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SEPSIS IN THE ICU (J LIPMAN, SECTION EDITOR)

What is New in Augmented Renal Clearance in Septic Patients?

Laura Baptista[1] · Inês Moura[2] · Catarina Mendes Silva[2] · João Pedro Baptista[2]

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Abstract

Purpose of Review In this narrative review encompassing relevant scientific publications regarding critically ill patients in the last 5 years, we discuss key questions regarding the concept, pathophysiology, identification, epidemiology, and implications of augmented renal clearance (ARC) in the treatment of sepsis.

Recent Findings Mathematical estimates of renal function show low accuracy when evaluating renal function in the intensive care unit, jeopardizing the correct dosing of antimicrobials. The description of ARC in critically ill patients in several, distant geographical areas worldwide reveals that this condition is more frequent than anticipated. Several new risk factors have been recently reported, needing future confirmation. Pathophysiology is still largely unknown; however, intact kidney physiology, inflammatory mediators, and tubular secretion seem to play a role. Several studies have demonstrated the association between ARC and subtherapeutic levels of several β-lactams, vancomycin, and fluconazole. Lately, there have been recommendations of dosage regimen adjustments for patients with ARC, namely, through increases in total daily dose or prolonged infusion for various antimicrobials. Literature is scarce describing the influence of ARC on clinical outcomes of patients receiving antibiotics, and results are contradictory.

Summary Growing body of evidence supports that measured creatinine clearance based on time-defined urine output is strongly recommended for the identification of ARC and for reliable evaluation of its prevalence and risk factors. Clinicians should be alert for the need to use off-label dosing of antimicrobials in septic patients showing ARC. Concise recommendations for antibiotic dosage regimens, based on clinical data, are still needed.

Keywords Antimicrobials · Augmented renal clearance · Critically ill patient · Renal function · Sepsis

Introduction

When a patient is critically ill, kidney function can be significantly altered, leading to profound physiological and clinical alterations. Clinicians used to focus on acute renal injury; however, concentrating solely on one end of the range of renal function can limit our understanding and hinder a comprehensive analysis. Augmented renal clearance (ARC) remains an underappreciated clinical condition, and strategies for managing it are still being developed. ARC can potentially decrease the plasma concentrations of renally eliminated drugs. This has been extensively demonstrated with antibiotics, but also with other drugs, such as enoxaparin [1], metformin [2], and levetiracetam [3–5].

Antibiotics are one of the touchstones of the treatment of sepsis, and their early and appropriate administration improves clinical outcome. Clinicians are used to adjusting antibiotics to *decreased* renal performance; however, the reverse is quite rare. Dosing adaptation in critically ill patients is crucial due to the complex interplay of physiological changes, altered drug pharmacokinetics, and multiple co-existing medical conditions. Consequently, standard dosing regimens may not achieve the desired therapeutic effect or could lead to adverse drug reactions. Particularly, the critically ill frequently shows ARC, and this condition shows a robust association with under-therapeutic serum concentrations of several antibiotics. ARC impact has been increasingly described in intensive care units (ICU) around the world and has become included in recent guidelines and recommendations [6–11].

Laura Baptista and Inês Moura shared the first authorship.

✉ João Pedro Baptista
joaopedrobaptista@gmail.com

[1] Serviço de Medicina Interna, Centro Hospitalar do Baixo Vouga, 3810-501 Aveiro, Portugal

[2] Serviço de Medicina Intensiva, Centro Hospitalar e Universitário de Coimbra, 3000-075 Coimbra, Portugal

Methodology

A literature search was conducted on PubMed/MEDLINE between January 2018 and July 2023 to focus on publications within the last 5 years. All references that reported information on definition, identification, epidemiology, pathophysiology, and clinical relevance in sepsis of ARC were included. The search was limited to adult humans and articles published in English.

Definition of Augmented Renal Clearance

Although its recognition is not recent [12], the concept of ARC was first proposed in 2010 by Udy et al. and defined as an "increased elimination of circulating solutes compared with an expected baseline, involving changes in glomerular filtration and renal tubular function" [13]. There is still no standard definition for ARC, but there is a broad consensus that a creatinine clearance (CL_{CR}) ≥ 130 ml/min/1.73 m^2 seems to be an acceptable and clinically important cut-off value to define ARC: it is clearly supra-physiological, and it is the most used value in investigation and is undoubtedly associated with underexposure to antibiotics. By definition, the critically ill patient is often in unstable condition, and renal function varies quite substantially during the ICU stay. For that reason, augmented renal function should be interpreted more as a *continuum* and less as a dichotomic factor (presence/absence of ARC), as there is a linear correlation between renal function and elimination of most hydrophilic antibiotics.

Identification of Patients with ARC

Variations of glomerular filtration rate (GFR) are poorly reflected by daily changes in serum creatinine concentrations in critically ill patients. For that reason, creatinine-based equations are flawed in the critically ill and will tend to significantly underestimate renal function in patients with ARC [14, 15]. Despite the overwhelming medical evidence demonstrating the insensitivity of these methods, clinicians and investigators persist in assessing renal function this way. These considerations are strengthened in several recently published studies in ICU settings, including studies where a significant percentage of patients exhibited ARC.

In a study by Troisi et al., adult critically ill patients who underwent therapeutic drug monitoring (TDM) for meropenem and for whom a 24 h urine collection for measuring CL_{CR} (24 h-CL_{CR}) was performed were retrospectively included [16]. One quart of the studied cohort had at least one episode of ARC. The authors evaluated the performance of Cockcroft-Gault (CG), Modification of Diet in Renal Disease (MDRD) study, and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations. They concluded that these mathematical formulas were not adequate for calculating the doses of meropenem necessary to achieve a therapeutic level and that renal function should be measured rather than estimated, especially for those displaying ARC. In a retrospective, single-center study, among 74 patients admitted to a neurocritical ICU, Monteiro et al. showed a weak statistical correlation between measured and estimated methods, with underestimation of ARC, and concluded that these discrepancies were not clinically acceptable [17•].

Relatedly, in a post hoc analysis of an observational study in 80 neurocritical patients, 8 h-CL_{CR} seems to translate into the most appropriate assessment of renal function in patients with aneurysmatic subarachnoid hemorrhage, after comparison with 14 mathematical Eqs. (18). Another retrospective, single-center, study including 82 critically ill patients (43% with severe acute coronavirus 2 respiratory syndrome (SARS-CoV-2)) showed the low concordance between the GFR estimated by the CKD-EPI formula and the 24 h-CL_{CR} [19]. In a sub-study of an ICU multicenter randomized controlled trial, the performance of CG, MDRD, CKD-EPI, and Jelliffe equations was evaluated against measured urinary CL_{CR} in 237 critically ill patients with different degrees of kidney function (38.4% had ARC based on 24 h-CL_{CR}). The conclusion was that such equations had limited ability to adequately estimate 24 h-CL_{CR} [20]. Identical conclusions were reached in a prospective observational study, encompassing 100 patients consecutively admitted to a medical ICU in Taiwan [21]. Cucci et al. performed a larger multicenter, retrospective study (383 ICU-admitted patients were included, providing 1708 8 h- or 24 h-CL_{CR} paired measurements) and reported that among ARC patients, there was a low correlation (r = 0.24–0.28), a low to moderate accuracy (range 38–70%), and a high bias (range of − 58.5 to − 21.6) between CG and measured CL_{CR} [22•].

In a retrospective cohort study, investigators showed that there was 25% discordance in drug dosing depending on the use of either estimated (CG) or measured renal function. In addition, 69% of the estimated values deviated ± 20% from the reference value (CL_{CR}) [23•]. Similar conclusions were reached in a prospective cross-sectional study (145 ICU patients), showing that none of the used mathematical estimates accurately detects the ARC as accurately as 12 h-CL_{CR} [24], as well as in another recent study investigating a cohort of 68 burn patients, even after using the new 2021 updated CKD-EPI Eq. [25•]. In a prospective, observational cohort study of critically ill Indigenous Australian and non-Indigenous patients, Tsai et al. included a total of 131 patients, showing a prevalence of ARC of 32%. CG and CKD-EPI equations showed limited agreement with measured CL_{CR} [26]. A recent multicenter retrospective study investigated the agreement between 24 h-CL_{CR} and

CG, CKD-EPI, and MDRD; a total of 51.604 ICU days were included, with an ARC prevalence of 20% [27•]. The authors concluded that all the studied estimates were flawed in the critically ill and showed a tendency to significantly under-evaluate renal function. Identical conclusions were reached in another multicentric study involving 561 critically ill patients, showing no concordance between the estimation of GFR by the CKD-EPI formula and 4 h-CL_{CR} [28•].

Recently, Huang et al., applying machine learning algorithms, developed and validated models for 1 day in advance daily prediction of CL_{CR} in ICU setting [29]. Among the ten most predictive variables of the three models, seven were related to 24 h-CL_{CR} on the previous day; however, unstable renal function incremented the attributable error. Taking into account the daily creatinine variation, a group of investigators studied the kinetic estimated GFR equation, based on two separated serum creatinine levels, in a cohort of 60 patients (180 paired samples with an ARC prevalence of 48%); they concluded that this "dynamic" formula is not a reliable alternative when compared to measured 24 h-CL_{CR} [30].

Of interest, in 232 adult *non-critically ill* surgery patients with a significant proportion displaying ARC, a remarkable disagreement and low precision were present between estimated and measured renal function (8 h-CL_{CR}), and studied equations underestimated renal function [31].

Mathematical equations for estimation of renal function are typically derived from non-ICU populations, such as patients with normal renal function or with mild dysfunction or normal individuals, and are not validated in the critically ill population. Therefore, in the ICU, any method of assessing kidney function that does not consider urine output should be considered unreliable. Of note, the 2020 Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock warn readers about the potentially inadequate results related to the use of estimates of renal function in the critically ill [6]. Similarly, for the optimization of β-lactam treatment in critical care patients, the French Society of Pharmacology and Therapeutics (2018) suggests estimating GFR by calculating urinary creatinine clearance instead of equations. [8].

In light of this information, we can state with some certainty that urinary creatinine clearance remains the more reliable, cost-effective, replicable, and biologically precise alternative compared to mathematical calculations for evaluating renal function at bedside and adequately detecting ARC in critically ill patients, particularly for the purpose of renal adjustment of antibiotic dosing. Although any time interval used for calculation of CL_{CR} is adequate and informative, the nighttime evaluation within a time period of 8 h coinciding with nursing shifts can be the most pragmatic and probably associated with less workload. Furthermore, in our experience, it provides "fresh data" for decision-making involving pharmacokinetic issues during the morning medical round.

Epidemiology of ARC

Prevalence of ARC

In the last 5 years, few studies have evaluated ARC prevalence in septic patients. We included in this review populations that are at high risk of infection and sepsis, namely, critically ill, trauma, and burn patients. Several studies reinforced the relevant prevalence of ARC in the critically ill patient, underlining that its presence is ubiquitous around the world, as depicted in Table 1. We focused only on studies using measured CL_{CR}, due to its higher reliability as mentioned above. A great variability in ARC prevalence was seen, ranging from 24.6 to 94%. These differences can be partially explained by the specific characteristics of the population, but also by the diversity of definitions used for ARC prevalence. Many authors have not yet defined with clarity the ideal method to identify ARC, which greatly hinders comparative analysis between studies. Generally speaking, ARC appeared to be more frequent in trauma and neurocritical patients.

Several studies have evaluated ARC prevalence in *general critically ill patients*, without specification of pathology, and some have analyzed its variation in time. In a retrospective, cohort study with 1328 critically ill patients, the adjusted prevalence of ARC was 47%, of which 624 (47%) had ARC during their stay at ICU, 272 (20.5%) had ARC throughout their stay that never resolved, 185 (13.9%) had ARC that resolved at some point during their ICU stay, and 167 (12.6%) had intermittent ARC that did not resolve during their stay [32]. Additionally, in the cases of an ICU stay ≥ 7 days, the ARC prevalence ranged from 22.1 to 24.9% over the first 7 days, and the median time to onset of ARC was 1 day, with more than 64% of patients developing ARC within 24 h. In a similar study that included 734 critically ill patients, the prevalence of ARC was 33.4%, with almost half of the cases showing ARC onset within the first 3 days of ICU admission. The median duration of ARC was 5 days and ended within 3 weeks in many cases [33]. In a retrospective, single-center study of 312 patients, Egea et al. reported an ARC prevalence during the ICU stay of 24.6%, with a maximum reached at day 6 (34.4%), decreasing from day 7 to day 12, remaining stable afterwards, around 20%; the cumulative incidence rate was near 60% at day 7 [34].

ARC prevalence in the specific population of critically ill patients with *sepsis* was evaluated in a prospective, single-center, observational study that encompassed 59 patients admitted to a surgical and trauma ICU and who had a diagnosis of severe sepsis [35]. An ARC prevalence of 61% was described. A smaller study by Tamatsukuri et al., on the other hand, observed a lower ARC prevalence of 35% in 17 patients with sepsis [36].

Table 1 Summary of characteristics of the included studies on ARC prevalence in adult critically ill patients based on measured CL_{CR}

Ref.	Country	Type of patients	Number of patients	Study design	Urine time collection (h)	ARC definition (mL/min/1.73 m^2)	Definition used for ARC prevalence	ARC prevalence
Morbitzer et al. [45]	USA	Neurocritical	80	Prospective observational	8	≥ 130	ARC on at least one occasion	94% (ASH); 50% (IH)
Campassi et al. [44]	Argentina	Neurocritical (TBI)	61	Prospective observational	8	> 130	ARC on at least one occasion	82%
Monteiro et al. [17•]	Portugal	Neurocritical (SAH and TBI)	74	Prospective observational	6	> 130	% of measured CL_{CR} samples > 130	78%
Lannou et al. [48]	France	Neurocritical (TBI)	30	Retrospective	24	≥ 150 (women); ≥ 160 (men)	ARC on at least one occasion	77%
Carrié et al. [49]	France	Neurocritical (TBI)	223	Retrospective	24	> 130	Undefinied	73%
Dhaese et al. [38•]	Belgium	COVID-19	129	Prospective observational	8	> 130	ARC on at least one occasion; proportion of ARC days	72%; 15.6/100 ICU days
Mueller et al. [25•]	USA	Burn	68	Retrospective	12	> 130	ARC on at least one occasion; proportion of 12 h-CL_{CR} assessments	70.6%; 66.3%
Damen et al. [46]	Belgium	Neurocritical; non-neurocritical	52; 304	Retrospective	8	> 130	Sample with the highest value	69.2%; 37.2%
Carrié et al. [35]	France	Sepsis (surgical and trauma)	59	Prospective observational	24	≥ 130	Undefined	61%
Mulder et al. [59]	USA	Trauma	207	Retrospective	24	≥ 130	Undefined	57%
Barragan et al. [40]	France	COVID-19	42	Prospective observational	Undefined	> 120	Undefined	54.8%
Dickerson et al. [58]	USA	Trauma	203	Retrospective	24	> 149	Point prevalence study (1 day of evaluation, within 4th to 14th day after TICU admission)	50%
Dang et al. [43]	China	Neurocritical (TBI)	54	Prospective observational	24	≥ 130	Undefined	50%
Huang et al. [29]	Belgium	COVID-19	120; 1064 patient days	Retrospective	24	> 130	ARC on at least one occasion; patient days	47.5%; 23.1%
Johnston et al. [32]	UK	Mixed	1328	Retrospective	6	> 130	ARC on at least one occasion; ARC throughout ICU stay	47%; 20.5%
Tomasa-Irriguible et al. [19]	Spain	Mixed	82	Retrospective	24	> 130	Undefined	39.1% (C); 25.5% (NC)

Table 1 (continued)

Ref.	Country	Type of patients	Number of patients	Study design	Urine time collection (h)	ARC definition (mL/min/1.73 m^2)	Definition used for ARC prevalence	ARC prevalence
John et al. [47]	USA	Neurocritical	20	Prospective observational	24	> 130	One-day ARC presence	35%
Tamatsukuri et al. [36]	Japan	Sepsis	17	Prospective observational	8	≥ 130	Undefined	35%
Mikami et al. [33]	Japan	Mixed	734	Retrospective	6–24	> 130	Undefined	33.4%
Nazer et al. [50•]	Jordan	Oncologic	363	Prospective observational	24	> 130	ARC on at least one occasion	32%
Bing et al. [60•]	Canada	Mixed	324	Retrospective	24	≥ 130	ARC on at least one occasion	25.3%
Beunders et al. [42]	Netherlands	COVID-19	24	Prospective observational	24	> 130	Undefined	25%
Baptista et al. [54]	Portugal	Mixed	446	Retrospective	8	≥ 130	Median value of 8 h-CL_{CR} during the ICU admission period ≥ 130; clearance days	24.9%; 25.4%
Egea et al. [34]	France	Medical 62.8% patients had SARS-CoV-2	312	Retrospective	24	> 130	Median daily prevalence during ICU stay	24.6%

Studies are ordered from the highest prevalence to the lowest. It was only included studies using measured CL_{CR}

ARC augmented renal clearance, *ASH* aneurysmal subarachnoid hemorrhage, *C* COVID-19 patients, CL_{CR} creatinine clearance, *ICU* intensive care unit, *IH* intracerebral hemorrhage, *NC* non-COVID-19 patients, *SAH* subarachnoid hemorrhage, *TBI* trauma brain injury

Unsurprisingly, patients with severe *coronavirus disease* (COVID-19) admitted to the ICU exhibit high prevalence of ARC, ranging from 25 to 72% [19, 37, 38•, 39, 40]. Male sex and young patients were predominant in the studied cohorts [38•, 39, 41]. The day of onset of ARC was variable, with some studies reporting an early onset (median first day being day 1 or 2 from ICU admission) [38•, 39], while others reported a much-delayed onset of ARC (median first day being day 13 to 28 from ICU admission) [37, 41, 42].

The large majority of studies have been conducted with *neurocritical and/or trauma* patients. A prospective observational study reported an ARC prevalence of 79% in 74 neurocritical patients with either traumatic brain injury (TBI) or subarachnoid hemorrhage, and this condition was sustained throughout the first 2 weeks after neurocritical ICU admission [17•]. In a prospective study to investigate ARC in 54 TBI patients, Dang et al. showed a prevalence of 50% [43]. Similarly, other investigators observed a prevalence of 82% in a cohort that encompassed 61 TBI patients admitted in an ICU. In this last study, it was also noted that ARC developed early after admission (29% of patients on day 1) [44]. In a prospective observational study conducted in a neurocritical ICU including a total of 80 patients, 94% of the participants with aneurysmal subarachnoid hemorrhage and 50% of those with intracerebral hemorrhage experienced ARC on at least 1 day during the ICU stay [45]. Damen et al. also reported, in a single-center, retrospective analysis, an ARC prevalence of 69.2% in neurocritical patients in a mix ICU population, with 17 patients (32.7%) demonstrating severe ARC ($CL_{CR} > 200$ mL/min) [46]. Other studies in neurocritical setting showed a prevalence between 35 and 77% [47–49].

Regarding the critically ill *burn* patients, Mueller et al. reported in a retrospective, single-center study, that ARC occurred at least once in 66.3% of total 12 h-CL_{CR} assessments ($n = 163$). Most patients were male (82%) and young [25•]. ARC also seems to be frequent in critically ill patients with *malignancy*, with a prospective observational study of 363 adult patients with solid and hematologic malignancies reporting an ARC prevalence of 32% on at least 1 day of the study days [50•]. Saito et al. also found a high prevalence of ARC in 133 patients with hematopoietic tumors, reporting that 41.4% of patients exhibited ARC [51].

Risk Factors for ARC

Since the first published studies on ARC in the critically ill patient, it was rapidly and consistently established an association between ARC and younger age, male gender, and trauma. Recent research continues to corroborate this association, but other risk factors have been reported.

As said above, one of the factors that has most consistently been linked to a high risk of ARC is *age* [32–34, 37, 38•, 41, 44, 47, 50•, 51–55], with most studies, including a recent systematic review, showing a difference of 10 to 20 years between patients with or without ARC [56]. Actually, ARC is significantly less frequent in patients over 50 years [32]. In a recent retrospective study, patients that developed ARC tended to be significantly younger as opposed to those that did not develop ARC (56 versus 68 years), with younger age being identified as an independent factor for development of ARC [32]. Likewise, in a retrospective cohort study involving 454 ICU admissions and 5586 8 h-CL_{CR}, the investigators concluded that the probability of a patient showing ARC decreased 7% for each additional year of life [54].

Male sex has also been reported to be associated with ARC [19, 33, 39, 53, 54]. A retrospective cohort study, that included 734 patients from a mixed ICU, reported that male sex, along with younger age, was an independent factor for development of ARC [33]. In a mixed cohort of medical, neurocritical, and surgical critically ill patients, authors concluded that men seem to be three times more at risk than women for exhibiting ARC [54]. This association was also found on a multivariate analysis in other studies [32, 57–59]. On the contrary, Bing et al. performed a retrospective study with 324 patients admitted to a mixed ICU and reported that male sex was predominant but was not significantly associated with ARC after the multivariate logistic regression analysis (OR 1.946; 95% CI 0.90–3.945, $p = 0.065$) [60•].

The presence of *trauma* has also been described as an independent significant risk factor for ARC in critically ill patients [32, 54, 58, 60•]. In the study by Bing et al., trauma at admission was found to be a significant risk factor for ARC (OR 2.3; 95% CI 1.12–4.5, $p = 0.02$) [60•]. In another retrospective study that included 203 adult patients admitted to a trauma ICU (ARC prevalence of 50%), severe TBI was also found to be significantly associated with ARC after a multivariate analysis [58]. Other authors also showed that trauma admission was an independent risk factor for expressing ARC in the ICU, reporting an adjusted risk two times higher [54].

One study evaluated ARC in a specific cohort of critically ill obstetric patients. This was a retrospective study including 427 patients, with an ARC prevalence of 47.1%. Multivariate analysis identified a series of independent risk factors, including gestational age, fewer caesarean section, higher albumin level, severe preeclampsia, vasoactive drugs, infection, acute pancreatitis, and hypertriglyceridemia [61•].

Other risk factors for ARC found in multivariate analysis include African American race, lower serum creatinine concentration, neutrophil percentage, higher body mass index, absence of cardiovascular comorbidities, high blood glucose levels, enteral nutrition, antibiotic treatment, red blood cell transfusion, leukemia, use of vasopressors, and mechanically assisted ventilation [32, 43, 51, 57–59, 60•].

Pathophysiology of ARC—What We Know

There are few reports on how ARC occurs, as the pathophysiology behind this entity is still largely unknown. Recent publications suggest that rather than a fixed chain of events where one single alteration gives way to another, it seems to result from various processes occurring simultaneously.

As a consequence of severe physiological stress related to sepsis or septic shock, the body appears to enter into an *inflammatory* hypermetabolic state in which pro-inflammatory mediators and cytokines are released [62, 63]. These compounds trigger profound metabolic and cellular changes that culminate into an increase in cardiac output and decrease in peripheral vascular resistance, which translates into increased renal blood flow and thus enhanced glomerular filtration. However, the increase in GFR seen in hyperinflammatory states may reflect a direct consequence of the inflammatory mediators as well, regardless of the hemodynamic changes they entail. In an experimental model of endotoxemia, after a lipopolysaccharide (LPS) derived from *Escherichia coli* was administered in healthy subjects, Beunders et al. [64] described an increased plasma concentration of pro-inflammatory cytokines, correlating with an increase in GFR (as measured by iohexol clearance). However, this increase in GFR did not appear to be dependent of perfusion pressure, as blood pressure was significantly lower compared to baseline during observation. In another recent study [65•], evaluating pathogenesis behind ARC at a transcriptional and metabolic level, the authors concluded that patients with ARC exhibited upregulation of L-arginine and L-glutamate, which indicated an increased consumption of arginine in critically ill patients with ARC. This in turn provides sufficient conditions for an increased production of nitric oxide (NO), ultimately increasing renal blood flow perfusion through NO-related inflammatory mediators. The authors also reported a direct regulation of GFR through N-methyl-D-aspartate receptor, which is regulated by glutamate. Finally, they concluded that the upregulation of cAMP leads to increased capillary permeability and extra-stromal precipitation.

Perhaps subjacent to the entire concept of ARC, closely linked to both the release of inflammatory mediators and a hypercatabolic state seen in sepsis, is the concept of *renal functional reserve* (RFR). RFR refers to the ability of the kidney to recruit previously dormant nephrons in times of biological stress, which results into increased renal blood flow and/or glomerular hyperfiltration. Although the exact mechanism behind the occurrence of RFR is yet unclear, recent studies reiterate the importance of protein loading and dilation of afferent glomerular arterioles after impaired renal auto-regulation, as well as complex interactions between tubuloglomerular feedback (TGF), the release of NO and vasodilator prostaglandins, and the metabolism of glucagon [66, 67].

Another mechanism behind ARC seems to be related to the severely *catabolic state* seen in these patients, which results into increased tissue destruction and excessive protein breakdown. Increased protein intake is thought to be associated with elicitation of RFR and thus enhanced GFR: an increase in the filtered load of amino acids reduces distal delivery of sodium chloride by increasing its tubular reabsorption, leading to inhibition of TGF, thus inducing afferent arteriolar vasodilation and consequently promoting hyperfiltration [66]. However, until recently, such a conclusion was derived from stable, healthy, and non-critical patients. In a recent retrospective single-center ICU study with around half of the cohort in sepsis [58], ARC was prevalent in approximately half of the patients admitted, who demonstrated marked protein catabolism (as evidenced by a worsened nitrogen balance), despite receiving a similar protein intake. Of note, the authors also found a significant association between ARC and increased protein intake (adjusted OR 2.06; 95% CI 1.09–3.91). Another study [68] concluded that patients with ARC presented a lower nitrogen balance and increased muscle loss despite receiving similar protein intake; patients with a higher protein intake had higher levels of CL_{CR}. Whether a renoprotective nutrition (e.g., low-protein diet) would improve patient outcomes by reducing glomerular pressure and thus ARC (while perhaps promoting sarcopenia and muscle wasting) is less clear and warrants further investigation.

Tubular secretion seems to play a part as well in patients displaying ARC. A single-center, retrospective study [69•] attempted to compare GFR measured with iohexol plasma clearance and CL_{CR} in critically ill patients with ARC. They concluded that half of the patients presenting ARC did not in fact have hyperfiltration and concluded that 6 h-CL_{CR} appears to overestimate renal function by taking into account basal tubular excretion of creatinine. In a recent case report [70•], the same mechanism was evidenced. These findings suggest that ARC is due not only to increased glomerular filtration but also increased tubular secretion, at least to some extent. This is of particular importance, since it may influence renal elimination for drugs subject to these mechanisms, namely, some antimicrobials (β-lactams [71, 72], antiviral drugs [72], vancomycin [73]).

Additionally, one must consider the *exogenous factors* that contribute to ARC which do not result from the body's own response to stimuli, but rather from medical intervention, such as aggressive fluid administration, use of vasopressor drugs, and inotropes. One study by Dhondt et al. [74] concluded that fluid resuscitation contributed more to the development of ARC than previously thought, after inducing a sepsis-like state in piglets through the continuous infusion (CI) of LPS from *E. coli*, except for one sham pig that only received the same amount of fluid treatment

(0.9% sodium chloride solution, 6 mL/kg/h), and demonstrating that both groups displayed an elevated GFR over the time course of the study.

There are other factors that have been put forward when attempting to explain the pathophysiology behind ARC, such as a possible link between renal function and TBI [75], with the identification of elevated circulating atrial natriuretic peptide levels, and a significant correlation between neuromonitoring data (intracranial pressure, cerebral perfusion pressure, and the cerebrovascular pressure reactivity index) and ARC-presenting patients [76]. However, further studies are needed in order to shed light on this matter. The various mechanisms involved in the occurrence of ARC are summarized in Fig. 1.

Clinical Relevance of ARC in Sepsis

Several studies have been published evaluating the influence of ARC in pharmacokinetics (PK)/pharmacodynamics (PD) of antibiotics, not only with the newest antibiotics but also with some of the old antibiotics, showing that ARC has been recognized as an important factor for adjusting antibiotics' doses. The three most reported antibiotics in recent years were vancomycin, meropenem, and piperacillin-tazobactam, which can be explained by the easy access to clinical data resulting from TDM. This is in accordance with current recommendations for routine TDM to be performed for aminoglycosides, β-lactam antibiotics, linezolid, teicoplanin, vancomycin, and voriconazole in critically ill patients [7].

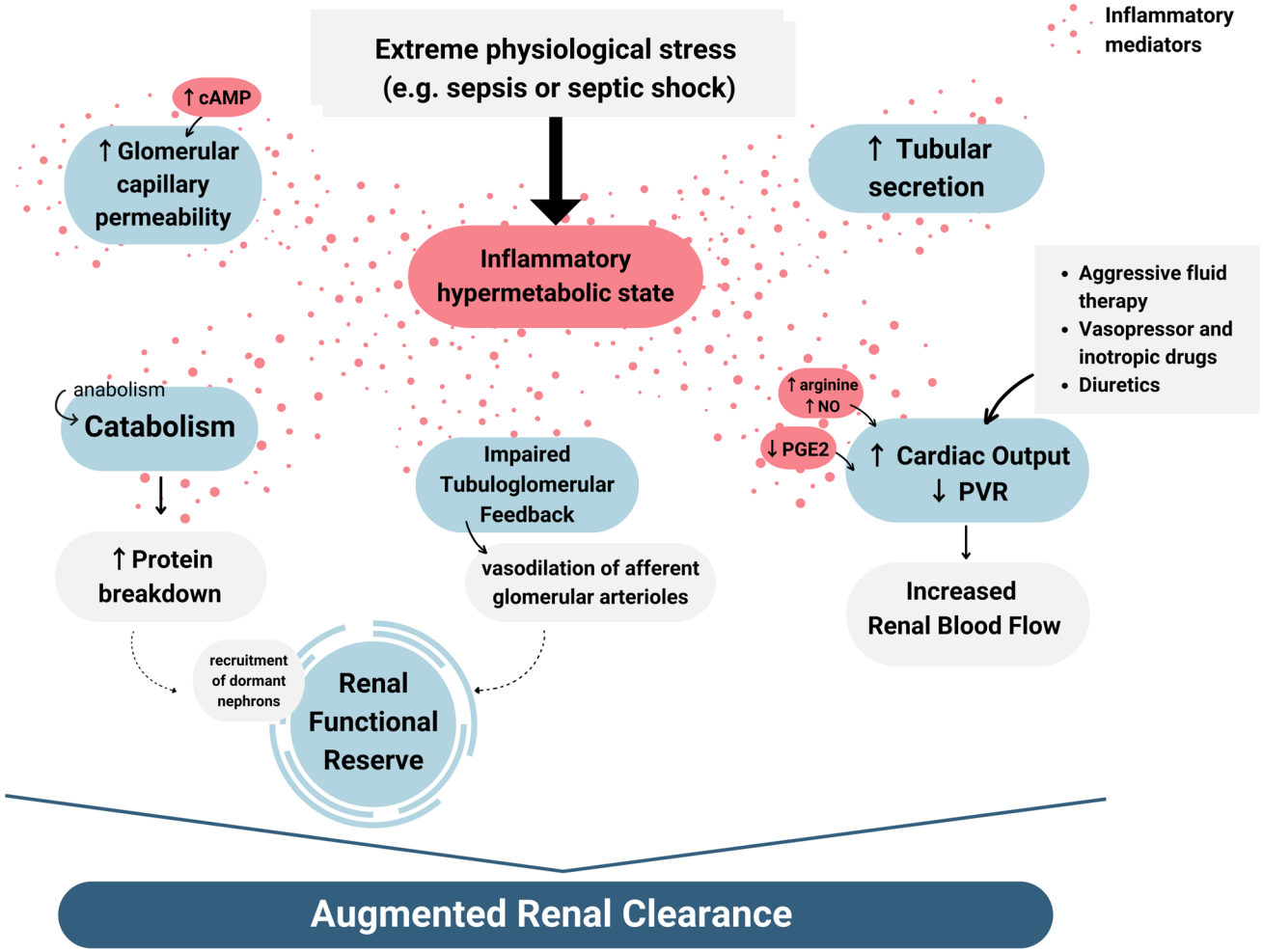

Fig. 1 Pathophysiology of ARC. Rather than one single process giving way to the other, the hyperinflammatory, hypercatabolic state seen in severe physiological stress (e.g., sepsis) sets in motion multiple simultaneous alterations. Mainly through the release of inflammatory mediators but also due to exogenous "iatrogenic" factors such as aggressive fluid administration, together they will trigger metabolic and cellular changes affecting glomerular filtration and tubular secretion, ultimately leading to ARC. cAMP, cyclic AMP; NO, nitric oxide; PGE2, prostaglandin-2; PVR, peripheral vascular resistance

Some of the published studies found in literature had the purpose of evaluating the association of ARC with subtherapeutic concentrations of antibiotics when using the standard dosage regimens, while others used population pharmacokinetic models and simulation to recommend dosage regimens for patients with ARC. Only few studies have explored the real impact of ARC on clinical outcomes, such as clinical cure, antimicrobial resistance, or mortality.

Association Between ARC and Underdosing of Antimicrobials

In the last years, several studies used TDM results to show that ARC leads to subtherapeutic plasma concentration of antibiotics. This has been extensively demonstrated for β-lactams. In a group of septic patients with ARC who received piperacillin-tazobactam, meropenem, cefepime, or ceftazidime, insufficient drug concentrations to treat infections due to *Pseudomonas aeruginosa* were observed in 55% of measurements [77]. In this study, the proportion of insufficient concentrations of meropenem and piperacillin increased with measured CL_{CR} from 120 to 300 mL/min [77]. In another study with critically ill septic patients receiving high doses of β-lactams administered by CI, the rate of underdosing ($< 4 \times$ minimal inhibitory concentration, MIC) was significantly associated with CL_{CR}, and a threshold for prediction was established at CL_{CR} values ≥ 170 mL/min [78]. In a group of 62 critically ill patients receiving β-lactam antibiotics, the presence of ARC, compared to non-ARC, decreased the probability of target achievement, with 23% vs 69% ($p < 0.01$) for a target of 100% of time of free plasma concentration maintained above the MIC ($fT > MIC$) [21]. When a CI of ampicillin/sulbactam was administered to critically ill patients, the fourfold MIC breakpoint was not reached by 57% of patients with ARC [79]. A retrospective study showed that subtherapeutic piperacillin concentrations were more frequent in the group consisting of neurocritical patients compared to non-neurocritical patients (83% vs 46%), and the only risk factor identified for subtherapeutic piperacillin concentrations (< 80 mg/L) was measured CL_{CR}, which was 173 and 99 mL/min, respectively [46].

Higher estimated GFR was associated with non-attainment of PK/PD target for meropenem, defined as plasma trough (C_{min}) or steady-state concentration (C_{ss}) ≥ 10 mg/L [80]. Furthermore, the only significant predictor for not achieving the therapeutic PK/PD target of a free trough concentration $4 \times$MIC was ARC [81]. In this study, only 22% patients with ARC achieved the PK/PD target, while 64% non-ARC patients achieved the PK/PD target.

Regarding vancomycin, several recent studies have shown an association between ARC and PK/PD indices, including trough concentration, area under 24-h time-concentration curve (24 h-AUC), and AUC/MIC [57, 61•, 82]. Patients with ARC were more likely to have subtherapeutic vancomycin PK/PD indices [57]. In a group of critically ill obstetric patients, the initial trough concentration and 24 h-AUC of vancomycin in ARC patients were significantly lower than in non-ARC patients [61•]. The trough concentration among febrile neutropenic patients with ARC was significantly lower than for those without ARC [82]. Furthermore, in another study, the percentage of trough concentrations lower than 10 mg/L was 84.9% in the ARC group [83]. In a retrospective analysis of vancomycin TDM in patients undergoing neurosurgery, the trough concentration achievement rate in the ARC group was only 19.2% [84]. Using vancomycin trough plasma concentration/maintenance daily dose ratio to assess correlation with renal function showed that lower ratio was observed in patients with ARC compared to non-ARC group [85].

In contrast with other systemic azoles, fluconazole is hydrophilic and predominantly excreted by renal route. In a group of critically ill patients treated with fluconazole, decreased trough concentrations were significantly associated with ARC [86].

Recommended Dosage Regimens

Reviews on literature regarding the need for antibiotic dosage adjustments for ARC patients have recently been published [87••, 88••, 89••, 90••]. Most of the suggestions found in literature are based on population PK and simulation analysis, mostly with Monte Carlo simulations (MCS). There are some studies that analyze TDM results to determine the adequate dose accomplishing the desired targets. Increased doses, higher frequency, or prolonged infusion is frequently recommended in order to achieve PK/PD targets.

In the last 5 years, the vast majority of studies have evaluated β-lactams. New antibiotics with combinations of β-lactams and β-lactamase inhibitors, namely, ceftazidime/avibactam [91, 92], ceftolozane/tazobactam [93–95], and imipenem/cilastatin/relebactam [96–99], did not require dosage adjustment in patients with ARC. On the contrary, for other new antibiotics, there have been recommendations for dose adjustment. An extended infusion of 2 g q6h over 3 h of cefiderocol was recommended for patients with $CL_{CR} > 120$ mL/min [100]. The dosage regimen recommended for ceftaroline in ARC patients was 600 mg as loading dose, followed by 1200 mg/day by CI [101].

Penicillins

Fournier et al. concluded that increased dosages of amoxicillin up to 2 g q4h over 2 h were necessary for patients with CL_{CR} 200 mL/min [102].

Piperacillin-tazobactam was evaluated in several studies [35, 103–105], and different dosing regimens were proposed. For a PK/PD target of 100% *f*T > MIC and a MIC of 16 mg/L (for *Pseudomonas aeruginosa*), a dosage of 20 g/day of piperacillin was needed for patients with ARC [35, 103, 104]. Selig et al. suggested even higher doses of 28 g/day by CI for the same target in a population of burn and trauma patients [105].

Cephalosporins

Cefazolin was studied by Bellouard et al. [106]. Plasma concentrations of patients treated with CI for bacteraemia or infective endocarditis were used to establish a nomogram for optimal daily dose. Considering a target of 100% *f*T > 4 × MIC, a dose of 8 g/day was suggested for patients with CL_{CR} 120 mL/min.

Different dosage adjustments for ARC patients were proposed for ceftriaxone, such as 2 g/day by CI [107] or 2 g q12h [108] considering the same target (100% *f*T > MIC and a MIC of 2 mg/L). Similar suggestions were made for a target defined as C_{min}/MIC > 1 [109]. A much higher target (100% *f*T > 4 × MIC), with a lower MIC (0.5 mg/L), was proposed in a population with bacterial meningitis, justified by the need to reach adequate concentrations in cerebral spinal fluid for *Streptococcus pneumoniae* [110]. For these conditions, the dose of ceftriaxone suggested for patients with ARC was at least 78 mg/kg/day with a twice-daily regimen, which corresponds to 5.8 g/day in a patient with 75 kg. Dreesen et al. also considered a target of 100% *f*T > 4 × MIC and suggested 2 g q12h for a MIC value of 4 mg/L [111].

Cefepime dosage adjustment in patients with ARC has been suggested [112]. To achieve a target of 100% *f*T > MIC for a MIC of 8 mg/L, a loading dose of 4 g followed by CI of 7 g/day was needed.

Carbapenems

In recent times, several studies have proposed dosage regimens for meropenem in ARC [36, 113–116]. Different PK/PD targets were used varying from 40% *f*T > MIC to 100% *f*T > 4 × MIC for a MIC value of 2 mg/L. In all studies, administration of extended or CI was suggested as an alternative to intermittent dosing or as the only strategy. For intermittent administration of meropenem, dosing varied from 1 g q6h to 2 g q6h. Administration by extended infusion ranged from 1 g q8h over 3 h to 1 g q4h over 2 h. Doses suggested for CI varied from 2 to 8 g/day.

A randomized clinical trial was conducted to determine the best meropenem dosage regimen to achieve 50% *f*T > MIC in patients with ventilator-associated pneumonia and ARC divided in 3 groups [117•]. Prolonged meropenem infusion (1 g q8h over 6 h) reached better results than dose increase (2 g q8h over 3 h), in comparison to 1 g q8h over 3 h, with rates of achievement of 100%, 40%, and 13%, respectively.

Glycopeptides

One study with CI of vancomycin [118] recommended doses of 3500 mg/day and 4500 mg/day for ARC patients with CL_{CR} 130–180 mL/min and > 181 mL/min, respectively. Another study using intermittent infusion of vancomycin [119] used a target trough level of 15 mg/L and proposed maintenance doses of 69 mg/kg/day for patients with ARC. For a patient of 70 kg, this would correspond to a daily dose around 4830 mg. Lower doses of 750 mg q8h were proposed using AUC 24-h 400–650 mg.h/L as target for patients with CL_{CR} > 180 mL/min [120]; however, in this study, the probability of target attainment was only 62%. In a population of patients with hematological malignancies and ARC, for achieving a target exposure of 24 h-AUC of 400–600 mg.h/L at the steady state, daily doses ranging 2.5–3.25 g were recommended [121].

Aminoglycosides

Two studies evaluated amikacin, using as target C_{max}/MIC > 8 after assuming a MIC of 8 mg/L, but different modelling approaches and covariates were used [122, 123]. Boidin et al. used an a priori control approach based on a nonparametric population PK model and body surface area (BSA) as a covariate, and for a median value of BSA of 1.9 m^2, the optimal initial amikacin dose was higher than 3.4 g in patients with ARC [122]. Carrié et al. developed a population PK model with adapted body weight (ABW) as a covariate, and applying a MCS, 35 mg/kg ABW was recommended for a CL_{CR} of 130 mL/min [123].

Fluoroquinolones

Two studies evaluated ciprofloxacin dose adjustments in ARC [124, 125]. Both studies suggested a dose of 600 mg q8h to reach the target of AUC/MIC > 125 in critically ill patients with ARC infected with pathogens with a MIC of 0.250 mg/L.

Oxazolidinones

Dosage adjustment of linezolid in critically ill patients with ARC was evaluated in two studies. Barrasa et al. administered linezolid as a CI, and the target was adjusted to C_{ss} > MIC [126]. An infusion rate of 75 mg/h (equivalent to 1800 mg/day) should be considered to ensure concentrations ≥ 2 mg/L. In the study of Wang et al., the therapeutic target comprised two pharmacodynamic indices (AUC/MIC > 80 and 85% T > MIC) [127]. For patients with ARC, a dose of 2400 mg 24-h CI was suggested.

Table 2 Characteristics and main results of studies describing the influence of ARC on clinical outcomes

Ref.	Study identifiers			Population			Antibiotic	Clinical outcomes evaluated	Main results
	Design/centers/country	ARC definition	CL_{CR} determination method	*N*	Age (mean or median)/female sex (%)	Type of pathology			
Studies using measured CL_{CR}									
Claus et al. [128]	Prospective, single center, Belgium	> 130 mL/min/1.73 m^2	Measured CL_{CR} 24 h	128	ARC: 54 y/27% Non-ARC: 66 y/39%	Critically ill	Any antimicrobial	Therapeutic failure (impaired clinical response and the need for alternate antimicrobial therapy)	ARC patients had therapeutic failure more often than non-ARC patients (27% vs 13%; $p = 0.04$)
Udy et al. [130]	Prospective, Multicenter, Multiple countries	≥ 130 mL/min	Measured CL_{CR} 8 h	254	ARC: 52 y/41% Non-ARC: 65 y/44%	Critically ill with severe sepsis	Beta-lactams: piperacillin/tazobactam, ticarcillin/clavulanic acid, meropenem	ICU-free days at day 28, clinical cure at 14 days following ceasing antibiotic, and 90-day mortality	No outcome differences between ARC and non-ARC
Carrié et al. [78]	Retrospective, single center, France	> 130 mL/min/1.73 m^2	Measured CL_{CR} 24 h	223	All: 36 y/17%	Traumatic brain-injured patients treated for a first episode of ventilator-acquired pneumonia	Any antimicrobial	Clinical failure (impaired clinical response with a need for escalating antibiotics during treatment and/or within 15 days after end of treatment), and recurrent infection	No significant association between ARC and overall clinical failure ARC was statistically associated with recurrent infections (OR 4.4; 95%CI 1.2–16; $p = 0.03$)
Carrié et al. [133•]	Retrospective before and after study, single center, France	≥ 150 mL/min	Measured CL_{CR} 24 h	177	Control: 45 y/23% Treatment: 45 y/13%	Critically ill treated for a first episode of hospital or ventilator-acquired pneumonia with ARC	Beta-lactams	Therapeutic failure within 28 days (persistent or worsening symptoms with a need for escalating antibiotics) and recurrence of pneumonia within 28 days	Therapeutic failure or pneumonia relapse within 28 days was significantly lower in the arm treated with increased beta-lactam dosing regimens compared to conventional dosing regimens (HR 0.35; 95% CI 0.15–0.81; $p = 0.014$)

Table 2 (continued)

Ref.	Study identifiers			Population			Antibiotic	Clinical outcomes evaluated	Main results
	Design/centers/country	ARC definition	CL_{CR} determination method	*N*	Age (mean or median)/female sex (%)	Type of pathology			
Studies using estimates of CL_{CR}									
Huttner et al. [129]	Prospective, single center, Switzerland	≥ 130 mL/min	Estimated CG	100	ARC: 41 y/22% Non-ARC: 51 y/31%	Critically ill with severe infection	Beta-lactams: imipenem/cilastatin, meropenem, piperacillin/tazobactam, cefepime	Clinical failure at day 28 (insufficient lessening of the signs and symptoms to qualify for improvement, including death or indeterminate)	ARC was not associated with clinical failure (OR 1.13; 95% CI 0.38–3.35)
Burnham et al. [131]	Retrospective, single center, USA	> 130 mL/min/1.73 m^2	Estimated MDRD and CKD-EPI	494	ARC: 41 y/66% Non-ARC: 61 y/47%	Enterobacteriaceae sepsis, severe sepsis, and septic shock	Any antimicrobial	30-day mortality	ARC was not associated with increased mortality
Kawano et al. [132]	Retrospective, two centers, Japan	> 130 mL/min/1.73 m^2	Estimated 3-variable Japanese equation	280	ARC: 46 y/53% Non-ARC: 75 y/48%	Infected critically ill	Any antimicrobial	ICU mortality	ARC was not a predictor of ICU mortality (OR 0.45; 95% CI 0.08–2.46; $p = 0.36$)
Cojutti et al. [134]	Prospective, single center, Italy	> 130 mL/min/1.73 m^2	Estimated MDRD	75	58 y 37%	Oncohaematological patients with febrile neutropenia	Meropenem	14-day all-cause mortality	14-day all-cause mortality was significantly associated with ARC (OR 10.846; 95% CI 1.534–76.672; $p = 0.017$)
Shorr et al. [95]	Prospective, multicenter, 34 countries	> 130 mL/min	Estimated CG	463	C/T: ARC: 50 y/19%; Non-ARC: 60 y/29% MER: ARC: 48 y/21%; Non-ARC: 59 y/32%	Critically ill with hospital-acquired/ventilator-associated pneumonia	Ceftolozane/tazobactam and meropenem	28-day all-cause mortality, clinical cure, and microbiologic cure	All outcomes were comparable between normal renal function and ARC groups
Roberts et al. [99]	Prospective, multicenter, country not mentioned	≥ 150 mL/min	Estimated CG	531	62 y 31%	Hospital-acquired/ventilator-associated pneumonia	Imipenem/cilastatin/relebactam	28-day all-cause mortality, clinical response, microbiological response	All outcomes were similar among participants with normal renal function and ARC

CG Cockcroft-Gault, *CKD-EPI* Chronic Kidney Disease Epidemiology Collaboration, *CI* confidence interval, *CL_{CR}* creatinine clearance, *C/T* ceftolozane-tazobactam, *ICU* intensive care unit, *MDRD* Modification of Diet in Renal Disease, *MER* meropenem, *OR* odds ratio, *y* years

Clinical Outcomes

Literature is scarce describing the influence of ARC on clinical outcomes of infected or septic patients receiving antibiotics (Table 2). After the first two studies published by Claus et al. [128] and Huttner et al. [129] that showed contradictory results, only a few more have explored this issue. Claus et al. found an association between ARC and antimicrobial therapeutic failure [128]. On the other hand, Huttner et al. did not observe an association between ARC and clinical failure of β-lactams administered to critically ill patients with severe infection [129]. The majority of the following studies did not show influence of ARC on clinical outcomes [95, 99, 130–132]. In these studies, different antibiotics were used, some with demonstrated influence of ARC on plasma concentrations, such as in the study of Udy et al., but other studies considered any antibiotic administered to the patient during the study period [131, 132], which may have included antibiotics that do not need dosage adjustment in ARC.

Carrie et al. found that ARC was associated with recurrent infection; however, there was no significant association with overall clinical failure [49]. There were subsequently two studies that showed a positive association between ARC and worst clinical outcomes [133•, 134], in which β-lactams and meropenem were evaluated.

These contradictory results may partially be explained by the variety of different definitions of ARC, method for its identification, population characteristics, and properties of antibiotics used. While some antibiotics have different dosage recommendations for patients with normal renal function and ARC, as mentioned previously, others do not need adjustments, and mixing these two types of antibiotics in the same study can be a confounding factor. Also, the majority of studies used estimates of CL_{CR}, instead of measured CL_{CR}, which lead to misidentification of patients and inconclusive results. Finally, standard dosage regimens may largely exceed the PK/PD targets for susceptible microorganisms with lower values of MIC, and even in the presence of ARC, therapeutic levels will be achieved.

Future Perspectives

Although there is an increased interest in ARC, there are still many issues requiring standardization, accuracy, or clarification:

1. Although renal function should be interpreted as a continuum and as a dynamic concept, a unanimous definition of ARC, defining one consensual cut-off value of CL_{CR} and the method used for its identification based only on *measured* CL_{CR} instead of using mathematical estimates, would be valuable for standardization and coherent interpretation of distinct groups of research.
2. With this in mind, it would become possible to carry out large multicenter studies in order to understand the true prevalence and risk factors for ARC in the ICU setting.
3. Another subject that is still not well understood is the pathophysiology of ARC. Based on current knowledge, efforts should be made to clarify the underlying mechanisms and this way better identify the patients at risk of ARC.
4. Most of the published literature on the influence of ARC on antibiotic therapeutic levels and recommended dosage regimens are based on studies using population PK and simulation analysis. There is an urgent need for more studies providing recommendations based on clinical data after antibiotic administration to ARC patients. Moreover, there is still a lack of evidence that subtherapeutic levels of antibiotics lead to worse outcomes in ARC patients. It would be of great value to conduct a large study with antibiotics that are evidently affected by ARC and analyze the influence of subtherapeutic levels on clinical outcomes, including clinical failure and antimicrobial resistance.

Conclusions

ARC is a well-recognized event with significant prevalence in the ICU around the world, with robust association with subtherapeutic levels of several antibiotics. However, there is still work to do on the correct identification of ARC patients through measured CL_{CR}, understanding better the pathophysiology behind ARC, defining conditions for dose adjustments of antibiotics, and establishing an association with clinical outcomes.

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- •• Of major importance

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