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Review Article

OPTIMIZING DRUG DOSING IN CRITICALLY ILL PATIENTS WITH AUGMENTED RENAL CLEARANCE: A COMPREHENSIVE REVIEW AND META-ANALYSIS

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ABSTRACT

Renal clearance plays a pivotal role in eliminating most administered drugs, particularly antibiotics, which is crucial for achieving therapeutic goals by maintaining plasma concentrations within the therapeutic window. Various pre-existing conditions such as renal replacement therapies, kidney or liver impairment, and enhanced excretory organ function can disrupt drug concentrations, leading to treatment failure. Augmented Renal Clearance (ARC) exacerbates this by causing rapid drug elimination, notably in critically ill patients. Consequently, careful monitoring and adjustment of drug dosages tailored to individual patient conditions and comorbidities are imperative to prevent sub-therapeutic outcomes or treatment failures. Our review highlights the necessity of dosage modifications informed by current research to optimize therapeutic outcomes in such cases. We provide a comprehensive table detailing effective antibiotics and their adjustments for ARC.

Keywords: Augmented renal clearance, Critically ill patients, Antibiotic dose adjustments, Treatment failure, Increased dose, eGFR, Creatinine clearance

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INTRODUCTION

A typical sign experienced by 30–65% of patients in the intensive care unit (ICU) is augmented renal clearance (ARC) [1]. The phenomenon in which the elimination of serum creatinine exceeds 130 ml/min/1.73 m^2, poses a substantial challenge in maintaining adequate serum antibiotic concentrations, particularly in septic patients [2]. In the initial stages of sepsis, the blood flowing through the kidneys and the glomerular filtration rate (GFR) are increased, resulting in increased elimination of the drug from the body due to hypermetabolic condition [3]. As a result, low levels of plasma drug concentrations were achieved, which potentially leads to treatment failure due to increased activity of excretory organs [4]. Altered pharmacokinetics, such as elevated volume of distribution and adaptations in protein binding, complicates the precise estimation of drug levels see fig. 1. Continuous renal replacement therapies (CRRT) and organ impairment can influence plasma levels of antimicrobials, warranting careful consideration [5]. In critically ill patients, dosage adjustment is essential to counteract the rapid drug elimination associated with ARC. The suggested protocol recommends increasing antibiotic doses two to threefold compared to the normal range to accomplish therapeutic concentrations greater than the minimal inhibitory threshold (MIC) [1].

Understanding and managing ARC become crucial in preventing misinterpretation of renal health indicators and ensuring appropriate medical interventions. Despite the potential impact of ARC on various pharmacologic agents, limited attention is often given to its consequences, especially in drug development and clinical practice. Patients with renal insufficiency frequently have their dosages of renally eliminated medications adjusted; nevertheless, the importance of ARC in this setting is frequently disregarded. Patients with ARC may experience therapeutic failure and poorer patient outcomes if they get regular, unadjusted dosages. Hence, recognizing and addressing ARC is essential for optimising patient care and treatment efficacy in the critically ill population.

Mechanism of arc

ARC is generally described as a hyperkinetic state, heightened cardiac output, and increased blood flow to major organs, potentially resulting in heightened kidney perfusion. Lowered vascular resistance, high cardiac output, and raised capillary permeability are manifested due to pro-inflammatory mediators and dysregulated cytokines, see fig. 2. Consequently, patients with ARC may experience augmented renal vascular flow, leading to improved elimination of hydrophilic drugs when combined with inotropic agents and intensive fluid therapy. Another potential mechanism suggests renal function reserve (RFR), highlighting the kidney's capacity to raise the glomerular filtration rate (GFR) in specific clinical conditions, such as hyperfiltration states and cardio-renal patient conditions [4].

Methodology

We conducted a comprehensive search on Google Scholar for articles published between 2010 and 2023, see fig. 3 focusing on augmented renal clearance (ARC) in patients who are on antibiotics. We aimed to derive personalised antibiotic dosage regimens for individuals with ARC.

The literature search involved exploring databases for relevant evidence related to ARC in humans. To ensure inclusivity of all studies on augmented renal clearance, we utilised keywords such as "augmented renal clearance," "increased drug clearance," "Therapeutic failure due to ARC," "glomerular hyperfiltration," "neurocritical care," "ARC in critically ill patients," "Renal dosage adjustment," "Increased kidney function," and "increased creatinine clearance (CrCl)."

Following the initial search, screening of the title and abstract was performed to determine and exclude duplicate studies and those unrelated to the topic. In instances where doubt arose about a study's relevance to ARC, we included it for a more detailed full-text review.

Measurement of creatinine clearance

Creatinine clearance (CrCl) is assessed differently in adults and children, reflecting the variations in kidney function and growth rates between these groups. The Cockcroft-Gault formula is used for adults to calculate the creatinine clearance (CrCl), whereas for children, the Schwartz formula is employed to determine CrCl.

Equation 1: Cockcroft gault formula

$$\text{CrCl (ml/min)} = \frac{(140 - \text{age}) \times \text{Lean Body Weight (kg)} \ (0.85 \text{ if female})}{\text{Serum Creatinine (mg/dl)} \times 72}$$

(Cockcroft DW, Gault H. Prediction of creatinine clearance from serum creatinine. Nephron. 1976 Nov 28;16(1):31-41.)

Equation 2: Schwartz formula

$$\text{eGFR (ml/min/1.73 m}^2) = k \times \text{Length / Sr. Creat (mg/dl)}.$$

Where,

k = 0.33, in preterm infants < 1 year old

k = 0.45, in full-term infants < 1 year old

k = 0.55, in 1-12 years old and adolescent girls

k = 0.7, in adolescent boys

eGFR: Estimated Glomerular filtration rate, Sr. Creat: Serum Creatinine

(Schwartz GJ, Mun A, Schneider MF, Mak RH, Kaskel F, Warady BA, Furth SL. New equations to estimate GFR in children with CKD. Journal of the American Society of Nephrology. 2009 Mar 1;20(3):629-37.)

If the calculated creatinine clearance (CrCl) exceeds 130 ml/min, the patient meets our criteria for augmented renal clearance. Therefore, it may be essential to adjust the antibiotic dose upwards or adhere to our evidence-based dosing guidelines tailored to the patient's specific conditions.

RESULTS

Augmented renal clearance (ARC) exhibited a higher incidence of treatment failure, potentially leading to antibiotic resistance. A comprehensive review revealed that the standard frequencies and concentrations typically employed for antibiotics proved ineffective in individuals with ARC. Consequently, optimising dosing regimens becomes crucial, either by maximising the dosage or implementing prolonged infusions. Future research must delve into the ramifications of accurately dosing drugs which are eliminated by the kidney in those with ARC, considering the potential impact on individual clinical outcomes. Clinicians must carefully assess the manifestations of ARC and should adapt the new dosing strategies.

Table 1: List of literatures

S. No.	Author	Study type	Population	Ref.	Result
1	Athena L. V. Hobbs, *et al.*	Review	Sepsis ICU, Trauma ICU,	1	Patients with trauma, sepsis, low SOFA score, TBI and SAH are at highest risk for ARC include age younger than 50–55 years; which can easily go unnoticed without routine screening in ICU patients where ARC is very common. As Literature for non-antimicrobial medications is limited,most dosing recommendations are established on empiric population pharmacokinetics studied in healthy volunteers or ambulatory patients, and clinicians are left to rely solely on clinical improvement to guide dosage adjustments.
2	Iris H. Chen *et al.*	Review	Critically ill patients, Trauma ICU, Pediatric ICU, Medical ICU, Surgical ICU, Septic ICU	2	It is very usual for ICU patients to have Augmented Renal Clearance, causing antibiotics to get eliminated so effectively that subtherapeutic concentrations and clinical failure becomes too common. Therefore, it is essential to accurately and regularly assess kidney function in these patients given the frequent need for antibiotics and their concentrations to be impacted. Dosing regimens should be optimised, either by maximising the dose or using prolonged infusions, or making the decision to switch to another agent.
3	Angela Huttnera, *et al.*	Single-centre, Observational prospective cohort study	Medical ICU, Surgical ICU,	3	ARC is commonly seen in the critically ill patients and strongly predicts lower beta–plasma in concentrations. Potentially impacting clinical outcomes and antimicrobial resistance, emphasizing the need for individualized antimicrobial therapy.
4	Idoia Bilbao-Meseguer, *et al.*	A systematic review	Critically ill patients, Mixed ICU	5	Augmented renal clearance (ARC), defined as a creatinine clearance (CrCl)>130 ml/min/1.73 m2, often measured in urine, affects 20-65% of critically ill patients. Risk factors include younger age, polytrauma, and lower severity of illness. ARC significantly impacts antimicrobial pharmacokinetics, consistently leading to subtherapeutic antibiotic levels.
5	Andrew A. Udy, *et al.*	Multicenter, prospective, observational study	Sepsis ICU, Trauma ICU,	6	The study indicated that a significant proportion of ICU patients exhibit markedly increased renal solute elimination within the initial 7 days, which may not be readily apparent to clinicians. Identifying patients vulnerable to augmented renal clearance (ARC) enables targeted measurement of CrCl, which is not standard practice in most units, to monitor renal function changes. Future research should expand understanding of the implications for precise dosing of renally excreted drugs in ARC patients. Moreover, given the study's high ARC prevalence (65.1%), further investigation is necessary to assess its potential impact on individual clinical outcomes.
6	Barbara O. M. Claus Pharm D, *et al.*	Prospective observational, mixed cohort study	Surgical ICU, Medical ICU	7	ARC was seen in 51.6% of the patients, with 12% of them permanently expressing the condition. It was observed that ARC resulted in higher number of therapeutic failuresi. e. 18 (27.3%) vs. 8 (12.9%); P =.04
7	Andrew A. Udya, *et al.*	A nested cohort study of the BLING-II randomised, placebo-controlled clinical trial	Sepsis ICU, Critically ill patients	8	The study found that in critically ill patients with severe sepsis receiving β-lactam therapy, augmented renal clearance (ARC) was not associated with adverse clinical outcomes. In fact, unadjusted analysis showed a higher rate of clinical cure. The results suggest that the outcomes in these patients are influenced by a complex interplay of co-morbidities, antibiotic exposure, and organ function, with organ impairment being as crucial as β-lactam exposure in determining therapeutic success.
8	Ryo Kamidani, *et al.*	Retrospective cohort study	Adult ICU	9	The study focuses on the need for vigilant monitoring in critically ill COVID-19 patients due to potential anticoagulation failure during augmented renal clearance (ARC). Despite requiring higher doses of unfractionated heparin (UH) to achieve therapeutically effective APTT prolongation during ARC, no significant increase in bleeding complications was reported. Therefore, considering higher doses in these scenarios is advisable.
9	Andrew A. Udy, *et al.*	Review	Sepsis ICU, Critically ill patients, Burns ICU, Trauma ICU, Meiloidosis, Abdominal ICU	11	The implications of enhanced drug elimination are significant, as subtherapeutic concentrations for extended periods during the dosing interval may lead to treatment failure and the emergence of resistant organisms. Since this issue has largely been neglected in clinical practice, more frequent estimations of CrCL and TDM are warranted to optimize individual dosing requirement.
10	Aaron M. Cook, *et al.*	Case report	Neuro ICU	12	The study developed a population pharmacokinetic model for vancomycin in infants, children, and adolescents with augmented renal clearance (ARC). Clearance of vancomycin was significantly influenced by weight and age. The

S. No.	Author	Study type	Population	Ref.	Result
					current recommended dose for pediatric patients with ARC is deemed insufficient. In view of vancomycin's efficacy and safety profile, we propose a revised therapeutic regimen recommending 75 mg/kg/day for infants and children aged 1 mo to 12 y, and 70 mg/kg/day for adolescents aged 12 to 18 y.
11	Cédric Carrié, Rachel Legeron, *et al.*	Prospective, observational study	Critically ill patients, Sepsis ICU	38	While targeting an upper limit theoretical MIC, to achieve desirable target of 100%f T>16 may not be possible in patients with CrCL of 170 ml/min or higher who are receiving PTZ dose 16 gm/2 gm/day continuously.
12	Fatma Hefny, *et al.*	Systematic Review and Meta-analysis	Trauma ICU, Neuro ICU, Sepsis ICU	44	ARC is frequently observed in critically ill patients including neurocritical care and trauma ICU population. Factors such asyoung age, male gender, and trauma increase the risk for ARC; apparently, patients with normal renal function can also exhibit such condition. Estimating CrCL using GFR mathematically estimated significantly underestimates ARC prevalence in critical care, emphasizing the necessity of measuring CrCL through urine collections and conducting more research on optimal drug dosing.
13	Cui-Yao He, *et al.*	To develop pharmacokinetic model	Paediatric ICU	45	The study developed a population pharmacokinetic model for vancomycin in infants, children, and adolescents with augmented renal clearance (ARC). Clearance of vancomycin was significantly influenced by weight and age. The current recommended dose for pediatric patients with ARC is deemed insufficient. In view of vancomycin's efficacy and safety profile, we propose a revised therapeutic regimen recommending 75 mg/kg/day for infants and children aged 1 mo to 12 y, and 70 mg/kg/day for adolescents aged 12 to 18 y.

Table 2: Drugs and their recommended doses for ARC

S. No.	Name of drug	Recommended dose for arc (>130 ml/min)
Antibiotics		
1	Amikacin	High-dose, extended-interval dosing: IV: 20-30 mg/kg OD for known/suspected sepsis [5, 11] or MIC of 8 mg/l: 40 mg/kg, and for MIC of 16 mg/l: 70 mg/kg [4]
2	Amoxicillin Clavulanic acid	IV: 1-2 gm q6 h [7]
3	Ampicillin Sulbactam	IV: 1.5-3 gm q4-6 h [5, 11]
4	Aztreonam	IV: 2 gm q6 h, prolonged infusion over 4 h [12, 13]
5	Cefazolin	IV: 2 gm q6 h or 100-150 mg/kg/d as a continuous infusion [4, 14, 15]
6	Cefiderocol	IV: 2 gm over 3 h q 6 h [2, 16]
7	Cefepime	IV: Initial: Empirically or MICs>4 mg/l: 2 gm q6 h infused over 3 h [17]
8	Cefepime/Enmetazobactam	IV: 2.5 gm q8 h infused over 4 h [18]
9	CeftarolineFosamil	IV: 600 mg q8 h, infused over 2 h [12]
10	Ceftazidime Avibactam	IV: 2.5 gm 8 hourly infuse 2-4 h [19-22]
11	Ceftolozane/Tazobactam	IV: 3 gm q8 h infused over 1 h [4]
12	Ceftobiprole Medocaril Na	IV: 667 mg IV every 6 h [23]
13	Ceftriaxone	IV: 2 gm 12 hourly [24]
14	Cefuroxime Sodium	IV Extended infusion: 1.5 gm q6 h infused over 3 h. or IV Continuous infusion: Loading dose: 1.5 gm, followed by 6 gm q24 h infused over 24 h [12, 25]
15	Ciprofloxacin	MIC ≤0.125 mg/l: 400 mg q8 h or MICs>0.125 mg/l: 600 mg q8 h, or utilise another agent [12, 26]
16	Colistin (Colistimethate Sodium)	IV: 10 to 12 million international units/day or 200,000 international units/kg/day administered as a 3 hour infusion has been suggested or 360 mg CBA/d [4, 12]
17	Daptomycin	IV: 10 mg/kg OD; may increase to 12 mg/kg OD for severe infections (e. g., VRE bloodstream infection or endocarditis) [12, 27, 28]
18	Doripenem	250-500 mg q8 h as a 1-or 4 h infusion, or 250-500 mg administered over 30 min q8-12 h [4]
19	Fosfomycin	IV: 24 g/day in 3 to 4 divided doses except for urinary tract infections [29, 30]
20	Gentamicin	High-dose, extended-interval dosing: IV: 6 to 8 mg/kg OD, dose and interval are adjusted based on serum concentrations [12]
21	Imipenem Cilastatin	500-1000 mg q6 h infused over 30 min. [4] or 1 gm q6 hourly infuse over 2 to 4 h [12]
22	Levofloxacin	Oral, IV: Loading 750 mg, then 500 mg q12 h or 1 g q24 h. [31] or 500-1250 mg OD or 750 mg q24 h as a 90 min infusion [4].
23	Linezolid	IV: 450 mg q8 h. Or 600 mg administered q12h or 2400 mg/d as a 24h continuous infusion. [12, 32-34]
24	Meropenem	2 gm Stat F/B 2 gm 8hourly infuse over 3 h or 8-10 gm/d [35-37].
25	Piperacillin Tazobactam	CrCl 130 to<170 ml/minute: IV: 4.5 g q6 h infused over 3 h or Loading dose: 4.5 g, followed by 18 g continuous infusion over 24 h immediately. CrCl ≥170 ml/minute: IV: Loading dose: 4.5 g, followed by 22.5 g continuous infusion over 24 h immediately [38, 12].
26	Sulbactam/Durlobactam	IV: Sulbactam 1 g and durlobactam 1 g every 4 h. [39]
27	Temocillin	IV: 2 gm/8 h. [7]
28	Tobramycin	Consider combination therapy or alternative agents for organism MIC greater than 1 g/ml. [4]
29	Vancomycin	*Intermittent infusion:* Loading dose: 25 to 35 mg/kg followed by 15 to 20 mg/kg q6-8 h Continuous infusion: Loading dose: 15 to 25 mg/kg Maintenance dose: 40 to 60 mg/kg/day; adjust to achieve a target steady-state concentration of 20 to 25 mg/l. [12, 40, 41]
Anti-viral agents		
1	Acyclovir	Use the indication-specific maximum allowable dose along with therapeutic drug monitoring when available [12]
2	Oseltamivir	Influenza, seasonal treatment: 75-150 mg twice daily [12].
3	Valacyclovir	Use the indication-specific maximum allowable dose along with therapeutic drug monitoring of acyclovir to support Valacyclovir dosing when available [5, 11].
Others		
1	Levetiracetam	Loading dose: 4 gm IV Maintenance dose: 1500 mg IV every 8 h [27, 42]
2	Heparin	S. C: 5000 – 30000 IU [9]

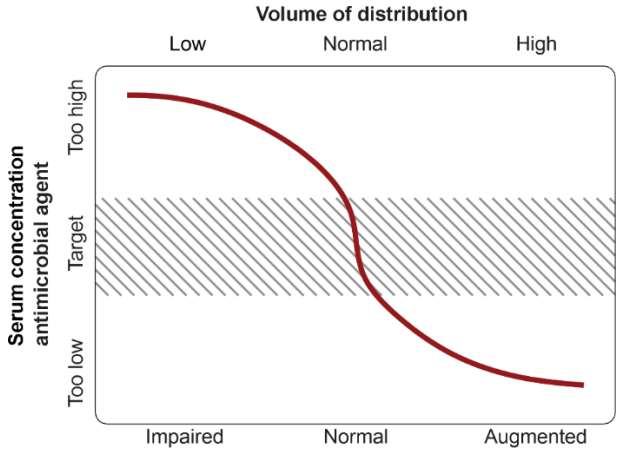

Fig. 1: Schematic illustration of the influence of increased volume of the distribution and augmented renal clearance on serum concentrations of hydrophilic antimicrobial agents ted renal clearance on serum concentrations of hydrophilic antimicrobial agents

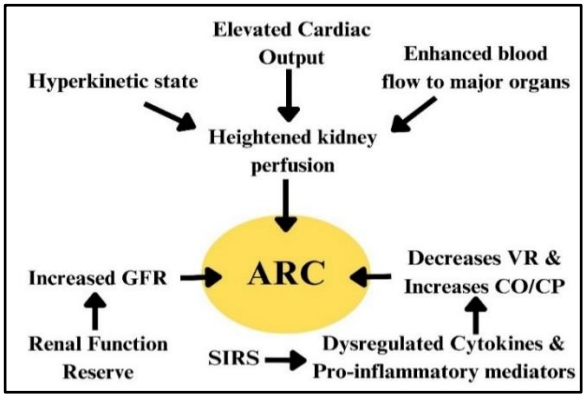

Fig. 2: Summarized mechanism of action for ARC, GFR: Glomerular filtration rate, VR: Vascular resistance, CO: Cardiac output, CP: Capillary permeability, SIRS: Systemic inflammatory response syndrome, ARC: Augmented renal clearance

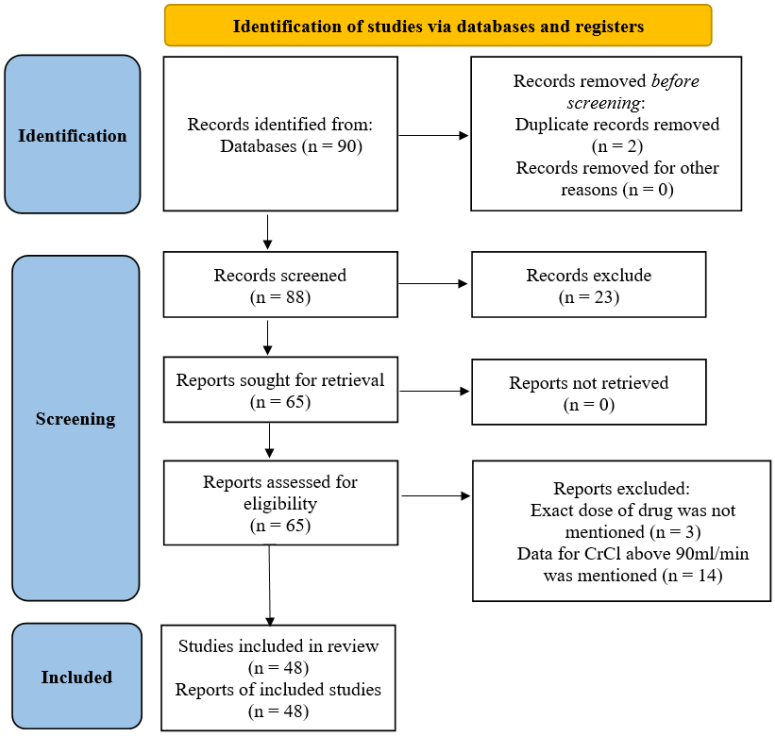

Fig. 3: Schematic form of identification and screening of the studies and literatures from the databases

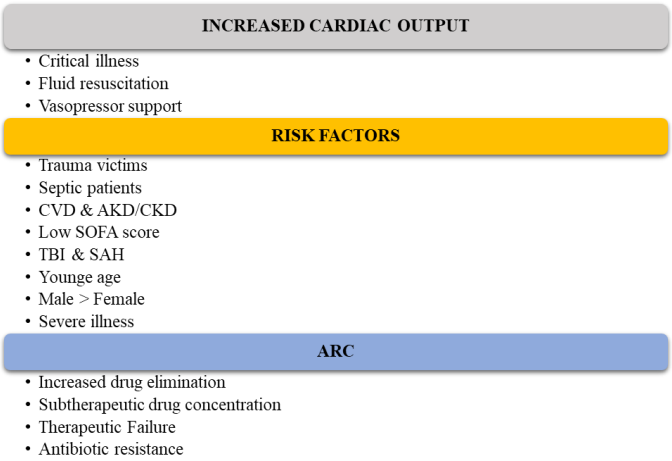

Fig. 4: Factors contributing to ARC and associated risks, CVD: Cardiovascular disease, AKD: Acute kidney injury, CKD: Chronic kidney injury, TBI: Traumatic brain injury, SOFA: Sequential organ failure assessment, SAH: Subarachnoid haemorrhage, ARC: Augmented renal clearance

DISCUSSION

Athena L. V. Hobbs *et al.* say ARC is frequently found among ICU patients and can be overlooked without regular screening. Those at highest risk include individuals under 50–55 years, trauma victims, subarachnoid haemorrhage (SAH), septic patients, those with low SOFA scores, and traumatic brain injury (TBI) patients [1].

ARC is frequently attended to in ICU patients, posing a substantial challenge as it can efficiently eliminate antibiotics, potentially leading to low concentrations and therapy failure. Kidney functions are monitored regularly in these patients, especially through urine collection for over 8 h in catheterized individuals. As the use of antibiotics and their concentrations get affected, optimising dosing becomes essential. This can involve increasing the dose, using prolonged infusions, or using alternative agents [2].

Huttner *et al.* found that among 100 patients studied, 64% had ARC at inclusion. Younger age, lesser comorbidities and patients with traumatic or neurological issues tended to have ARC. Two weeks later, 84% of ARC patients were still assessable, with 76% continuing to exhibit ARC. Low or undetectable trough levels of antibiotics show inadequate clinical outcomes [3].

A-Xi Shi *et al.* described patients with ARC often eliminate antibiotics more quickly, increasing the risk of treatment failure. Thus, tailoring dosing for each patient is crucial to address this issue. Urinary CrCl measurement is preferable to overestimated GFR for ARC diagnosis. Regular drug examination is advisable to enhance the efficacy of treatment and reduce the possibility of failure or antibiotic resistance [4].

ARC is a predominant phenomenon that profoundly influences the optimal exposure of drugs primarily wiped out through the kidneys. Consequently, there is a need to consider individualised dosing regimens to address these challenges. If the required drug concentration couldn't be achieved within time, it would lead to increased morbidity and mortality [4].

Meseguer *et al.* say ARC significantly affects antimicrobial plasma levels, but its impact remains unclear and warrants further investigation. ARC is dynamic; dosage adjustments are based on daily changes in renal clearance. PK/PD analysis can help simulate various antimicrobial dosage strategies, such as high doses or prolonged infusions, to determine the most effective approach for improving clinical outcomes [5].

A notable finding is the widespread occurrence of augmented renal clearance (ARC), in the initial seven days, around 65% of patients showed ARC at least once during the study, with a strong link to higher clearances on the first day, and this exists not only due to ongoing fluid loading. Individuals with ARC consistently show lower plasma creatinine concentrations, yet they exhibit sustained elevation in creatinine clearance (CLCR) and excretion rates, with no significant difference in 24 h fluid balance, reinforcing this observation [6].

The identification of fairly low CrCL in certain patients underscores the importance of assessing "renal function" beyond merely identifying "kidney injury." Identifying patients at risk of ARC enables targeted CrCL measurements (which are not routine in most units) to scrutinise adaptations in renal function [6]. This research aims to enhance the understanding of the importance of accurately dosing drugs that are eliminated via the kidney in patients with ARC.

Barbara *et al.* examined 128 patients undergoing antimicrobial therapy over 599 days. They found that 51.6% experienced ARC, with 11.7% having persistent ARC and 18.0% experiencing transient ARC. Younger age groups and men are more prevalent than women for ARC. Patients with ARC were more prone to therapeutic failure, 4 patients due to antibiotic resistance versus 1 without ARC. Therapeutic failure due to permanent ARC was 33.3% and 17.4% of cases were due to transient ARC [7].

Moreover, Udy *et al.* found no correlation between ARC and negative outcomes. Interestingly, unadjusted analysis revealed a correlation between ARC and improved clinical cure rates. These findings suggest that outcomes in septic patients are influenced by an involved interplay of comorbidities, antibiotic administration, and organ function. Notably, once organ impairment sets in, it may be as pivotal in determining treatment efficacy as the choice of β-lactam therapy [8].

Ryo Kamidani *et al.* tell ARC patients experienced high chances of deep vein thrombosis and pulmonary embolism. Additionally, in ARC patients receiving enoxaparin for thrombosis treatment, anti-Xa activity decreased. In critical care, anticoagulation is commonly used for thrombosis prevention. In Japan, continuous IV unfractionated heparin (UH) is frequently preferred for this purpose, particularly in critically ill patients, to achieve a specific APTT range. However, some patients may not reach the target APTT despite increased UH doses. They suggest careful monitoring in COVID-19 patients due to probable anticoagulation failure during ARC. Although higher UH doses may be needed for adequate APTT prolongation during ARC, no observations of raised bleeding complications indicate higher doses should be considered in such cases [9].

Cook *et al.* authored the initial article on augmented renal clearance impacting the elimination of Vancomycin and Levetiracetam in patients with traumatic brain injury see fig. 4). It highlights inadequate doses of essential medications not received by the patients during the hyper-dynamic phases of their illness. Doctors should be aware of the potential for ARC and closely monitor

medications that could be affected, including beta-lactams, vancomycin, aminoglycosides, levetiracetam, and other drugs that are eliminated through the kidneys. Despite being similar to antibiotics like beta-lactams, levetiracetam lacks routine serum concentration monitoring. Given its primarily renal elimination, it too may be influenced by ARC, posing a risk of treatment failure with standard dosages in critically ill patients [10].

CONCLUSION

Our study proposes revised dosing protocols for commonly utilized antibiotics to address issues related to suboptimal concentrations and potential treatment failure. We have included a comprehensive chart delineating effective antibiotics, their recommended dosage adjustments based on the Augmented Renal Clearance (ARC), and suggested durations to optimize patient care outcomes in table 2. While the scope of ARC extends beyond antibiotics to include other medications such as heparin and Levetiracetam, comprehensive evidence for non-antibiotic drugs is still under investigation. Our article provides a concise overview of the listed antibiotics and compiles data on dosage regimens sourced from reputable platforms including Micromedex, Lexicomp, Stanford, and recent scholarly articles. Physicians are encouraged to integrate these updated regimens into their practice to mitigate the risk of therapy negligence. Additional research endeavours are warranted to establish comprehensive ARC drug protocols, especially for emerging medications.

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AUTHORS CONTRIBUTIONS

All authors have contributed equally

CONFLICT OF INTERESTS

Declared none

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