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A Narrative Review: Augmented Renal Clearance and Its Effect on Drug Therapy

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Abstract

Background: Augmented renal clearance (ARC) is a common condition in critically ill patients, particularly in intensive care units, characterized by enhanced renal elimination. The accelerated elimination of drugs can significantly impact therapeutic efficacy, potentially resulting in suboptimal treatment outcomes. This review aims to provide a comprehensive overview of drugs impacted by ARC, offering a better understanding of the impact of ARC on drug therapy.
Method: A narrative review was conducted to explore previous studies from Scopus, PubMed, and ScienceDirect. PRISMA flow chart was used to guide the article selection process.
Result: A total of 14 articles were comprehensively reviewed and discussed regarding drugs affected by ARC, the impact of ARC on the pharmacokinetic/pharmacodynamic properties of drugs, and their clinical outcomes. Classes of drugs affected by ARC include beta-lactam antibiotics, glycopeptide antibiotics, anticoagulants, and anticonvulsants.
Conclusion: Antibiotics are the most frequently reported drugs to be impacted by ARC, followed by anticoagulants and anticonvulsants. The impact of ARC on anticoagulants is inconsistent. ARC reduces free drug concentration, requires a higher dose to achieve the therapeutic target, and is associated with a higher risk of treatment failure. However, no significant differences were found in clinical response and mortality compared to non-ARC.

Keywords: augmented renal clearance, clinical outcome, drugs, pharmacodynamics, pharmacokinetics

1. INTRODUCTION

Augmented renal clearance (ARC) is a common condition in critically ill patients, particularly in intensive care units, characterized by enhanced renal elimination. The pathophysiology of ARC is complex and multifactorial, involving increased cardiac output and renal blood flow, mobilization of functional nephron reserve, and endocrine responses, including the release of atrial natriuretic peptide (ANP) (1, 2). ARC can occur directly or indirectly. The direct mechanism is related to the systemic inflammatory response syndrome, which can be initiated by multiple factors, including trauma, burns, autoimmune disorders, pancreatitis, sepsis, and surgery. In contrast, indirect mechanisms of ARC are related to ICU care, including the administration of vasoactive agents, fluid resuscitation, and diuretic use (3). ARC has been identified in sepsis, subarachnoid hemorrhage, intracranial hemorrhage, traumatic brain injury, trauma, burns, and neutropenic fever patients (4). Most frequently in neurocritical patients, with an incidence of 74% (5). There are

two distinct perspectives regarding ARC. On one hand, some studies suggest that ARC is associated with a higher risk of therapeutic failure (6, 7). On the other hand, ARC has been proposed as a physiological response to certain clinical conditions, aiming to restore physiological homeostasis, which may indicate a good prognosis (2, 8–10).

Numerous studies have investigated the prevalence, risk factors, and effect on clinical outcomes of ARC. Previous studies have mostly focused on the impact of ARC on antibiotics, but have been limited to other medications (3, 11). The potential for therapeutic failure due to ARC poses a challenge for healthcare professionals, who must provide optimal treatment strategies. ARC potentially affects the efficacy of various drugs, particularly those eliminated through renal excretion. Drugs with renal elimination will undergo faster excretion than expected, increasing the risk of treatment failure. Therefore, this study aims to provide a narrative review of drugs reported to be affected by ARC within the last decade and gain a deeper understanding of the impact of ARC on drug therapy, including the drug's pharmacokinetic/ pharmacodynamic and clinical outcomes. This review will help healthcare professionals monitor and develop appropriate therapeutic strategies for patients with ARC.

2. METHODS

In this study, we conduct a narrative review that examines previous studies from Scopus, ScienceDirect, and PubMed as literature references. The search strategy uses the Boolean keyword ("Augmented Renal Clearance" OR "ARC") AND ("drug" OR "medication" OR "pharmacotherapy" OR "pharmaceutical") AND ("effect" OR "impact" OR "influence") AND ("clearance" OR "elimination" OR "renal function") AND ("dosing" OR "adjustment"). This study included articles that met the following criteria: (1) relevant to the keywords, (2) published within the last 10 years, and (3) with full-text articles accessible. Review articles were excluded from the study (Figure 1).

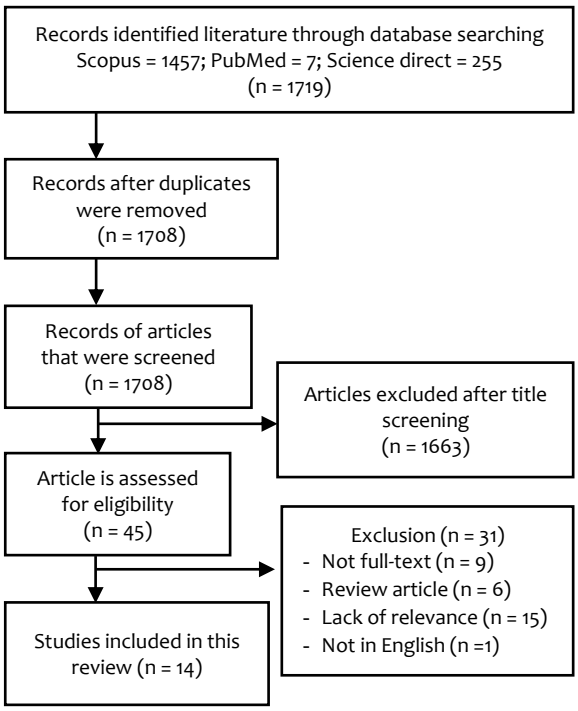

Figure 1. Study Selection Flowchart

3. RESULTS

a. Study Characteristic

The articles reviewed were frequently published in 2024. More than 50% of the design study was an observational prospective study, which was conducted in several countries, with China being the most reported study setting. The population in most articles consisted of critically ill patients, with sample sizes ranging from 22 to 1,135 participants (Table 1).

Table 1. Study Characteristics

Authors	Study location	Methodology	Population	Sample
Lanini et al (17)	Italy	Cohort, retrospective	Critically ill patient	52
Kamidani et al (25)	Japan	Cohort, retrospective	COVID-19 patients ≥ 20 years	38
Cook et al (14)	United Stated	Pharmacokinetic study, prospective	Traumatic brain injury patients	22

Xu et al (16)	China	A case series, retrospective	Critically ill patients with pulmonary, central nervous system, and biliary tract infection	40
Roberts et al (20)	Multinational	Randomized double-blind (RESTORE-IMI 2 study)	Pneumonia patients (hospital-acquired and ventilator-associated bacterial)	513
Corrochano et al (26)	Spain	Observational, single centre, prospective	Patients with DOACs	1135
Zhao et al (19)	China	Observational, multicentre, prospective	Adult patients with Gram-positive infections	414
Chen et al (18)	China	Observational, retrospective	Patients after neurosurgery	104
Wu et al (15)	Taiwan	Observational, prospective	Medical ICU patients	100
Carrié et al (24)	France	Observational, prospective	Critically ill patients	79
Abdel El et al (12)	Egypt	Observational, prospective	Critically ill patients	50
Hirai et al (21)	Japan	Observational, retrospective	ICU and general ward patients	292
Huttner et al (22)	Switzerland	Cohort, prospective	Critically ill patient in the medical and surgical ICU	100
Udy et al (23)	Australia	Observational, prospective	Sepsis patients, 18 – 80 years	48

b. Definition of ARC

ARC is defined as an enhanced renal clearance, and most studies define ARC as when CrCl is 130 mL/min or higher, calculated using the Cockcroft-Gault formula. Some studies also calculated CrCl based on creatinine and urine volume over a specific time period. The urine volume was collected in 2, 4, 8, 12, and 24 hours (12–16).

c. Drugs Affected by ARC

Most reported drugs affected by ARC were antibiotics (15–24). Other medications, including anticoagulants and anticonvulsants, were also affected (12, 14, 25, 26). The observed parameters to assess the effects of ARC on these medications included pharmacokinetic profiles, clinical outcomes, mortality rates, and medication-specific parameters such as activated partial thromboplastin time (APTT) and anti-Xa activity for anticoagulants (Table 2).

Table 2. Drugs Affected by ARC

Effect on Drug Pharmacokinetic/Pharmacodynamic (PK/PD)			
Authors	**Drugs (class)**	**Parameter Observed**	**Main Result**
Lanini et al (17)	Ceftazidime - avibactam (Antibiotic)	Free-ceftazidime (CAZ) and free-avibactam (AVI) plasma level, CAZ-AVI ratio	• A 10 ml/min increase in CrCl is expected to reduce free-CAZ level by 7.31% and free-AVI level by 9.23% • Risk of suboptimal exposure to free-CAZ and AVI is significantly higher in the ARC group compared to the non-ARC
Kamidani et al (25)	Unfractionated Heparin (Anticoagulant)	APTT, bleeding complication	• Higher dose UH was needed to achieve therapeutic APTT prolongation during ARC ($p < 0.001$)
Cook et al (14)	Levetiracetam (Anticonvulsant)	Cmax and AUC of levetiracetam	• Patient with ARC had significantly lower mean levetiracetam concentration (2.5 mcg/ml vs. 5.1 mcg/ml) • Mean AUC in ARC group was 62 µg.hr/ml and 120.7 µg/hr/ml in non-ARC group ($p = 0.028$)

Xu et al (16)	Ceftazidime-avibactam (Antibiotic)	Css/MIC ratio, Css/CT ratio, microbiology eradication, clinical efficacy, 28-day mortality	• One patient met the optimal PK/PD target (75%) and microbiological eradication • All patients had favourable clinical outcomes, and 0% of 28-day mortality rate
Corrochano et al (26)	Edoxaban, epixaban, rivaroxaban, dabigatran (Anticoagulant)	Anti-Xa activity	• Post-dose activity anti-Xa was similar between both groups (p=0.801) • The two groups had similar edoxaban plasma concentrations, with no statistically significant differences (p =0.312) • The two groups showed similar rates of complication (thromboembolic and haemorrhagic), with no significant differences observed (p=0.470 and p=0.871)
Zhao et al (19)	Vancomycin (Antibiotic)	Cmin and AUC24/MIC	• The proportion of Cmin <10 mg/L in the ARC was 71.6% and 53.7% in the non-ARC group (p = 0.003). ` • The proportion of AUC24/MIC <400 was 63.6% in the ARC group and 33.1% in the non-ARC
Wu et al (15)	Piperacillin -tazobactam, cefepime, meropenem (Antibiotic)	fT>MIC	• The achievement of conservative target (50%fT>MIC) was not significantly different between the ARC and non-ARC group (90% and 100%, respectively) • The achievement for more stringent targets (50% fT >4MIC; 100% fT > MIC; 100% fT>4MIC) was less in the ARC compared with the non-ARC group (p < 0.01). The results were 33% vs 75%; 23% vs 69%; 3% vs 25%, respectively.
Abdel El et al (12)	Enoxaparin (Anticoagulant)	Serum anti-factor Xa	• ARC group exhibited significantly lower Anti-Xa activity levels at 12 hours (p = 0.001) and 24 hours (p = 0.05) post-treatment compared with the control group
Hirai et al (21)	Vancomycin (Antibiotic)	Cmin	• The median Cmin was significantly lower in ARC patients (7.4 mcg/mL) compared to non-ARC patients (12.2 mcg/mL)
Udy et al (23)	Piperacillin – tazobactam (Antibiotic)	%fT>MIC, piperacillin drug clearance	• Moderate correlation was observed between higher CrCl and enhanced elimination of piperacillin (r=0.58, p<0.01) • Higher CrCl corresponds to a decrease in the probability of achieving %fT>MIC
Roberts et al (20)	Imipenem -Relebactam (Antibiotic)	Day 28 all-cause mortality (ACM), clinical, and microbiologic response	• ARC and normal renal function participants had comparable rates of day 28 ACM and good clinical responses, as well as similar rates of favourable microbiologic responses
Chen et al (18)	Vancomycin (Antibiotic)	Cmin, treatment prognosis, and adverse reaction	• Mean serum concentrations in the ARC group were 6.45 mg/L and 10.72 mg/L in the non-ARC group • The achievement rates of the target trough concentration were 41.03% and 19.23%, respectively, for the non-ARC and ARC groups • No significant differences for treatment prognosis • No adverse reactions occurred

Carrié et al (24)	Piperacillin-tazobactam, Cefazoline, Ceftazidime, Cefepime, Cefotaxime, Meropenem (Antibiotic)	free drug concentration, %fT>MIC, rate of therapeutic failure	• The risk of underdosing (<4×MIC) was significantly higher in patient with CrCl ≥ 170 ml/min (p = 0.001) • A significant association was found between suboptimal antibiotic exposure (<4×MIC, $fT_{>MIC}$ < 100%) and increase risk of therapeutic failure (p=0.03)
Huttner et al (22)	Imipenem, Meropenem, Piperacillin /tazobactam, Cefepime (Antibiotic)	Cmin, clinical outcome	• ARC was a strong predictor of undetectable Cmin. In total, 20% of Cmin were undetectable, and 71% were suboptimal. • ARC was not linked to clinical failure (OR = 1.13)

4. DISCUSSION

a. Impact ARC on Antibiotic

1) Beta Lactam

The majority of previous studies indicate that ARC significantly impacts the pharmacokinetic of antibiotic, characterized by shorter half-lives, decreased peak and trough levels, and lower area under the concentration-time curve (3,27). A study by Lanini et al (17) measured the effects of renal function on plasma concentrations of ceftazidime (CAZ) and avibactam (AVI) in critically ill patients. It was shown that an increase in renal function leads to suboptimal drug concentrations, increasing the risk of inadequate drug exposure and therapeutic failure. A similar trend was observed between CAZ and AVI. The free concentration of CAZ and AVI is predicted to decrease by 7.31% and 9.23% for every 10 mL/min increase in creatinine clearance (CrCl), respectively. In addition, the risk assessment indicated that ARC patients have a higher risk of inadequate exposure to free-CAZ and AVI, with concentrations falling below 32 mg/L and 4 mg/L, respectively. A study by Xu et al (16) examining the pharmacokinetics and pharmacodynamics (PK/PD) of CAZ-AVI in critically ill patients with ARC concluded that standard dosing for most patients with ARC may be inadequate to reach optimal PK/PD targets. The optimal PK/PD targets were defined as achieving a ratio of Css/MIC ≥ 4 for CAZ and a ratio of Css/CT > 1 for AVI. Meet only one of these targets was considered quasi-optimal, and failing to meet either was deemed suboptimal. The findings revealed that only 25% of ARC patients achieved both the PK/PD target and microbial eradication, whereas the remaining patients had suboptimal outcomes without microbial eradication. Further studies have confirmed that ARC impacts the pharmacokinetics and attainment of beta-lactam antibiotic targets. A study conducted by Wu et al (15) found that ARC patients were less likely to reach more stringent targets. A more stringent target means that the plasma antibiotic concentration should exceed the MIC or 4x MIC for a longer proportion of the time. As mentioned in previous studies, these targets were associated with better clinical outcomes (28,29). An increase in CrCl correlated with a decrease in the probability of achieving %fT > MIC, as shown in a study by Udy et al (23). The study demonstrated a moderate correlation (r = 0.58) between increased creatinine clearance (CrCl) and piperacillin elimination. Furthermore, patients with CrCl values ≥ 170 mL/min were associated with higher rates of underdosing and therapeutic failure, as reported in a study by Carrie et al (24). The association between ARC and therapeutic outcomes was investigated in a study by Roberts et al (20). The outcomes assessed included 28-day all-cause mortality (ACM), clinical response, and microbiological response at the end of therapy (EOT). Clinical response was evaluated 7-14 days after the EOT. The results showed that on Day 28 (ACM), favorable clinical and microbiologic response rates were comparable between patients with ARC and normal renal function. Additionally, no association was found between ARC and clinical failure in another study by Huttner et al (22) in patients treated with beta-lactam antibiotics.

Prolonged alterations in drug pharmacokinetics can compromise the efficacy of therapy in patients. The impacts of altered pharmacokinetic profiles on ARC have been investigated in traumatic brain injury (TBI) patients who received antibiotic therapy in a study by Carrie et al (13). This study demonstrated that clinical failure, superinfections, and recurrent infections occurred more frequently in patients with ARC. Statistical analysis revealed a significant correlation between ARC and recurrent infections (p=0.03). Compared to the article reviewed, the effect of ARC on patients' clinical outcomes remains uncertain. Therefore, close monitoring of patients with ARC is still necessary.

2) Glycopeptide

A study by Hirai et al (21) showed that ARC significantly affected vancomycin clearance, which was 1.6 times higher in ARC compared to non-ARC patients. Subtherapeutic vancomycin levels were more common in the ARC group than in the non-ARC group (68.8% vs 32.8%). The median trough serum concentration was significantly lower in patients with ARC. Similar results were found in two of the newest studies. Chen et al (18) suggested that the normal group achieved a target trough concentration rate of 41.03%, compared to 19.23% in the ARC group. A study by Zhao et al (19) showed that the ARC group had a significantly higher proportion of Cmin values below the recommended target of 10 mg/L, at 71.6%, compared to 53.7% in the non-ARC group. The ARC group had a significantly higher proportion of AUC24/MIC values below the targets compared to non-ARC (63.6% vs. 33.1%) (21).

Based on these findings, enhanced clearance in ARC patients alters the pharmacokinetic profile, resulting in reduced plasma concentration of antibiotics. Inadequate attainment of the optimal target concentration potentially impaired the ability of the antibiotic to eradicate the microorganism and achieve clinical efficacy.

b. Impact ARC on Anticonvulsant

Levetiracetam is a commonly prescribed, effective antiepileptic medication that is generally well tolerated. Levetiracetam is primarily excreted unchanged in the urine (60%). Consequently, its dosage should be adjusted based on creatinine clearance (30,31). In this review, only one study was found that discusses the impact of ARC on levetiracetam. Patients with ARC had significantly lower concentrations compared to those without ARC. The Area Under the Curve (AUC) was lower in ARC patients (62 vs. 120.7 ug*hr/mL, p = 0.028) (14)

c. Impact ARC on Anticoagulant

Anticoagulants, which are predominantly cleared through the renal system, are also susceptible to the effects of ARC. Similar to antibiotics, increased renal clearance in ARC patients can lead to decreased plasma concentrations of anticoagulants, affecting their therapeutic efficacy. All direct oral anticoagulants (DOACs) are cleared by the kidneys; however, the clearance rate varies among different DOACs. The renal clearance of dabigatran, as a direct thrombin inhibitor, accounts for 80% of its total elimination. In contrast, direct factor Xa inhibitors, such as edoxaban, rivaroxaban, and apixaban, have lower renal excretion, representing 50%, 35%, and 27% of the absorbed dose, respectively (32). The three studies that assessed the effects of ARC on anticoagulant therapy yielded different outcomes. Unfractionated heparin (UFH), as observed by Kamidani et al (25), required higher doses to achieve therapeutic APTT (activated partial thromboplastin time) prolongation during ARC. Despite the dose increase, no significant rise in bleeding complications, indicating that while dosing adjustments are necessary, the risk of bleeding remains manageable. However, the need for careful monitoring and individualized treatment regimens is crucial for ensuring therapeutic efficacy while minimizing risks. Similarly, enoxaparin, an anticoagulant, demonstrated decreased duration of action in ARC patients. Abdel et al (12) found no significant difference in anti-Xa activity, a surrogate biological effect marker for enoxaparin, between the ARC and non-ARC groups at the 4-hour measurement; however, significant differences were observed at 12 and 24 hours. This suggests that while initial doses may be adequate, extended monitoring and possible dose adjustments are necessary to maintain anticoagulant efficacy, particularly in patients at high risk of complications.

In contrast, a study conducted by Corrochano et al (26) assessed the influence of renal function

on the pharmacodynamics and pharmacokinetics of DOACs. The results showed that the anti-Xa activity of edoxaban, rivaroxaban, and dabigatran, as well as plasma concentrations of edoxaban, were not affected by renal function. The study included patients with atrial venous thromboembolism and atrial fibrillation who were treated with DOACs and categorized into two groups based on their glomerular filtration rate (≥ 90 and < 90 mL/min). Result revealed no significant differences in post-dose anti-Xa activity for apixaban, rivaroxaban, and edoxaban, or in dabigatran's anti-IIa activity. Edoxaban plasma concentrations and the risk of complications (thromboembolic and haemorrhagic) were also similar between the two groups. The findings of two studies on anticoagulants have been inconsistent. For heparin, studies have demonstrated that higher doses are required to achieve therapeutic targets. In relation to the mechanism of ARC leading to therapeutic failure, increased renal clearance accelerates heparin elimination, resulting in inadequate standard doses. Furthermore, some studies have suggested that the effect of ARC on therapy is only observable within a specific timeframe, highlighting the importance of close monitoring in high-risk patients who are susceptible to ARC.

Specific strategies are required to address or anticipate therapeutic failure in patients with ARC. Increasing the long-term dosing regimen for drugs eliminated through the renal in ARC patients should be considered as an approach to mitigate the impact of ARC on drug pharmacokinetics. ARC persistence in a longer period potentially decreased drug exposure, leading to therapeutic failure and prolonged treatment periods (9). A review article encompassing previous studies on antibiotic dosing regimens for ARC patients suggests several strategies for optimizing outcomes, including extended infusion times, continuous infusion, using the maximum approved dosing regimen, increasing dosing intervals, employing combination regimens, and switching to non-renally eliminated agents (29).

5. CONCLUSIONS

Antibiotics are the most frequently reported drugs to be impacted by ARC, followed by anticoagulants and anticonvulsants. The impact of ARC on anticoagulants is inconsistent. ARC reduces free drug concentration, requires a higher dose to achieve the therapeutic target, and increases the risk of treatment failure. Nonetheless, clinical outcomes and mortality rates remain similar to those without ARC.

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