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REVIEW ARTICLE

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Methods for dose quantification in continuous renal replacement therapy: Toward a more precise approach

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Abstract

Periodic dose assessment is quintessential for dynamic dose adjustment and quality control of continuous renal replacement therapy (CRRT) in critically ill patients with acute kidney injury (AKI). The flows-based methods to estimate dose are easy and reproducible methods to quantify (estimate) CRRT dose at the bedside. In particular, quantification of effluent flow and, mainly, the *current dose* (adjusted for dialysate, replacement, blood flows, and net ultrafiltration) is routinely used in clinical practice. Unfortunately, these methods are critically influenced by several external unpredictable factors; the estimated dose often overestimates the real biological delivered dose quantified through the measurement of urea clearance (the *current effective delivered dose*). Although the *current effective delivered dose* is undoubtedly more precise than the flows-based dose estimation in quantifying CRRT efficacy, some limitations are reported for the urea-based measurement of dose. This article aims to describe the standard of practice for dose quantification in critically ill patients with AKI undergoing CRRT in the intensive care unit. Pitfalls of current methods will be underlined, along with solutions potentially applicable to obtain more precise results in terms of (a) adequate marker solutes that should be used in accordance with the clinical scenario, (b) correct sampling procedures depending on the chosen indicator of transmembrane removal, (c) formulas for calculations, and (d) quality controls and benchmark indicators.

KEYWORDS

clearance, dialysance, nomenclature, sieving coefficient, urea

1 | INTRODUCTION

The concept of "dose" identifies the amount of blood cleared of waste products and toxins by an extracorporeal device per unit of time.[1,2] Prescription and delivery of an appropriate extracorporeal treatment dose are fundamental to effective renal replacement therapy (RRT).[3,4] Several studies have demonstrated a direct relationship between RRT dose and patient survival.[5,6] In order to avoid harmful under- and over-treatment (both associated with worst patients' outcome[7]), the most updated guidelines recommend delivering an effluent volume of 20-25 mL/kg/h in patients

[Correction added on 11th May 2022, after first online publication: CRUI funding statement has been added.]

with acute kidney injury.[8] For this reason, increasing attention has been paid in the last decades to the differences between prescribed and delivered RRT dose, particularly in continuous renal replacement therapy (CRRT).[7] Continuous monitoring of the delivered RRT dose should routinely be performed in critically ill patients with acute kidney injury (AKI) to adjust the prescribed dose based on the patient's actual needs ("dynamic prescription") and determine actual solute transmembrane clearance.[9] For the purpose of this review, it should be underlined that the broader concept of "dose" includes various "dose" measures, each one precisely defined and representing different aspects of the original concept. A multidisciplinary panel (the Nomenclature Standardization Alliance) has recently standardized all definitions and formulas to calculate and describe the multiple practical components of CRRT dose[1,2]; these definitions are summarized in Table 1. The dose practically set in the machine (the "*target machine dose*") and initially prescribed to the patient should be periodically reassessed (at least once every 24 hours or more often) and continuously readjusted to meet rapidly changing needs of patients. This dynamic process aims to deliver the most appropriate "*target dose,*" that is, the amount of clearance that the prescribing clinician wants to achieve in that patient, with that particular clinical condition, in that specific moment.[10] In spite of a specific *target machine dose*, an unpredictable range of actual solute extracorporeal clearances (the "*current effective delivered dose*") should be assumed.[1,2] Extracorporeal solute clearance should be periodically assessed (measured) and the discrepancy between *target* and *current effective delivered dose* was routinely quantified to monitor the quality of delivered CRRT dose. Periodic dose assessment (estimated or measured) is quintessential for both dynamic prescription and quality measures. For this reason, measurement or, at least, estimation of the delivered dose should be considered as a standard practice. This article aims to describe current practice in dose quantification in critically ill patients with AKI undergoing CRRT in the intensive care unit (ICU). Pitfalls of current methods will be underlined, along with solutions potentially applicable to obtain more precise results.

2 | CURRENT METHODS TO ESTIMATE THE DOSE

Dose assessment in critically ill AKI patients treated with CRRT is often based on bedside evaluation of the effluent flow. In order to simplify bedside CRRT in everyday clinical practice, the effluent flow (expressed in mL/kg/h) is considered as an acceptable surrogate of CRRT *efficiency*.[1] Following the concept of dynamic prescription, the effluent flow rate may be increased or decreased during monitoring in response to changes in clinical needs or metabolic status.[11] Interestingly, new-generation CRRT machines have advanced software that enables safe and correct provision of the effluent flow-estimated dose that will be theoretically obtained at the end of a 24-hour treatment.[9,12] These machines can also automatically increase the effluent flow to compensate for downtime and reduce patients undertreatment (ie, downtime compensation technology).[13]

Quantification of the CRRT dose by the effluent flow rate is an easy and reproducible method. However, several factors may affect the capability of the effluent flows-based method in realistically estimate the real biological dose delivered to the patient. First, since the effluent flow is considered a unique variable, diffusive and convective clearances are regarded as equal contributors in transmembrane clearance, and the same holds true for pre- and post-dilution. Furthermore, in this estimation method, blood flow seems irrelevant for the transmembrane clearance.

In view of the above, a formula that takes into account the blood, dialysate, and replacement flows represents a more accurate method to estimate the delivered dose. Beside the effluent flow, the machine flows-estimated dose that more accurately estimates the delivered dose is the *current dose* (ie, the instantaneous clearance calculated—not measured––from the instantaneous flows in the extracorporeal circuit). The formula adopted by the Nomenclature Standardization Alliance to estimate the *current dose* is[1,2]:

$$K_{Cr} = \frac{\left(Q_R^{PRE} + Q_D + Q_{UF}^{NET} + Q_R^{POST}\right)}{B.W.} \cdot \frac{Q_B}{Q_B + Q_R^{PRE}} \quad (1)$$

TABLE 1 Definition of doses according to the nomenclature standardization alliance

Dose	Definition
Target dose	The clearance that the prescribing clinician wants to achieve in a patient in his/her specific clinical condition
Target machine dose	The clearance that the prescribing clinician sets in the CRRT machine
Current dose	The clearance at the present time estimated from the flow rates in the extracorporeal circuit
Current effective delivered dose	The clearance at the present time measured from solute concentrations in the circuit lines

where K_{Cr} is the *current dose*; Q_R^{PRE} is the replacement flow rate in pre-dilution; Q_D is the dialysate flow rate; Q_{UF}^{NET} is the net ultrafiltration flow rate; *B.W.* is the patient's body weight; Q_B is the blood flow rate; and Q_R^{POST} is the replacement flow rate in post-dilution.

Interestingly, this formula considers all the determinants that limit diffusive and convective removal mechanisms through a semipermeable membrane. In particular, it contemplates the impact of a prefilter dilution of plasma by a replacement fluid. Nonetheless, similarly to the effluent flows-based method, this estimation method does not consider all the biological (unpredictable) variables contributing to divert actually delivered solute clearance from *target dose*.

3 | CURRENT METHODS TO MEASURE THE DOSE

The flows-based dose estimation is an easy and reproducible method to quantify CRRT dose.[1] However, the estimated dose practically represents the real CRRT *efficiency* only if all of the following conditions are met[10,14]: (a) urea is considered as a marker of solute removal; (b) a single-pool urea kinetic model is assumed; (c) urea nitrogen generation rate is negligible; (e) renal function is absent and unchanged during treatment; (e) dialysate is entirely saturated by blood-diffusing solutes; (f) urea continuously maintains a sieving coefficient of 1 during the treatment (protein layer, concentration of polarization, and membrane clotting are not considered); (g) adsorption is not considered; (h) patient fluid volume is only affected by the treatment and its changes over time are solely due to net ultrafiltration rate; and (i) density of plasma water equals 1 Kg/dm^3. These conditions very rarely occur in critically ill patients with AKI treated with prolonged or continuous RRT. Thus, discrepancies may exist between *current dose* (estimated) and actual biologically measured delivered clearance (the "*current effective delivered dose*"). These discrepancies occur more frequently in the acute setting,[15] and are common problems when applying CRRT to critically ill patients.[16] Several factors contribute to reduce the biological dose delivered to the patient, including, for instance, vascular access dysfunction and blood recirculation, anticoagulation issues, and membrane fouling. These factors are not quantifiable through flows-based estimation of the dose. Despite being often technically unrelievable, progressive fouling of the filter membrane leads to a clinically relevant reduction in the delivered CRRT dose.

For all these reasons, precise measurement—rather than estimate—of real biological clearance is crucial in clinical practice at the bedside. The most appropriate method to quantify the real biological dose delivered to the patient during CRRT is to measure the *current effective delivered dose*, that is, the instantaneous amount of clearance observed at every moment during the treatment period. Unlike the *current dose*, the *current effective delivered dose* is calculated starting from solute concentrations (instead of flows) measured into the extracorporeal circuit. It mainly depends on the specific RRT modality, treatment settings, and other technical and clinical factors that qualitatively and quantitatively affect the extracorporeal clearance. These include (a) differences between displayed and actual flows of blood and effluent rates; (b) adequacy of vascular access; (c) incorrect priming procedure; (d) loss of membrane surface area due to clotting or air entrapment; (e) loss of filter permeability due to clotting of the membrane, protein cake deposition on its inner layer, or concentration polarization; and (f) high hematocrit and blood viscosity within the filter caused by a high filtration fraction.[1]

A measured, solutes-based *current effective delivered dose* significantly below the flows-estimated *current dose* should induce the physician to reconsider CRRT modality, vascular access and anticoagulation regimen, or plan a filter replacement (Figure 1). Urea is recognized as a marker of uremic toxicity retained during AKI and a useful indicator of protein catabolism. Because urea is easily removed by RRT, it is the most commonly used marker to quantify dose[17] worldwide. Furthermore, the ratio of effluent-to-plasma urea concentration is an effective way to monitor membrane fouling.[18]

For all these reasons, measurement of urea instantaneous clearance represents the most widely adopted method to measure the *current effective delivered dose* worldwide. The formula adopted by the Nomenclature Standardization Alliance to measure the *current effective delivered dose*[1,2] is:

$$K_{Cd} = \left(Q_B \cdot \frac{C_{Bi} - C_{Bo}}{C_{Bi}} + Q_{UF} \cdot \frac{C_{Bo}}{\left(\frac{C_{Bi} + C_{Bo}}{2} \right)} \right) \cdot \frac{1}{B.W.} \quad (2)$$

where K_{Cd} is the *current effective delivered dose*; C_{Bi} is the prefilter blood concentration of the reference solute; C_{Bo} is the postfilter blood concentration of the reference solute; and Q_{UF} is the ultrafiltration flow rate.

Although the *current effective delivered dose* is undoubtedly more precise than the flows-estimated dose in quantifying CRRT efficacy, some limitations are also reported for urea-based dose measurement. In particular, measurement of urea from different solutions sampled from the extracorporeal circuit cannot be performed at the bedside, but instead requires a cooperation with the central lab. Furthermore, difficulties in laboratory management of effluent solution require a strong and continuous connection between ICU healthcare workers and the laboratory staff.

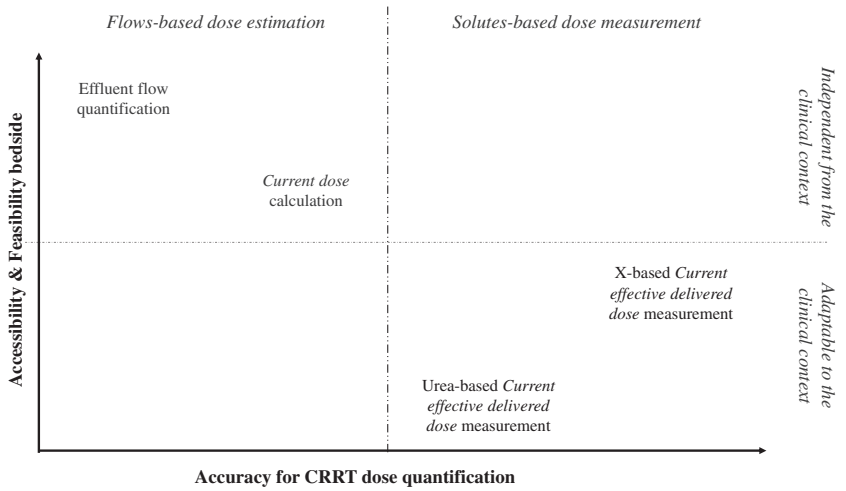

FIGURE 1 Advantages and drawbacks of flows-based dose estimation and solutes-based dose measurement. Flows-based methods to estimate dose are certainly easier and feasible to apply at the bedside. Among solutes-based methods to measure dose, the identification of marker solutes that could be easily measured in real time, at a low cost, at the bedside could provide a feasible alternative to the standard urea-based approach. Measurement of the *current effective delivered dose* certainly quantifies biologic (real) clearance more accurately than the flows-based estimation methods. Furthermore, in accordance with the clinical scenario and the specific patient's needs, specific and more "precise" solutes might be chosen for measuring the *current effective delivered dose* (eg, those solutes whose clearance was the main objective of the extracorporeal treatment). However, the flows-based methods provide an estimation of dose which is independent from the clinical scenario (eg, from the occurrence of membrane fouling or vascular access recirculation) and from the specific indications for continuous renal replacement therapy (CRRT) (eg, hypermyoglobinemia)

4 | STRATEGIES FOR INCREASING ACCURACY IN DOSE MEASUREMENT

4.1 | Choice of marker solutes

Ideally, measurement of the *current effective delivered dose* should be determined based on the concentration of the specific target solutes. Unfortunately, most solutes are not practically measurable in routine clinical practice, and thus surrogate marker solutes (eg, urea) are currently used to quantify the *current effective delivered dose*. Similarly to urea, the solute used to quantify extracorporeal clearance should undergo the same biological retention mechanisms described in critically ill patients affected with AKI. Notably, retention of the chosen solute should be associated with impaired kidney function, as in the case of urea. Also, the marker solute should be characterized by stable volume of distribution and negligible generation rate, and should theoretically not be influenced by nutritional status or muscle mass. Beside these characteristics, only rarely achievable in real practice, the ideal solute should be able to quantify extracorporeal clearance of the molecules that actually represent the treatment targets. In particular, high molecular weight molecules should be considered as marker solutes if the aim of the extracorporeal treatment is to remove molecules larger than 35-40 KDa (eg, cytokines and inflammatory mediators). Middle molecular weight molecules should be considered as marker solutes if the treatment aims at removing molecules characterized by a molecular weight that approximates 5-35 KDa (eg, β2-microglobulin or myoglobin). Finally, adoption of small molecules (eg, urea and creatinine) as marker solutes to quantify the dose should be confined to those treatments aimed at removing isolated small molecules, with a molecular weight below 5 KDa (Table 2). Beside molecular weight, other molecular dimensions influencing transmembrane clearance should be taken into consideration when choosing a marker solute. Molecular radius should be evaluated, particularly in the case of nonspherical molecules (eg, myoglobin). Molecular surface electric charge should also be considered for the repulsion/attractive forces that influence adsorption onto the surface membrane via the Gibbs-Donnan effect. Ultimately, the ideal target solute for quantification of extracorporeal clearance should be retained during AKI and be as close as possible to the target molecules that we desire to remove via extracorporeal blood purification in terms of weight, dimensions, and electric charge. However, CRRT is rarely applied in the ICU with a single aim, making it impossible to identify a single target solute in a univocal manner (eg, in critically ill septic patients, where cytokines and small uremic solutes are all objectives of treatment). Under these circumstances, not a single marker solute, but a panel of different marker solutes with different molecular characteristics should be considered in order to effectively represent the entire spectrum of extracorporeal clearances of those solutes that represent the different treatment aims. Overtime reduction of the current effective delivered dose obtained from molecules of different sizes can inform about the occurrence

TABLE 2 Characteristics and properties of marker solutes potentially measurable to quantify dose during continuous renal replacement therapy in critically ill patients with acute kidney injury (AKI). Biologic appropriateness is evaluated against the clinical scenarios of AKI in the intensive care unit

	Solute	Molecular weight	Biological appropriateness	Bedside real-time availability	Costs	Analysis method
Small molecular weight	Fluoride ion	42 Da	Small	Yes	Low	Ion selective probe
	Urea	60 Da	High	No	Low	Colorimetric kinetic
	Creatinine	113 Da	Small/Medium	No	Low	Colorimetric kinetic
Middle molecular weight	Vitamin B12	1.3 kDa	Limited	No	Medium	Chemiluminescent assay
	β2 Microglobulin	11 kDa	Limited	No	Medium	Chemiluminescent assay
	Cystatin C	13 kDa	High	No	High	Immunophelometric assay
	Myoglobin	16.7 kDa	High (only for hypermyoglobinemia)	No	Medium	Chemiluminescent assay
High molecular weight	Interleukin 18 (IL-18)	24 kDa	High	No	High	ELISA
	Albumin	66.5 kDa	High	No	High	Colorimetric
	Kidney injury molecule-1 (KIM-1)	65-110 kDa	High	No	High	ELISA

of membrane fouling (usually observed for large molecules early in the course of treatment). Beside the occurrence of membrane fouling and its effects on membrane's permeability and porosity, treatment modality itself can influence the current effective delivered dose obtained from solutes of different sizes. Particularly for middle and large molecules, a current effective delivered dose smaller than the target dose allows the physician to identify undertreatment and thus readjust CRRT prescription (eg, by increasing current dose or transmembrane ultrafiltration, ie, convection). The choice of marker solutes for CRRT monitoring should be based on a multiparametric approach that, beside functional (retention during AKI) and geometric (dimension/electrical charge) characteristics, takes into account the feasibility of bedside measurement. Type of laboratory analysis, real-time bedside determination, and cost of measurement are essential to use of marker solutes in routine clinical practice. In particular, solutes concentrations in the extracorporeal circuit should be available as soon as possible to modulate treatment settings in accordance with the concept of dynamic prescription.

In a recent "in vitro" study, Villa et al evaluated the use of fluoride as a possible marker solute for CRRT dose measurement.[19] Fluoride is retained during renal dysfunction and exhibits similar properties to urea in terms of sieving (SC) and saturation coefficients (SA), transmembrane clearance, and solute mass lost in the effluent during treatment. The authors found that measured SA/SC and extracorporeal clearance of urea and fluoride yielded negligible differences at each assessment point in time. Moreover, use of fluoride showed several advantages compared to urea, such as simple bedside measurement, lower costs, and direct quantification.[19] Future directions related to this study would be to identify a solute that is similar to fluoride in terms of bedside management and costs, but is present in biological fluids and therefore represents a measurable and evaluable biomarker of the *current effective delivered dose* in CRRT.

4.2 | Choice of variables to be measured

Blood purification can be achieved by extracorporeal transmembrane (diffusive or convective) removal and membrane adsorption. Historically, solute "transmembrane" removal is the primary mechanism recognized for the concept of "clearance" and thus identifiable with the "dose." It should be remembered that this assumption tends to underestimate the real concept of solute removal, as it does not consider adsorption characteristics deriving from newly developed technological biomaterials and spinning technology for membrane manufacturing. A more comprehensive concept of dose should consider adsorption mechanisms along with transmembrane clearance to quantify extracorporeal solute removal.

Transmembrane removal might be quantifiable via measurement of "clearance" or "dialysance," depending on the nature of the chosen marker solute. Although the concept of clearance is most frequently applied in this field, it should be substituted by the measurement of dialysance in dialytic

therapies where the marker solute is already present in the dialysate. In this case, the formula to be used is:

$$D = \left(Q_B \cdot \frac{C_{Bi} - C_{Bo}}{C_{Bi} - C_{Di}} + Q_{UF} \cdot \frac{C_{Bo}}{(C_{Bi} - C_{Di})} \right) \quad (3)$$

where D is the dialysance and C_{Di} is the solute concentration in the dialysate going into the hemodialyzer.[20]

In all other cases, the classical clearance formula can be used to realistically estimate extracorporeal removal. Different formulas can be used to quantify extracorporeal clearance, mostly depending on (a) nature of the sampled solutions used for measuring solutes concentration and (b) convective or diffusive clearances (Table 3). In hemofiltration, blood and effluent samples should be obtained and the convective clearance (K_{Conv}) is calculated as:

$$K_{Conv} = Q_{UF} \cdot \frac{C_{eff}}{\left(\frac{C_{Bi} + C_{Bo}}{2} \right)} \quad (4)$$

where C_{eff} is the solute concentration in the effluent. In hemodialysis, in the absence of Q_{UF}^{NET}, only blood samples can be obtained and dialytic clearance K_{Dial} is calculated as:

$$K_{Dial} = Q_B \cdot \frac{C_{Bi} - C_{Bo}}{C_{Bi}} \quad (5)$$

However, if only dialysate and effluent samples are obtained, clearance is calculated as:

$$K_{Dial} = Q_D \cdot \frac{C_{Di} - C_{Do}}{C_{Bi}} \quad (6)$$

Due to similarities with convective treatments, in the absence of Q_{UF}^{NET}, extracorporeal clearance in hemodialysis can also be quantified using blood and effluent concentration, according to the following formula:

$$K_{Dial} = Q_D \cdot \frac{C_{eff}}{\left(\frac{C_{Bi} + C_{Bo}}{2} \right)} \quad (7)$$

In hemodiafiltration (ie, the most frequently prescribed treatment worldwide), prefilter and postfilter solute concentrations can be measured using formula (1) of KCr described above, that practically represents the addition of diffusive and convective clearances.

Removal by membrane adsorption can be evaluated through quantification of solute mass lost as blood flows through the hemodiafilter. Specifically, the difference between solute mass in the solution (blood) entering the hemodiafilter and solute mass in the solution (blood and effluent) leaving the hemodiafilter can approximate solute mass adsorption according to the following formula:

$$M_{Ads} = (Q_{Bi} \cdot C_{Bi}) - (Q_{Bo} \cdot C_{Bo}) - (Q_{eff} \cdot C_{eff}) \quad (8)$$

where M_{Ads} is the solute mass adsorbed to the hemodiafilter, Q_{Bi} and Q_{Bo} are the blood flows, respectively, entering and leaving the hemodiafilter, and Q_{eff} is the effluent flow.

Depending on the indicator of solute removal (clearance, dialysance, or adsorption) and nature of the marker solute, a prefilter blood sample should be obtained along with a postfilter blood or an effluent sample. The former is usually obtained from a specific sampling port into the circuit inflow line (usually marked with red color), whereas

TABLE 3 Formulas for dose estimation and dose measurement in treatments performed with (right column) and without (left column) net ultrafiltration. Notably, flows-based dose estimation and solutes-based dose measurement restitute results both measured as a clearance normalized by body weight (eg, mL/kg/h). However, adsorption is measured as a mass per unit of time (eg, mg/h)

Flows-based dose estimation		
	$K_{Cr} = \frac{(Q_R^{PRE} + Q_D + Q_{UF}^{NET} + Q_R^{POST})}{B.W.} \cdot \frac{Q_B}{Q_B + Q_R^{PRE}}$	$K_{Cr} = \frac{(Q_R^{PRE} + Q_D + Q_{UF}^{NET} + Q_R^{POST})}{B.W.} \cdot \frac{Q_B}{Q_B + Q_R^{PRE}}$
Solutes-based dose measurement		
Hemodialysis	$K_{Dial} = Q_B \cdot \frac{C_{Bi} - C_{Bo}}{C_{Bi}} \cdot \frac{1}{B.W.}$	$K_{Cd} = \left(Q_B \cdot \frac{C_{Bi} - C_{Bo}}{C_{Bi}} + Q_{UF} \cdot \frac{C_{Bo}}{C_{Bi}} \right) \cdot \frac{1}{B.W.}$
	$K_{Dial} = Q_D \cdot \frac{C_{Di} - C_{Do}}{C_{Bi}} \cdot \frac{1}{B.W.}$	$K_{Dial} = \left(Q_D \cdot \frac{C_{Di} - C_{Do}}{C_{Bi}} + Q_{UF} \cdot \frac{C_{Bo}}{C_{Bi}} \right) \cdot \frac{1}{B.W.}$
	$K_{Dial} = Q_D \cdot \frac{C_{eff}}{\left(\frac{C_{Bi} + C_{Bo}}{2} \right)} \cdot \frac{1}{B.W.}$	$K_{Dial} = \left(Q_D \cdot \frac{C_{eff}}{\left(\frac{C_{Bi} + C_{Bo}}{2} \right)} + Q_{UF} \cdot \frac{C_{Bo}}{C_{Bi}} \right) \cdot \frac{1}{B.W.}$
Hemofiltration	$K_{Conv} = (Q_R^{PRE} + Q_R^{POST}) \cdot \frac{C_{eff}}{\left(\frac{C_{Bi} + C_{Bo}}{2} \right)} \cdot \frac{1}{B.W.}$	$K_{Conv} = (Q_R^{PRE} + Q_R^{POST} + Q_{UF}^{NET}) \cdot \frac{C_{eff}}{\left(\frac{C_{Bi} + C_{Bo}}{2} \right)} \cdot \frac{1}{B.W.}$
Hemodiafiltration	$K_{Cd} = \left(Q_B \cdot \frac{C_{Bi} - C_{Bo}}{C_{Bi}} + (Q_R^{PRE} + Q_R^{POST}) \cdot \frac{C_{Bo}}{C_{Bi}} \right) \cdot \frac{1}{B.W.}$	$K_{Cd} = \left(Q_B \cdot \frac{C_{Bi} - C_{Bo}}{C_{Bi}} + (Q_R^{PRE} + Q_R^{POST} + Q_{UF}^{NET}) \cdot \frac{C_{Bo}}{C_{Bi}} \right) \cdot \frac{1}{B.W.}$
Solutes adsorption		
	$M_{Ads} = (Q_{Bi} \cdot C_{Bi}) - (Q_{Bo} \cdot C_{Bo}) - (Q_{eff} \cdot C_{eff})$	$M_{Ads} = (Q_{Bi} \cdot C_{Bi}) - (Q_{Bo} \cdot C_{Bo}) - (Q_{eff} \cdot C_{eff})$

postfilter blood and effluent samples are obtained from a sampling port into the circuit outflow line (usually marked with blue) and in the effluent line (usually marked with yellow), respectively. In circumstances where dialysate samples are required, these are often obtained directly from the dialysate bag.

4.3 | Sampling methods and circuit characteristics

From a practical point of view, it is essential that the samples obtained from the extracorporeal circuit for dose quantification are taken from every blood or effluent sampling port at the same time. In particular, the aspiration flow of the samples and the amount of solution taken should be precisely the same and obtained simultaneously. In doing so, the volume obtained from the sample and the instantaneous flow into the extracorporeal circuit are approximately equal. The sample aspiration flow is critically correlated with the flows within the extracorporeal circuit. Indeed, the lower the solutions flow into the extracorporeal circuit, the slower should be sample aspiration to guarantee an appropriate blood mixture into the extracorporeal line. As a rule of thumb, with flows usually adopted in routine clinical practice (Q_B = 100-150 mL/min, Q_{eff} = 25-35 mL/kg/h), sample aspiration flow should not be greater than 1 ml for every 5-10 seconds. The procedure is highly influenced by the flows set into the extracorporeal circuit. Thus, it is often suggested that the same extracorporeal prescription is applied for overtime monitoring in the same patient/treatment. Furthermore, it might be useful to use a Q_{UF}^{NET} of zero so as to reduce further variability.

4.4 | Quality control

In order to verify the quality of the results in terms of solutes concentration in the different samples, a quality control indicator should be adopted before measuring the indicator of extracorporeal solute removal and, in particular, before using the results for clinical purposes and dynamic prescription. The mass balance error ($M_{balError\%}$) should be quantified as a quality indicator for the sampling method. It is calculated starting from the prefilter, postfilter, and effluent solute concentrations according to the following formula:

$$M_{balError\%} = \frac{\left(M_{Art} - M_{Ven} - M_{Eff}\right)}{M_{Art}} \quad (9)$$

where M_{Art}, M_{Ven}, and M_{Eff} represents the solute mass in the inlet, outlet, and effluent lines, respectively.

A mass balance error below 5% identifies an optimal sampling procedure, while a mass balance error of 5%-10% identifies an acceptable sampling procedure. Both these results allow the physician to use the obtained solutes concentrations for dose measurement. A mass balance error higher than 10% identifies an inappropriately high error during the sampling procedure; in this case, the obtained prefilter/postfilter/effluent concentrations should not be used for dose measurement. The concept of mass balance error cannot be applied if the membrane presents adsorption characteristics. In this case, the mass balance error is expected to be higher than 10%, not due to sampling errors but due to the loss of solute mass retained into the hemodiafilter.

Finally, the measured dose should be compared with the estimated dose. In particular, it is generally accepted that measured and estimated doses can be similar in small marker solutes during the early phase of treatment when membrane fouling has not yet occurred. In all other cases, the measured dose can be smaller than the estimated dose. In the absence of clinically relevant membrane adsorption properties, the measured dose cannot realistically be higher than the estimated dose. In the latter case, occurrence of an error should be hypothesized, either in the sampling or in the calculation process.

5 | CONCLUSIONS

Periodic dose assessment is crucial for dynamic dose adjustment and quality control of CRRT in critically ill patients with AKI. Methods currently used to estimate or measure transmembrane clearance are imprecise under certain clinical or technical conditions and often fail to provide clinical information relevant to adjusting extracorporeal treatment settings and improving patients' outcomes. Critical care physicians should be aware of these limitations. In particular, they should be able to select adequate marker solutes in accordance with the clinical scenario, perform correct sampling procedures depending on the adopted index of transmembrane removal, correctly apply formulas and calculate indexes, and perform quality control measures.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest with the contents of this article.

AUTHOR CONTRIBUTIONS

Corresponding author and has contributed to conceive and draft the article (manuscript concept, writing, editing of text, and approval of final manuscript): Villa

Contributed to draft the article (drafting article, editing of text, and approval of final manuscript): Fabbri, Samoni, Cecchi

Contributed to write and critically review the article and have approved the final version of the manuscript: Fioccola, Scirè-Calabrisotto, Mari, Pomarè Montin, Romagnoli.

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