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GUIDELINE

Recommendations for the timing and dosing of CRRT in critically ill patients with AKI

H.M. Oudemans-van Straaten[1], C.S.C. Bouman[2], M. Schetz[3], A.B.J. Groeneveld[4], A.C. de Pont[2], A.M. van Alphen[5], H. de Geus[6], W. Boer[7]

[1] Department of Intensive Care, VU University Medical Center, Amsterdam, [2] Academic Medical Center, Amsterdam, [3] Universitary Hospital Leuven, Belgium, [4] Erasmus Medical Center, Rotterdam, [5] Department of Nephrology, Maasstad Hospital, Rotterdam, [6] Erasmus Medical Center, Rotterdam, [7] Hospital Oost Limburg, Genk, Belgium

Correspondence

H.M. Oudemans-van Straaten – e:-mail: h.oudemans@vumc.nl

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Introduction

This guideline is part of the guideline for renal replacement therapy (RRT) in intensive care (IC) patients and concerns recommendations for the timing and dosing of continuous renal replacement therapy (CRRT) in IC patients with acute kidney injury (AKI). Below we present a summary of the guideline. The full version and a summary of appraised studies is presented on http://www.nvic.nl/. Intermittent hemodialysis is an alternative option for stable IC patients. However, the considerations that need to be made for the choice between continuous or intermittent treatment are beyond the scope of this guideline.

Considerations regarding the timing of initiation

Early initiation can improve metabolic homeostasis, volume balance and body temperature and thereby contribute to the stabilization of the circulation and improve clinical outcome. In contrast, early initiation may unnecessarily expose the patient to possible adverse effects associated with the treatment should renal function recover soon. Late initiation may contribute to worsening of the patient's condition as a result of metabolic disturbances, fluid accumulation and circulating uremic toxins.

The following aspects should be considered when timing CRRT:

- The etiology and short-term reversibility of the acute renal insufficiency. With persistent need of high dose vasopressors and continued exposure to other risks of AKI, renal function will likely not recover soon.
- Urinary output in the context of the patient's fluid balance and fluid needs.
- The severity and consequences of the fluid overload for the individual patient (e.g. gas exchange, tissue perfusion and cellular oxygen delivery).
- The severity of the metabolic disturbance and associated harm for the patient (e.g. consequences of acidosis and uremic toxicity on circulation, respiratory distress, inspiratory pressures, oxidant stress).
- The trend of renal function (a decreasing-upward or downward slope of the serum creatinine curve in time indicates improvement of function).
- Metabolic consequences of fluid removal. In contrast to the use of diuretics, ultrafiltration during CRRT allows the iso-osmotic removal of large amounts of fluids without inducing inevitable diuretic related disturbances of acid base and electrolyte balance.
- Costs and adverse effects. CRRT is a complex and expensive extracorporeal treatment with inevitable blood activation, needing catheter insertion and anticoagulation, and there are associated risks of bleeding, thrombosis and metabolic derangements.

Considerations regarding the dose

The dose of CRRT corresponds to effluent flow (dialysate+-filtrate volume for continuous hemodialysis or hemodiafiltration, CVVHD(F), or filtrate volume for continuous hemofiltration, CVVH), expressed per time and kilograms of body weight) (ml/kg/h). The large randomized studies used the body weight before ICU admission[1] or at randomization[2]. It should be noted that the dose of CRRT (25-45 ml/kg/h) is always less than normal renal function (120 ml/min). Dose should minimally be adequate to remove uremic toxins and metabolic acidosis[3]. The production of uremic toxins and metabolic acids is likely to be higher in hypermetabolic patients with sepsis, while the loss of beneficial substances, such as water soluble vitamins and drugs is also higher when CRRT dose is high.

Furthermore, delivered dose is always lower than prescribed dose. The so-called filter down-time is due to a delay in the exchange of bags, stagnation of flow due to access or circuit clotting, discontinuation of treatment due to interventions, investigations or the circuit change. Prescribed dose should be corrected for down-time, which is often 20-25%. In case of predilution, dose should further be corrected for the dilution of blood in the filter. Correction factor is (blood flow +ultrafiltrate flow)/blood flow.

Based on the available randomized controlled trials, there is currently no proof that a CRRT dose of 35 ml/kg/h, as was

recommended in the previous guideline, provides a better patient survival than a dose of 20-25 ml/kg/h. The benefit of a higher dose (35-45 ml/kg/h) as found in previous single center clinical trials[1,2] was not confirmed in the two recent large multicenter trials[3,4].
Furthermore, previous non-randomized clinical and animal studies suggested a benefit of early high volume hemofiltration in patients with severe septic shock on stabilization of the circulation[5]. However, a recent meta-analysis including randomized controlled trials and subgroups from randomized controlled trials could not show any benefit of CRRT versus no CRRT or a higher dose of CRRT in patients with severe sepsis or septic shock on survival, hemodynamics, pulmonary gas exchange, multiple organ dysfunction syndrome or length of stay[6]. The effect of CRRT on survival was not modified by CRRT dose. Finally, preliminary results of the multicenter IVOIRE study (http://www.clinicaltrials.gov), which compared hemofiltration doses of 35 ml/kg/h to 70 ml/kg/h in patients with septic shock, AKI, and multiple organ failure, do not show a survival benefit of the higher dose (personal communication). Therefore, the best available evidence does not support the routine use of high-volume CRRT in patients with severe sepsis or septic shock. However, CRRT is recommended in patients with AKI and metabolic derangement or diuretic-resistant fluid overload, and dose should be sufficient for the control of acidosis.

Appraisal of the literature and grading of the recommendations

We appraised the literature according to the guidelines of the NVIC (A-D), but decided to grade the recommendations (1-2) in agreement with the KDIGO Guidelines (http://www.kdigo.org/), which are derived from the GRADE classification[4], used in the sepsis guidelines. KDIGO is an acronym for *Kidney Disease Improving Global Outcomes*, an initiative of the National Kidney Foundation. In the KDIGO system there is room for giving a strong recommendation on clinical grounds while the level of evidence is low.
We finally based the grade of recommendation on the level of evidence in the literature, the physiological effects and the risks and costs of the treatment (see *table 1*).

Table 1. Grading of guideline recommendations

Grade of recommendation	Implications	Policy
Level 1 "We recommend"	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
Level 2 "We suggest"	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with his or her values and preferences.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.
No grade	Used, typically, to provide guidance based on common sense or where the topic does not allow adequate application of evidence.	

Recommendations

1. The timing of initiation of CRRT

Absolute indications

We recommend initiating CRRT immediately in patients with life-threatening AKI-related symptoms of fluid, electrolyte and acid-base balance (1C).

Relative indications

We suggest starting CRRT if, despite optimization of the circulation and other supporting interventions, the patient has AKI *and*

- persistent AKI-related metabolic derangements *and/or*
- severe diuretic-resistant fluid overload

if and when uremic complications and organ damage are expected to develop (2C).

Consider starting CRRT in a patient with AKI and AKI-related metabolic derangements

- before the patient is being exposed to new risk factors for AKI to improve his metabolic and fluid status and optimize his condition (no grading).

Do not apply RRT if

- AKI is mild (mild metabolic derangements) and probably transitory (2D);
- treatment is expected to be futile (no grading).

2. The dose of CRRT

We recommend delivering an effluent (filtrate+dialysate) dose of at least 20-25 ml/kg/h for CRRT in AKI. (IA)
We recommend compensating for a decrease of dose due to

- filter down-time;
- predilution.

We recommend assessing the actual delivered dose and adjust prescription to reach target. (1B)
CRRT dose can be increased individually to correct severe metabolic derangements more rapidly (no grading).

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