences between groups. Significance levels were defined as follows: ns: $p > 0.05$, *$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$, ****$p \leq 0.0001$.

3. Results

3.1 Differences in estimated GFR

Data from N=229 patients were collected (Figure 1, Table 1). According to the CKD-EPI and MDRD equations, 57.2% and 55.5% of cases were classified as appropriately dosed, respectively. However, 7.4% (N=17) of patients who were considered appropriately dosed by these equations were reclassified as inappropriately dosed when assessed using the CG equation.

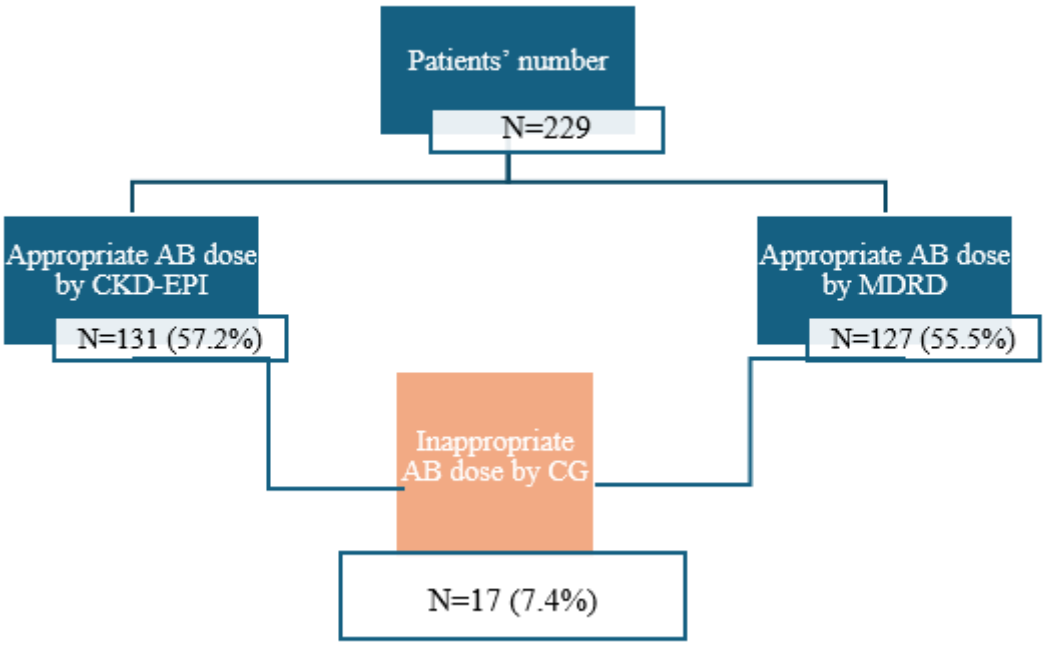


Figure 1: Appropriateness of the antibiotic dose based on kidney function calculated by different equations.

Table 1: Demographic and clinical characteristics of patients.

Equations	Male gender (%)	Age (years) mean±SD, (range); median	BW (kg) mean±SD, (range); median	CCI mean±SD, (range); median	CKD stage mean±SD, (range); median
CKD-EPI appropriate	61.1	63.95±14.66 (20-92); 67	75.75±22.24 (27-140); 70	4.10±2.26 (0-10); 4	1.89±0.97 (1-5); 2
MDRD appropriate	62.2	63.91±14.99 (20-92); 66	76.06±21.99 (27-140); 70	4.02±2.21 (0-9); 4	1.85±0.93 (1-5); 2
CG inappropriate	64.7	69.00±12.27 (36-86); 71	83.41±28.83 (40-125); 90	5.29±2.20 (0-9); 5	2.47±1.01 (1-4); 3

SD: standard deviation; BW: body weight; CCI: Charlson Comorbidity Index; CKD: Chronic Kidney Disease.

Considering all included patients (N=229), the mean estimated GFR values calculated by CKD-EPI and MDRD did not differ significantly from CG (67.85 ± 25.53 ml/min and 67.70 ± 24.98 ml/min vs 67.89 ± 24.53 ml/min, respectively) (Figure 2).

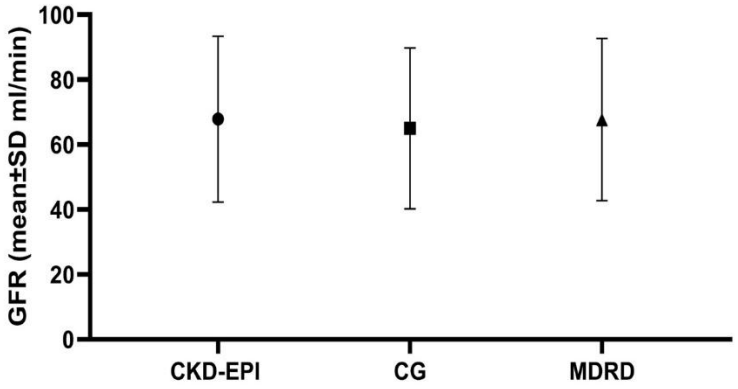


Figure 2: Mean GFR values calculated by different equations considering all included patients (N=229).

However, when comparing median values, the CG equation showed a difference of approximately 20 mL/min compared to CKD-EPI and MDRD (74 ml/min vs 52 ml/min and 50 ml/min, respectively), a shift large enough to alter renal dose-adjustment categories (Figure 3).

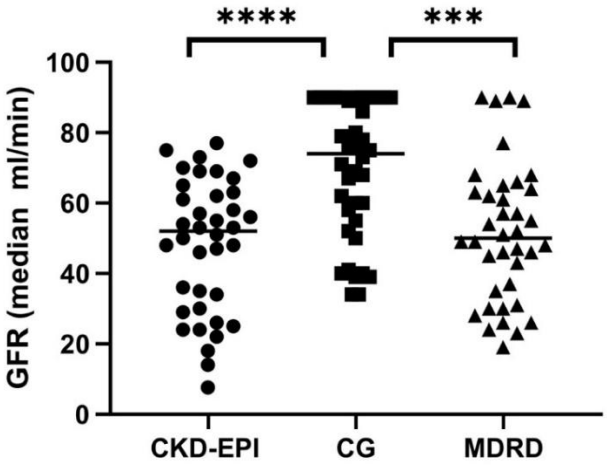


Figure 3: Median GFR values calculated by different equations.

3.2 Influencing Factors of Inappropriate Antibiotic Dose

Gender and Age

Among patients with inappropriate AB dosing according to the CG equation (7.4%), males were affected more frequently than females (11/17, 71% vs. 6/17, 29%). No significant age difference was observed between genders (males: 65.19 ± 12.42 years vs. females: 69.82 ± 6.16 years) (Figure 4).

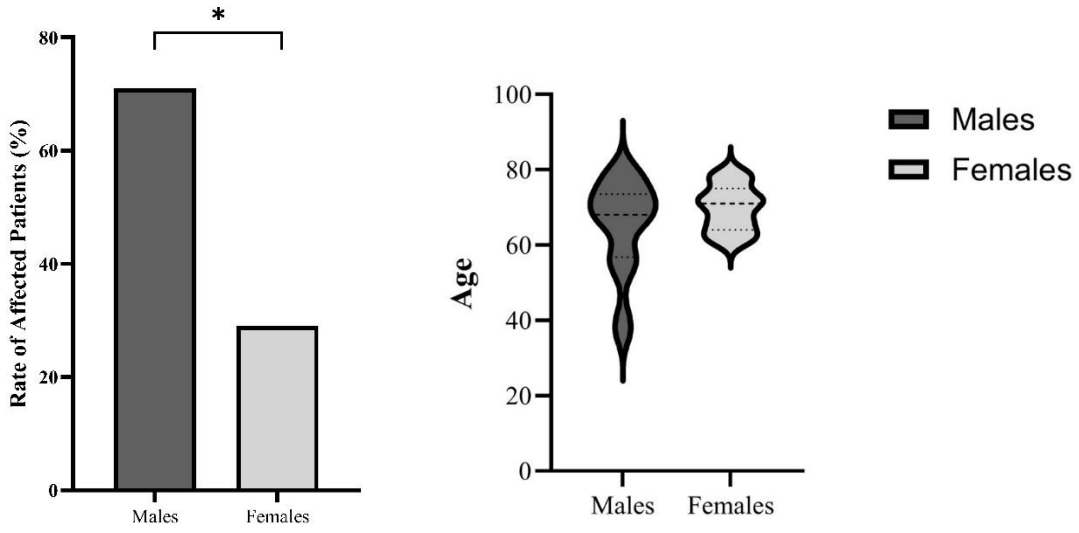


Figure 4: Gender and age as influencing factors in the calculation of estimated GFR by CG.

Although a higher proportion of inappropriate dosing occurred in males (71%), this finding should be interpreted cautiously, as it may be influenced by the overall gender distribution of the study population.

Age and Body Weight

When comparing appropriately and inappropriately dosed patients based on the CG equation, older age was significantly associated with inappropriate AB dosing (median: 71 vs 66 years, respectively). Higher body weight showed a similar trend (median: 90kg vs 70kg, mean ± SD: 83.41 ± 28.83kg vs 75.12 ± 20.80kg, respectively), although this difference was not statistically significant (Figure 5).

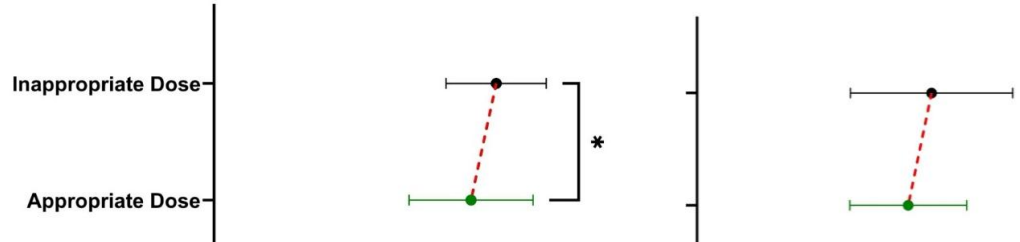


***Figure 5*:** Age and body weight as influencing factors in GFR estimation by CG.

CCI

Patients with higher CCI scores (5.29 ± 2.20 range 1-9, median 5 vs 3.82 ± 2.17 range 0-9 median 4, p=0.01) were significantly more likely to receive inappropriate antibiotic dosing according to the CG equation (Figure 6).

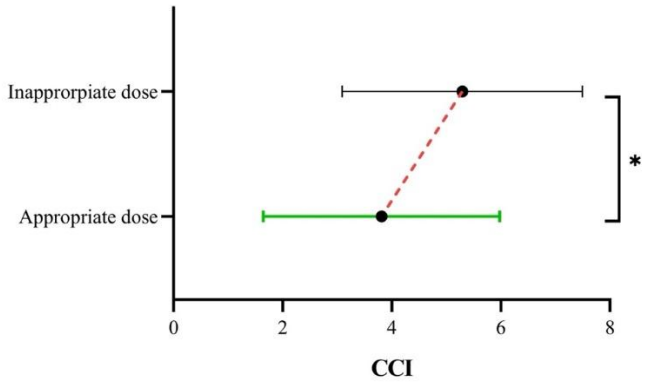


Figure 6: CCI as an influencing factor in GFR estimation by CG.

3.3 Inappropriate Dose: Affected antibiotics

Initial ICU-antibiotic therapy showed the highest rate of inadequacy when assessed using the CG equation (CG 111/118 - 94.1% vs CKD-EPI 98/131 - 74.8% and MDRD 102/127 - 80.3%) (Figure 7).

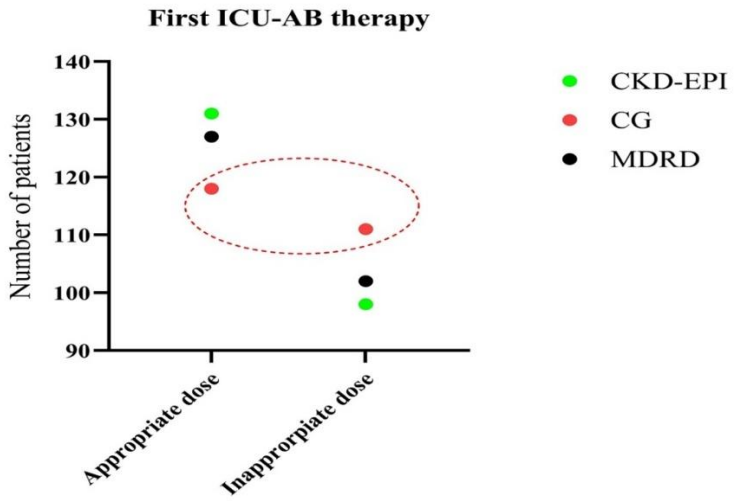


Figure 7: The frequency of inappropriate antibiotic dosing by different equations.

Piperacillin–tazobactam had the highest number of underdosed cases, whereas clarithromycin, cefepime and amikacin were frequently overdosed, increasing the risk of toxicity (Figure 8).

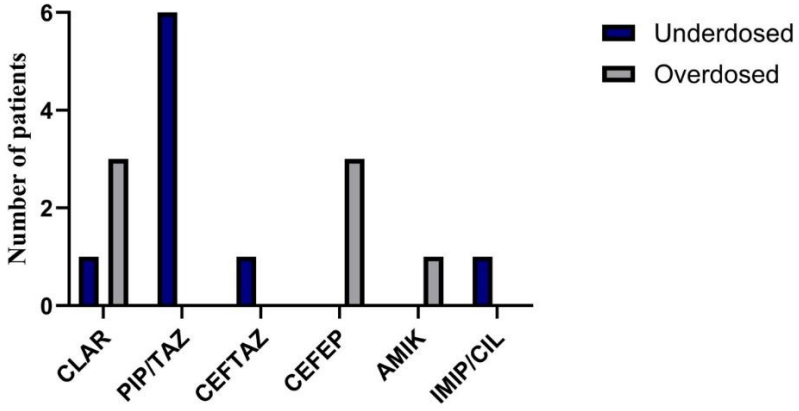


Figure 8: Antibiotics affected by dosing discrepancies based on CG-estimated GFR.

CLAR: clarithromycin; PIP/TAZ: piperacillin/tazobactam; CEFTAZ: ceftazidime; CEFEP: cefepime; AMIK: amikacin; IMIP/CIL: imipenem/cilastatin.

Recommended dose adjustments for the affected antibiotics are presented in Table 2 . The rates of antibiotic under- and overdosing, considering the different equations, are presented in Figures 9-10.

Antibiotics	Recommended dose for an adult - 70 kg (SmPC)	Recommended dose adjustment (SmPC)	
		CrCl (ml/min)	BW (kg)
clarithromycin	po or iv 250-500mg bid	< 30: 125-250mg bid	
piperacillin/tazobactam	iv 4.5g tid-qid	40-20: 4.5g tid	
		< 30: 4.5g bid	
cefepime	iv 1-2g tid	50-30: 0.5-1g tid	
		29-11: 1g bid	< 40kg
		≤ 10: 1g qd	
amikacin	iv 25-30mg/kg/day	80-70: 7.6-8 mg/kg/day	
		69-60: 6.4-7.6 mg/kg/day	
		59-50: 5.4-6.4 mg/kg/day	
		49-40: 4.2-5.4 mg/kg/day	
		39-30: 3.2-4.2 mg/kg/day	
		29-20: 2.1-3.1 mg/kg/day	
		19-15: 1.6-2.0 mg/kg/day	

Table 2: Recommended dose adjustment based on kidney function (21).

AB: antibiotic; CLAR: clarithromycin; PIP/TAZ: piperacillin/tazobactam; CEFEP: cefepime; AMIK: amikacin.

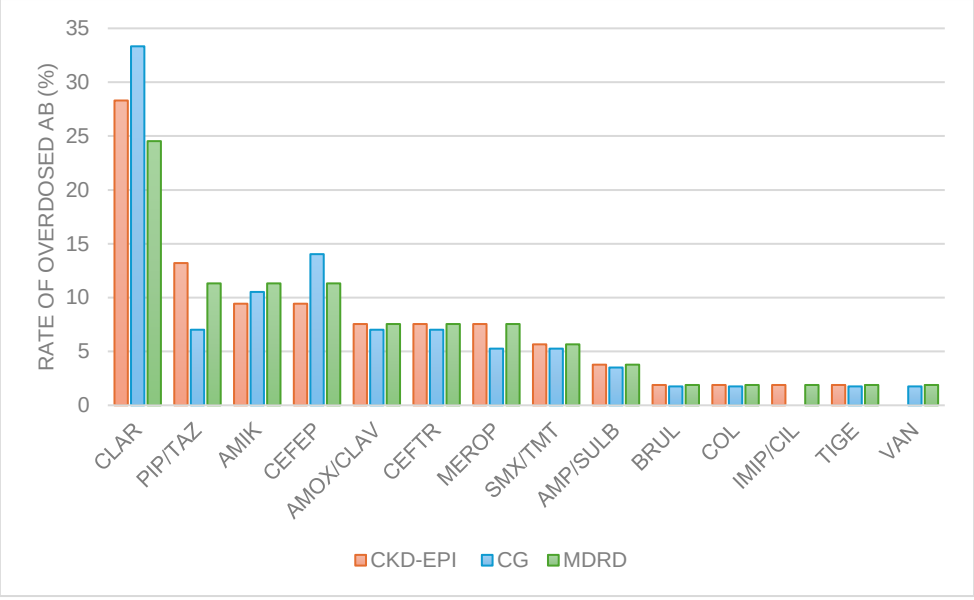


Figure 9: The rate of antibiotic overdosing using the CKD-EPI, CG, and MDRD equations in this study.

AB: antibiotic; CLAR: clarithromycin; PIP/TAZ: piperacillin/tazobactam; AMIK: amikacin; CEFEP: cefepime; AMOX/CLAV: amoxicillin/clavulanic acid; CEFTR: ceftriaxon; MEROP: meropenem; SMX/TMT: sulphamethoxazole/trimethoprim; AMP/SULB: ampicillin/sulbactam; BRUL: tobramycin; COL: colistin; IMIP/CIL: imipenem/cilastatin; TIGE: tygecyclin; VAN: vancomycin.

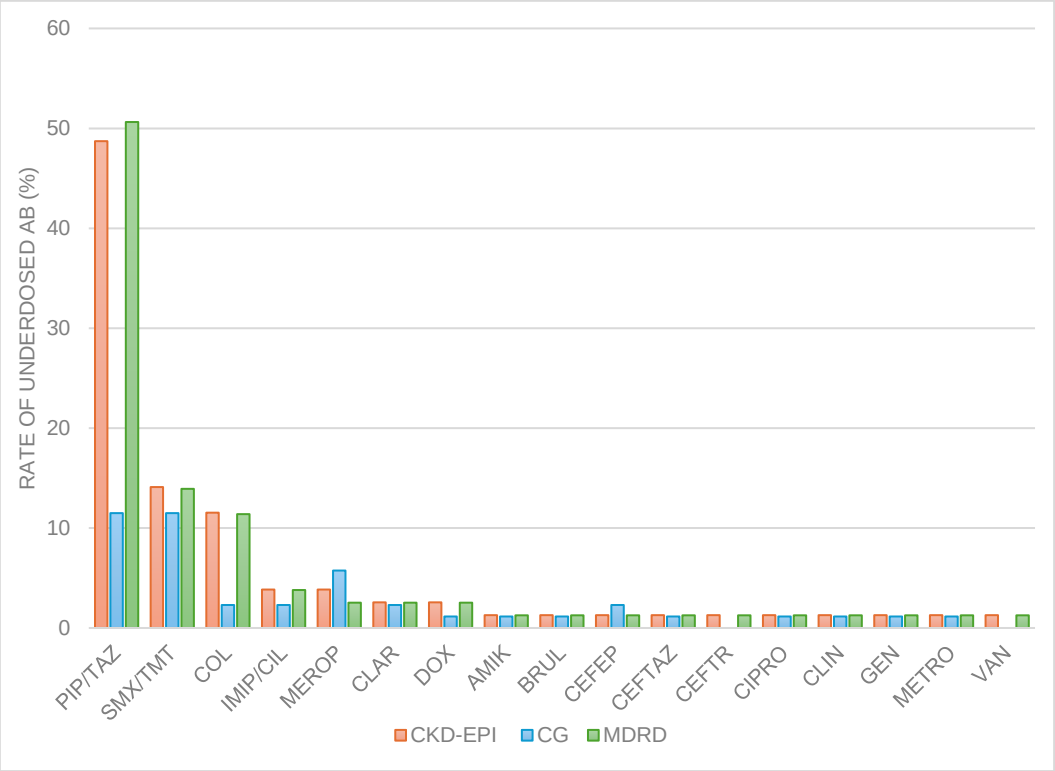


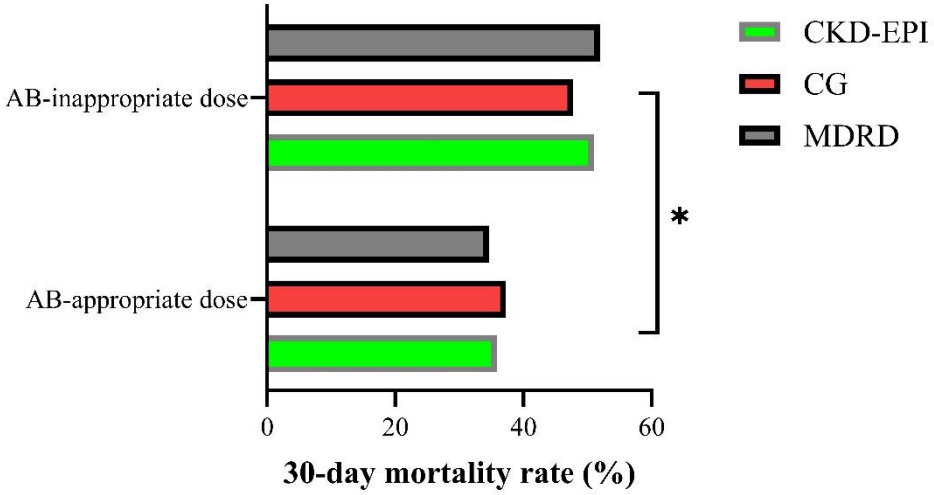
Figure 10: The rate of antibiotic underdosing considering the CKD-EPI, CG and MDRD equations in this study.

AB: antibiotic; PIP/TAZ: piperacillin/tazobactam; SMX/TMT: sulphamethoxazole/trimethoprim; COL: colistin; IMIP/CIL: imipenem/cilastatin; MEROP: meropenem; CLAR: clarithromycin; DOX: doxycycline; AMIK: amikacin; BRUL: tobramycin; CEFEP: cefepime; CEFTAZ: ceftazidime; CEFTR: ceftriaxon; CIPRO: ciprofloxacin; CLIN: clindamycin; GEN: gentamycin; METRO: metronidazole; VAN: vancomycin.

3.4 Clinical outcomes

30-day mortality

30-day mortality was significantly higher in the inappropriate-dose group across all equations. However, no differences were observed between GFR estimation methods (Figure 11).

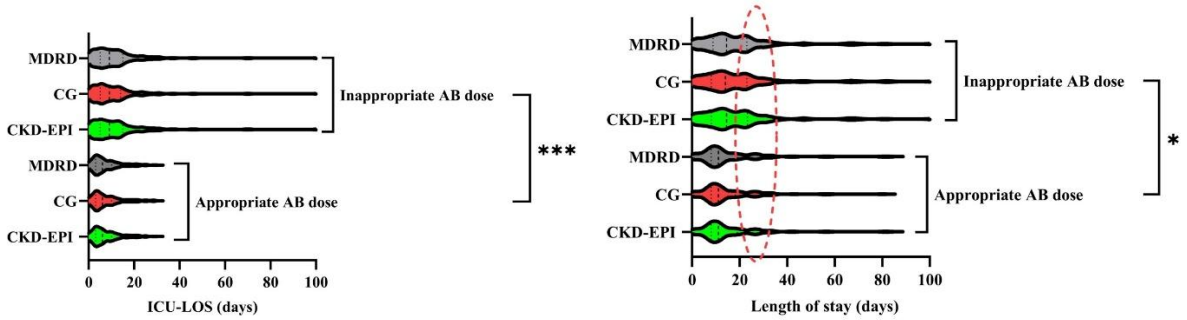


30-day mortality	CKD-EPI	CG	MDRD
AB-appropriate dose	47/131 (35.9%)	44/118 (37.3%)	44/127 (34.7%)
AB-inappropriate dose	50/98 (51.0%)	53/111 (47.8%)	53/102 (52.0%)

Figure 11: 30-day mortality rate based on antibiotic dosing appropriateness and GFR estimation method. (AB: antibiotic)

Length of Stay (LOS)

Inappropriate dosing was associated with delayed recovery and prolonged hospitalization. Total LOS was significantly longer in the inappropriate-dose group (median 14 vs 11 days), with a more pronounced difference in ICU-LOS (median: 9 vs 6 days). However, no differences in LOS were observed between GFR estimation methods for either appropriate or inappropriate dosing groups (Figure 12).



	Appropriate AB dose			Inappropriate AB dose		
ICU-LOS	CKD-EPI	CG	MDRD	CKD-EPI	CG	MDRD
mean±SD	14.96±13.12	14.41±11.84	14.97±13.31	18.95±17.02	19.07±17.50	18.78±16.71
median	11	11	11	14.5	14	14.5
LOS						
mean±SD	7.33±5.87	7.53±6.32	7.21±5.91	12.31±13.87	11.50±13.12	12.25±13.60

median	6	6	6	9	9	9

Figure 12: Length of stay based on antibiotic dosing appropriateness and GFR estimation method.

Survival analysis

Inappropriate AB dosing was associated with significantly worse 30-day survival, with a steeper early decline, suggesting that the early dosing errors in patients with renal impairment have sustained clinical consequences. Long-term survival also remained lower in the inappropriately dosed group. However, no differences in survival were observed between GFR estimation methods, regardless of dosing appropriateness (Figure 13).

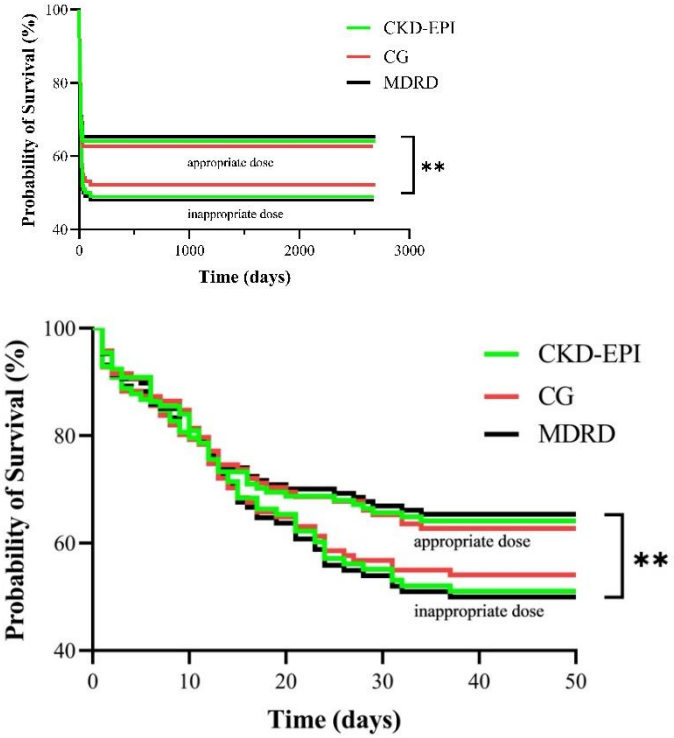


Figure 13: Probability of survival based on antibiotic dosing appropriateness and GFR estimation method.

4. Discussion

In this study, we found that the choice of renal function estimation method significantly influences the assessment of antibiotic dosing appropriateness in critically ill patients. Although mean GFR values calculated by CKD-EPI, MDRD, and CG equations were comparable, substantial differences were observed in median values, resulting in

clinically relevant reclassification of dosing categories. Notably, 7.4% of patients who were considered appropriately dosed according to CKD-EPI and MDRD were identified as receiving inappropriate antibiotic dosing when evaluated using the CG equation. This finding highlights the potential for systematic misclassification when relying solely on eGFR-based equations for drug dosing decisions.

Our results are consistent with previous studies indicating that discrepancies between CrCl and eGFR-based estimates may significantly affect dosing decisions, particularly in populations with altered physiology (12, 22-24). The observed ~20 mL/min difference in median renal function between CG and eGFR-based equations is of particular clinical importance, as it may shift patients across renal dosing thresholds, thereby altering recommended antibiotic regimens. This is especially relevant for antibiotics with narrow therapeutic windows or predominantly renal elimination.

We also identified several factors associated with inappropriate dosing by CG. Male sex and higher comorbidity burden (CCI) were significantly associated with dosing inaccuracies, while older age was more prevalent in the inappropriately dosed group. Although higher body weight showed a trend toward increased risk, this did not reach statistical significance. These findings suggest that patient-specific characteristics—particularly those affecting muscle mass and creatinine production—may contribute to discrepancies in renal function estimation and subsequent dosing errors.

From a pharmacological perspective, both underdosing and overdosing carry important risks. In our cohort, piperacillin/tazobactam was most frequently underdosed, potentially compromising therapeutic efficacy, whereas clarithromycin, cefepime, and amikacin were more commonly overdosed, increasing the risk of toxicity. These findings are clinically relevant, as inappropriate dosing of these agents has been associated with treatment failure, nephrotoxicity, and other adverse outcomes (25-28).

Importantly, inappropriate antibiotic dosing was associated with worse clinical outcomes. Although 30-day mortality differences did not reach statistical significance between renal function estimation methods, patients in the inappropriate-dose group showed a consistent trend toward higher mortality. Furthermore, inappropriate dosing

was associated with significantly higher 30-day mortality, prolonged hospital and ICU-LOS, as well as reduced survival probability over time. The early divergence in survival curves suggests that initial dosing decisions may have lasting consequences in critically ill patients (29-33).

These findings underline the complexity of AB dosing in the ICU and the limitations of relying on a single renal function estimation method. While CG remains the standard for drug dosing in many guidelines, its use in routine clinical practice is often inconsistent, with clinicians frequently relying on automatically reported eGFR values. This discrepancy between recommended practice and real-world application may contribute to the observed rate of inappropriate dosing.

In this context, the role of clinical pharmacists is particularly important. Pharmacists are uniquely positioned to bridge the gap between renal function assessment and individualized dosing by critically evaluating different estimation methods, identifying discrepancies, and providing patient-specific dosing recommendations. Their involvement in antimicrobial stewardship programs has been shown to reduce medication errors, improve dosing accuracy, and optimize clinical outcomes. In complex cases - such as critically ill patients with fluctuating renal function - pharmacist-led interventions can support timely dose adjustments and enhance adherence to evidence-based guidelines (34-36).

Despite these strengths, our study has several limitations. As a single-center retrospective analysis, the findings may not be generalizable to other settings. The relatively small proportion of patients with inappropriate dosing may limit statistical power for some subgroup analyses. In addition, renal function was estimated using serum creatinine-based equations, which may be influenced by non-renal factors such as muscle mass and fluid status, particularly in critically ill patients. Moreover, another limitation of this study is that mortality tracking was restricted to intra-institutional mortality (available through the UD-MED system); however, given the relatively large statistical significance observed between the appropriate and inappropriate dosing, the lack of out-of-institution mortality data is unlikely to alter the overall clinical conclusions.

5. Conclusion

In conclusion, our findings highlight that the choice of renal function estimation equation can significantly impact antibiotic dosing decisions in critically ill patients. The use of eGFR-based equations alone may lead to clinically relevant misclassification compared to the Cockcroft–Gault method. Inappropriate dosing is associated with prolonged hospitalization and worse survival, underscoring the importance of accurate renal function assessment. In addition, inappropriate antibiotic combinations may also lead to other undesirable pharmacokinetic changes. Integrating clinical pharmacists into multidisciplinary care teams may help mitigate these risks by improving dosing accuracy and supporting individualized antibiotic therapy. Future prospective studies are warranted to validate these findings and to explore strategies for optimizing renal dosing practices in critically ill populations.

Acknowledgements

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Data Availability Statement:

Data are available from the corresponding author upon reasonable request.

Abbreviations

AB: Antibiotic
AMR: Antimicrobial resistance
ANOVA: Analysis of variance
ASP: Antibiotic stewardship program
CCI: Charlson comorbidity index
CG: Cockcroft-Gault
CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration
CrCl: Creatinine clearance
DDD: Defined daily dose
eGFR: Estimate glomerular filtration rate
GFR: Glomerular filtration rate
ICU: Intensive care unit

ICU-LOS: Intensive care unit length of stay

LOS: Length of stay

MDRD: Modification of diet in renal disease

SmPC: Summary of product characteristics

UD-MED: University of Debrecen medical informatics system

USD: United States dollar

WHO: World Health Organization

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