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POINT OF VIEW

Augmented renal clearance: Much more is better?☆

Aumento del aclaramiento de creatinina: ¿Cuánto más, mejor?

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Introduction

Augmented renal clearance (ARC) is a phenomenon that can lead to therapeutic failure in critically ill patients. In the case of sepsis, the inadequate dose of an antibiotic (AB) worsens prognosis and increases the generation of resistances.[1]

Definition and epidemiology

Although this phenomenon was already described back in the 1970s,[2] the ARC is defined today as creatinine clearance (CrCl) levels >130 mL/min/1.73 mm^2.[3] The ARC is relevant in patients treated with renal clearance drugs as long as it is significant, that is, as long as the CrCl levels are more than150 mL/min/1.73 m^2 in women and >160 mL/min/1.73 m^2 in men for, at least, four days.[3] The prevalence varies between 14% and 80% depending on the type of ICU the study was conducted at.[3]

Physiopathology and risk factors

The phenomenon of ARC is due to an acute insult, it can appear at admission in a significant number of patients, and it can remain during the entire first week after its debut at the ICU. Since it is a dynamic phenomenon, follow-up during the entire hospital admission is mandatory in order to avoid overdose or therapeutic failures.[4]

Some contributing factors are high temperature, brain injury, and the systemic inflammatory response syndrome (SIRS). This systemic inflammatory response can be found in trauma patients, pancreatitis, TBI, autoimmune alterations, ischemia, major surgery and sepsis.[4] The profile of a hyperfiltrating patient is that of a young (<55 years old) male trauma patient or with an SIRS and lower scores in the severity scales (lower SOFA, SAPS II or APACHE II). Urine creatinine levels >45 mg/mL are also considered a risk factor. Several ARC risk scoring systems have been developed so far[5,6] (Table 1).

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Table 1 ARC risk scoring systems.

	ARC Scoring System[5]	ARCTIC[6] (for trauma patients)
Criteria	Age ≤50 years old: 6 points Trauma: 3 points SOFA ≤4: 1 point	Serum creatinine <62 μmol/L: 3 points Sex: male: 2 points Age <56 years old: 4 points Age 56–75 years old: 3 points
Interpretation	0–6 points: low risk 7–10 points: high risk	<6 points: low risk >6 points: high risk

ARC, augmented renal clearance; ARTIC, augmented renal clearance in trauma intensive care.

Creatinine clearance: estimation methods

In the routine clinical practice, in order to estimate the glomerular filtration rate (GFR) we use the concentration of serum creatinine or equations based on the level of creatinine, sex, race, ethnic group, etc. However, this is not adequate in cases of ARC, and to be completely sure about diagnosis it needs to be achieved using the GFR. The GFR is the correlation between the urine creatinine level of a volume of urine per unit of time (between 2 and 24 h) and the plasma creatinine level.[7,8]

Drug clearance in augmented renal clearance

The antibiotics that most commonly are involved and relevant in the hyperfiltrating patient are beta-lactam antibiotics (BLAs) (penicillins, cephalosporins, piperacillin-tazobactam, carbapenems and monobactams), aminoglycosides, vancomycin and quinolones such as levofloxacin (Table 2). As a matter of fact, any drugs that are cleared through urine can be affected in cases of ARC. The ARC of these drugs reduces the half-life of the drugs ($t_{1/2}$). This is particularly important in time-dependent antibiotics.

Given the characteristics of BLA whose bacterial carrying capacity is time-dependent, we should consider keeping adequate concentrations of the drug whether using the most common doses or extended or continuous infusions.

In the particular case of vancomycin there are already validated nomograms that illustrate how important it is to stratify the ARC[9] and, in the case of meropenem, a tool has been developed that predicts the risk of not achieving the therapeutic goal that consists of a free easy-to-use calculator – the «MeroRisk Calculator».[10]

The load dose that needs to be adjusted to the volume of distribution should not be modified by the fact that a subject is a hyperfiltrating patient.

In the case of aminoglycosides, it is recommended to shorten the interval of administration to 18 h instead of using daily administration.

Monitoring the plasma levels is essential if we wish to achieve our therapeutic goals, but it is not always available in the routine clinical practice for most drugs.

In this sense, it would be convenient and necessary to design guidelines on drug dose use based on hyperfiltrating patients and probably adjust the dose to the stratification of the ARC, the same thing that happens with guidelines for renal failure. Here is the stratification we could have: (1) mild ARC (CrCl 130–150 mL/min/1.73 m^2) where the highest doses usually recommended should be used; (2) moderate ARC (CrCl 150–200 mL/min/1.73 m^2) where there should be titration to a higher dose in a given percentage; (3) high ARC (CrCl 200–250 mL/min/1.73 m^2) where there should be titration to a higher dose in a higher percentage than in moderate ARC; (4) very high ARC (CrCl 250–300 mL/min/1.73 m^2) where there should be titration to a higher dose in a higher percentage than in high ARC, and (5), and extreme ARC (CrCl > 300 mL/min/1.73 m^2), where there should be titration to a higher dose in a higher percentage than in very high ARC. Thus, we need to design dosing patterns for the routine clinical practice, although today there is still no consensus on this regard.

Diagnosis and management algorithm when suspected augmented renal clearance

The diagnosis and management algorithm when suspected ARC is shown on Fig. 1 where the risk factors for ARC are shown and where it is advisable to determine the glomerular filtration rate. Similarly, a few recommendations are given, and the periodic re-evaluation of ARC is suggested.

Conclusion

In sum, the critically ill patient can be hyperfiltrating and his diagnosis depends on the degree of clinical suspicion. Since the plasma creatinine level does not stand out, a normal renal function is presumed, and the doses of renal-clearance drugs are titrated consequently. The possible implications that the ARC has are therapeutic failure and the generation of resistances when using antibiotics. Younger age, less severity, inflammatory or neurocritical state are risk factors here. In order to confirm ARC, the glomerular filtration rate should be estimated from the urine collected over a 24-h period of time (between 2 and 24 h), follow-up being necessary given the dynamic situation of the critically ill patient.

Conflicts of interest

The author declares no conflicts of interest whatsoever.

Table 2 Drug dose in hyperfiltrating patients (ARC).

Drug	Normal dose (normal GFR) (Mensa 2017)	Dose suggested for ARC[4]	Special cases
levofloxacin	500 mg/24 h iv	750 mg/24 h iv	For infections due to *S. pneumoniae*, *P. aeruginosa* and *S. aureus* 1000 mg/24 h iv
Cefepime	1–2 g/8–12 h iv	2 g/8 h iv	
Meropenem	0,5–1 g/6–8 h iv	2 g/8 h iv	>8 g/day may be necessary to achieve the therapeutic goal
Piperacillin-tazobactam	2–4 g/6–8 h iv Maximum dose 4 g/4 h iv	4.5 g/4–6 h	36 g/day may be necessary to achieve the therapeutic goal
Vancomycin	15–20 mg/kg/8–12 h iv Maximum dose 4 g/day	45 mg/kg/day in 3 doses or continuous infusion	Based on nomogram and ARC stratification: If mild ARC (CrCl 130–150 mL/min/1.73 m^2) give the highest doses usually recommended If moderate ARC (CrCl 150–200 mL/min/1.73 m^2) give between 3–4 g/day If high ARC (CrCl 200–250 mL/min/1.73 m^2) give between 4–4.5 g/day If very high ARC (CrCl 250–300 mL/min/1.73 m^2) give between 4.5–5.5 g/day If extreme ARC (CrCl > 300 mL/min/1.73 m^2) give 6 g/day

Source: Mahmoud and Shen's modified Table[4]. ARC, augmented renal clearance.

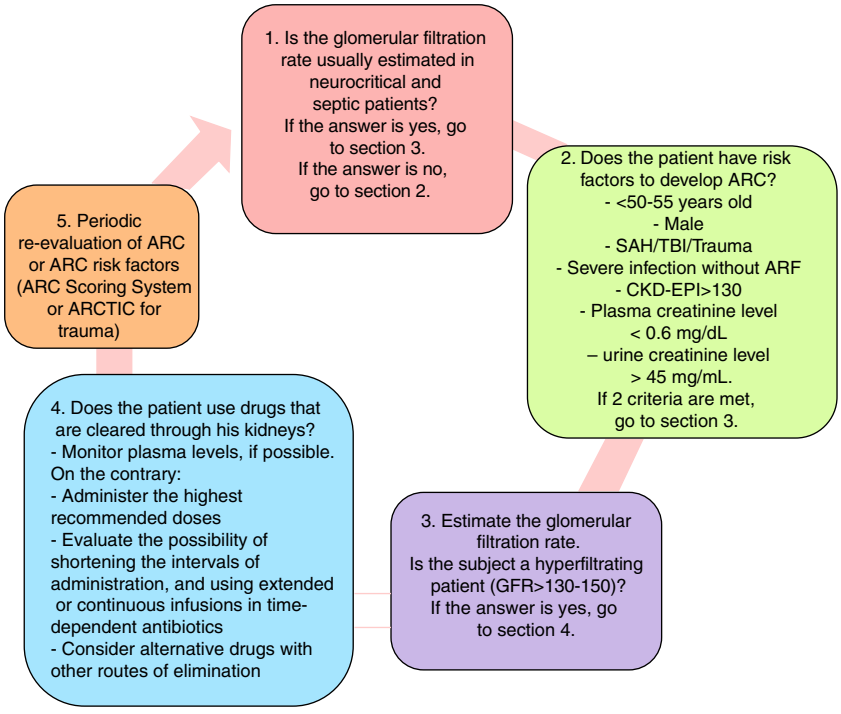

Figure 1 Diagnosis and management algorithm when suspected ARC. ARC, augmented renal clearance; ARTIC, augmented renal clearance in trauma intensive care. *Source*: Mahmoud and Shen's modified algorithm[4].

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