

Guidelines for timing, dose, and mode of continuous renal replacement therapy for acute renal failure in the critically ill.

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(See appendix)

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ABSTRACT

Objective

To provide evidence-based recommendations for clinical practice on timing, dose, and mode of CRRT in critically ill patients with ARF admitted to the ICU.

Methods

Literature search was done in Pubmed database for human studies. Studies were rated at five levels to create recommendations grades from A to E, grade A being the highest.

Conclusions

In critically ill patients with ARF it is recommended:

- to define ARF according to the RIFLE classification system into ARF_{risk}, ARF_{injury} and ARF_{failure}
- to base the decision when to start RRT not only on the severity of ARF, but also on the severity of other organ failure (grade E). Initiation of RRT is to be considered in oliguric patients (RIFLE_{risk-oliguria} or RIFLE_{injury-oliguria}), despite adequate fluid resuscitation, and/or a persisting steep rise in serum creatinine, in addition to persisting shock (grade E). RRT may be postponed when the underlying disease is improving, other organ failure recovering and the slope in the serum creatinine rise declines, in order to see if renal function is also recovering (grade E).
- to continue RRT as long as the criteria defining severe oliguric ARF (RIFLE_{failure-oliguria}) are present (grade E). If the clinical condition improves, it may be considered to wait before connecting a new circuit to see whether renal function recovers. RRT should be restarted in case of clinical or metabolic deterioration.
- to achieve a delivered (not prescribed) ultrafiltrate (dialysate) flow during CVVH(D) of 35 mL/kg/h in postdilution (grade A). A higher dose applied for a short period may be considered in sepsis/SIRS (grade E). The dose needs to be adjusted for predilution using the dilution factor, and for filter down time.
- In non-shock patients, continuous and intermittent treatments are equivalent regarding survival (level I). However, CRRT is recommended over IHD for patients with ARF who have, or are at risk for, cerebral oedema (grade C). CRRT is preferred in the management of patients with ARF and shock (grade E).
- CRRT should be applied in the venovenous mode (grade B)

HF in patients with sepsis or SIRS without ARF is not supported by enough evidence to be recommended in daily clinical practice.

INTRODUCTION

Up to now, there are no standard guidelines for the application of CRRT in critically ill patients with ARF. Practice patterns vary widely between individual centers [1,2]. CRRT for the critically ill patient with ARF was introduced in 1977 by Kramer et al. [3]. Since then, many studies have reported on CRRT in the critically ill, but for several reasons comparison among studies is difficult: Various treatment modalities have been applied in heterogeneous populations that differ not only in co-morbidities, but also in the clinical setting and underlying molecular biological mechanisms that initiate and maintain ARF. Furthermore, there are more than 35 definitions of ARF [4]. Recently a process of international consensus and evidence-based statements in the definition and management of ARF was proposed by the ADQI [5,6]. Aim of the present contribution is to provide evidence based recommendations for clinical practice on the timing, treatment dose, and mode of CRRT in critically ill patients admitted to the ICU. Anticoagulation strategies, substitution fluids, membranes and non-renal indications are beyond the scope of the present paper.

CONSENSUS DEFINITION OF ACUTE RENAL FAILURE

Figure 1 summarizes the ADQI consensus criteria for ARF [6]. ARF is classified into three levels: ARF_{risk}, ARF_{injury}, and ARF_{failure}, based on glomerular filtration rate or urine output criteria, whichever is more severe.

METHODS

Studies were identified using the MeSH terms *acute kidney failure* OR *acute renal failure* OR *shock* combined with the words *hemofiltration* OR *haemofiltration* OR *hemodialysis* OR *haemodialysis* in PubMed, from 1984 until March 2006, and by scanning the lists of publications found by database searches and on the ADQI workgroup findings at www.ADQI.net. Searches were limited to adult human studies and English language. The identified studies were eligible if they fulfilled the following criteria: (a) critically ill patients with ARF or SIRS, and (b) renal replacement therapy (RRT) with specified treatment characteristics including at least mode, dose and/or timing. We excluded studies on CAVH, molecular adsorbent techniques, and plasmapheresis. We also excluded studies applying haemofiltration during cardiac surgery and in patients with cardiac failure, because these studies specifically focus on the beneficial effects of fluid removal. We classified evidence and formulated recommendations according to evidence based medicine methodology (Table 1) [7]. Criteria for the qualification 'level I' and 'level II' with respect to the size of the RCT are not well settled. In the present review, we defined 'level I' studies to be those including at least 50 patients per randomized group.

TIMING

There is significant variation in the timing of initiation of RRT, with up to two-fold differences in the reported values of BUN, creatinine, or urine output at RRT initiation [8-11]. There are two RCTs [12,13], four non-randomized studies [14-17] and one observational study [18], investigating the effect of timing of RRT on mortality, and/or recovery of renal function in critically ill patients with documented ARF or in patients with sepsis/SIRS and imminent ARF (Table 2).

Acute renal failure

1. In a two-center RCT (n=106), in critically ill patients with oliguric ARF (diuresis of <180 mL in 6 hours, despite fluid resuscitation, inotropic support and high-dose diuretics), 28-day survival and recovery of renal function were not increased when CVVH was started early (within 12 hours after the onset of oliguria) as compared to late (urea of >40 mmol/L, and/or severe pulmonary oedema with PO_2/FiO_2 of <150 mm Hg and 10 PEEP cm H₂O) (level II) [12]. Of note, in this study, late was not as late as in earlier studies. Because of pulmonary reasons, nearly half of the patients in the late group started CVVH before serum urea reached 40 mmol/L. Median delay between the start of treatment and the development of oliguria was 42 hours.
2. A single-center, retrospective, non-randomized cohort study (n=100) in trauma patients, used BUN as a surrogate of 'timing of intervention' [16]. Survival was 39% in the early group (RRT started at a mean BUN of 42.6 mg/dl (15 mmol/L) compared with 20% in the late group (RRT started at a mean BUN of 94.5 mg/dl (34 mmol/L) (level III). However, this approach is likely to be seriously flawed, because BUN may reflect many factors other than time of initiation.
3. In a single-center retrospective cohort study in cardiac surgery patients, hospital mortality was higher in the late CVVH group (n=28) compared with the early CVVH group (n=36) (43% vs 22%, $p < .05$) (level IV) [15]. In the late group, CVVH was started on conventional reasons (urea of ≥ 30 mmol/L, creatinine of ≥ 250 μ mol/L, or potassium of ≥ 6.0 mmol/L despite glucose-insulin infusion), regardless of urine output. In the early group, CVVH was started when urine output was <100 mL within 8 hours, despite furosemide infusion.
4. In a single-center retrospective study in patients with ARF following cardiac surgery hospital mortality decreased after the introduction of early CVVHDF compared with a historical control group (23.5% vs 55%, $p=0.02$) [14]. In the early group (n=34), CVVHDF was started for oliguria (urine output of <100 mL within 8 hours), and in the late group (n=27), CVVHDF was started for conventional criteria (creatinine of >444 μ mol/L) (level IV).

Sepsis or SIRS

5. In a small RCT (n=37), in patients with severe pancreatitis without documented ARF, early CVVH (within 48 h after onset of abdominal pain) improved hemodynamics and short-term survival, compared with late CVVH (96 h after onset abdominal pain) (level II) [13].
6. In a single-center retrospective study (n=80) in patients with septic shock and oliguric ARF, the application of early CVVH improved hemodynamics, gas exchange, successful weaning, and 28-day survival compared with a historical

control group receiving conventional therapy (level IV) [17]. However, only 75% of the patients in the conventional group received CVVH, despite overt renal failure, and the applied dose was lower (20 mL/kg/h) than in the early treatment group (mean daily dose 30-35 mL/kg/h).

7. In the cohort study by Honoré et al., in patients with refractory septic shock, *post hoc* analysis showed an association between increased survival and earlier start of hemofiltration (level V) [18].

Discontinuation RRT

There are no clinical data on stopping criteria for RRT in critically ill patients with (recovering) ARF.

Discussion

In the above-mentioned studies there is a clear trend toward a better outcome with earlier timing of RRT. However, one small RCT did not confirm this trend. In the absence of large RCTs comparing early to late initiation of RRT, no firm overall recommendations for timing of RRT can be made. When initiation of RRT is considered, it is important to realize that the consequences of ureamic toxicity, metabolic acidosis and/or fluid overload are likely to be more severe in the critically ill patient. Moreover, renal function is unlikely to recover within a short period during persistent and severe failure of other organs. Furthermore, various inflammatory mediators are cleared by the kidney.

TREATMENT DOSE

The importance of 'adequacy of dialysis' is widely recognized in patients with ESRD; however, much less attention has been paid to the concept of 'adequacy of dialysis' in critically ill patients with ARF [19]. In IHD, dose is generally expressed as Kt/V [20], where K = clearance, t = treatment duration and V = the volume of distribution. In ESRD a minimum Kt/V of 1.2 thrice weekly should be delivered, a lower dose is associated with higher mortality [19]. However, higher doses may be beneficial in critically ill patients with ARF. In CRRT, treatment dose is generally expressed as filtrate volume/kg per time, for pure convective transport with postfilter replacement, and as Kt/V for other modalities. To calculate the treatment dose for predilution HF, the recommended ultrafiltrate rate should be multiplied by the dilution [21]. It is to be emphasized that dose quantification in acute RRT is not thoroughly validated and associated with numerous problems [21;22]. Recently, single pool Kt/V appeared to be a useful way to prescribe dose for different modalities of CRRT [23]. Moreover, dose estimates do not take into account differences between the pore size of membranes and mode. The middle molecular clearance is better when high cut off membranes are compared with low cut off membranes, and when haemofiltration is compared with hemodialysis. Furthermore, the removal of middle molecules declines when membranes are used for longer periods.

There are at present six RCTs (one applying IHD) [12,24-27], and one retrospective study [28], on the effect of renal replacement dose on mortality and recovery of renal function and/or physiologic endpoints, in critically ill patients with ARF (Table 3). After

the first observations of Gotloib et al. [29] on the beneficial effects of haemofiltration in the septic acute respiratory distress syndrome, four RCTs [13,30-32] and four observational cohort studies [18,33-36] evaluated the effects of dose of RRT in patients with SIRS without documented ARF.

Acute renal failure

1. In a RCT in 146 critically ill patients with ARF, survival (14 days after the last IHD session) was significantly higher in the patients treated with daily IHD compared with alternate day IHD [27] (level I). Patients with hepatorenal syndrome or cardiogenic shock were excluded from the study and treated with CRRT. Patient characteristics were comparable between groups. Daily IHD resulted in a better control of uraemia, fewer IHD related hypotension, and faster resolution of ARF, compared with alternate day IHD. In a multiple regression analysis, less frequent IHD was an independent risk factor for death. Unfortunately, although the prescribed dose of dialysis was 3.6 Kt/V per week in the alternate day group, the delivered dose was far less (about 3.0). All the surviving patients, except the two with Goodpasture's disease, had full recovery of renal function.
2. A positive association between survival time and ultrafiltrate dose was also described in a large (n=425) RCT in patients with multiple organ failure, and ARF, treated with CVVH [26] (level 1). Small, but significant differences were present for age, APACHE II score, and BUN levels at baseline. Survival, 15 days after discontinuation of CVVH, was significantly lower in the group receiving 20 mL/kg/h (41%), compared with the higher volume groups receiving 35 mL/kg/h (57%) and group 45 mL/kg/h (58%). The difference in the duration of CVVH, and the rate of renal recovery were not significantly different among the survivors of the three groups.
3. In a RCT in 206 critically ill patients with ARF, 28-day survival was significantly increased in the group receiving a higher replacement dose by adding a dialysis dose to CVVH [32]. Renal recovery rate among survivors was comparable between the high dose CVVHDF group and the low dose CVVH group.
4. An association between survival time and ultrafiltrate dose was not found in a smaller RCT (n=106) in critically ill, ventilated patients with shock and oliguric ARF (level II) [12]. The patients were randomized into three groups: early high-volume hemofiltration (EHV, 72-96 L/24h), early low-volume hemofiltration (ELV, 24-36 L/24h), and late low-volume hemofiltration (LLV, 24-36 L/24h). Early treatment started within 12 hours after the onset of oliguria, and late when the patient fulfilled the conventional criteria for RRT (as in paragraph on timing). The 28-day survival was 74.3% in EHV, 68.8% in ELV and 75% in LLV (p=0.80). All hospital survivors had recovery of renal function.
5. In a RCT in 70 patients with ARF secondary to severe malaria or sepsis, the risk of death was higher in the group receiving peritoneal dialysis (70 L/day) compared with the group receiving CVVH (25 L/day) [25] (level II). The estimated Kt/V per week of 5.5 in the CVVH group was comparable to the low intensity groups in the studies of Ronco et al. [26] and Bouman et al. [12]. Unfortunately, the authors did not report the measurements necessary to calculate effective Kt/V in the peritoneal dialysis, but we can speculate that it was lower than in the CVVH group because the peritoneal dialysis group had

a lower rate of resolution of acidosis and a slower rate of decline in plasma creatinine levels.

6. In a crossover study that compared high-volume (6 L/h) with low-volume CVVH (1 L/h) in 11 septic shock patients with ARF, the dose of norepinephrine required for the maintenance of target MAP decreased more during high-volume CVVH than during low-volume CVVH ($p=0.02$) (level II) [24].
7. In a non-randomized prospective interventional pilot study ($n=56$), Brause et al. [28] compared very low-volume CVVH (1 L/h), with low-volume CVVH (1.5 L/h), and assessed the effect on the daily Kt/V. As expected the 1.5 L/h group achieved a higher Kt/V (0.80 per day versus 0.53 per day) and better control of ureamia and acid base (level III). Mortality was high in both groups (73% and 69%, $p=NS$), but the study was not powered for survival as an endpoint.

Sepsis or SIRS

1. In a small ($n=24$) RCT in patients with early septic shock or organ dysfunction, CVVH at 2 L/h did not affect clinical outcome compared with no CVVH (level II) [30]. The study was not powered for survival as an endpoint.
2. In a small RCT in 37 patients with severe pancreatitis, hemodynamics and short term survival rate improved more during high-volume CVVH (4 L/h) compared to low-volume CVVH (1 L/h) (Level II) [13]. The study was not powered for survival as an endpoint.
3. In a RCT in 61 patients after cardiac arrest, very high-volume HF (100 L in 8 hours) with, or without hypothermia significantly increased 6-months survival compared with standard care (level II) [31].
4. In a large observational study ($n=306$) in critically ill patients receiving CVVH (100 L/day) mortality was significantly lower (33%) than predicted by APACHE II (76%) and SAPS II (71%) illness severity scores [34].

Improved hemodynamics and increased survival were also reported in four smaller cohort studies (level IV) in:

5. Patients with intractable septic shock ($n=20$) treated with short-term very high-volume HF (35 L in 4 hours) [18].
6. Patients with septic shock ($n=24$) treated with high-volume CVVH (40-60 mL/kg/h) [33].
7. Patients with severe sepsis treated with pulse very high-volume HF (85 mL/kg/h for 6-8 hours) [35].
8. Patients with severe septic shock treated with short-term very high-volume HF (100 mL/kg/h for 12 h) [36].

Discussion

In some of the above-mentioned studies, Kt/V in the low-volume groups was extremely low, even lower than the Kt/V currently recommended for chronic dialysis [25,27,28] and nearly as low as the dose in earlier CAVH studies yielding a mortality rate of 80%. From the foregoing, it can be concluded that delivered RRT dose should not be too low. The highest evidence indicates a recommended dose of at least 35-45 mL/kg/h for CVVH(D) [26,32] and daily sessions for IHD [27]. The 35 mL/kg/h dose corresponds to a single pool Kt/V of 1.4 per day [23]. In contrast, a smaller RCT, suggests that 1.5 L/h (~ 20 mL/kg/h) is as good as 4 L/h (~55 mL/kg/h) [12]. The

differences in outcome of the randomized studies may result from differences in case mix, ICU format, membrane, substitution fluid or concomitant treatment [37]. There are three multicenter RCTs underway looking at dose of RRT in ARF: The Acute Renal Failure Trial Network (ATN) Study in the US run by Palevsky [38], The Renal Study in Australia and New Zealand run by Bellomo [39], and the IVOIRE study in Europe run by Joannes-Boyau [40]. It is to be emphasized that in daily clinical practice the prescribed ultrafiltrate flow should be adjusted, in order to achieve the intended delivered ultrafiltrate flow.

Evidence for a beneficial effect of (short-term) high, or very-high volume in patients with SIRS/sepsis and imminent or no ARF is still low. The studies are not randomized or underpowered for survival [13,31]. Low-volume (2 L/h) CVVH [30] seems to have no positive effects in patients with sepsis/SIRS and imminent ARF (level II).

MODES OF ACUTE RENAL REPLACEMENT THERAPY

In the ICU, renal replacement therapies are primarily limited to conventional IHD and CRRT. During IHD, intensive dialysis is performed for 3-4 hours at variable intervals, whereas during CRRT, continuous and gradual removal of fluid and toxins is provided at lower blood flow. More recently several hybrid therapies [41] have been described, with a treatment duration between CRRT and conventional IHD, (ie extended dialysis [42], sustained low-efficiency dialysis [43], short-term HF [18] or pulse HF [35]).

The nomenclature and definitions of the various CRRT techniques are based on their operational characteristics [44] (Table 4).

Haemodialysis and haemofiltration are the two main principles of solute transport of CRRT.

During haemodialysis, removal of solutes is driven by diffusion (solute transport across a semi-permeable membrane generated by a concentration gradient). During haemofiltration, removal of solutes is based on convection (water and solute transport across a semi-permeable membrane generated by a pressure gradient). There are no data showing any given modality as superior with regard to clinical outcomes. Haemofiltration resembles most the principle of glomerular filtration and increases the middle molecule clearances [45]; however, whether this is beneficial in ARF is unknown. Factors that may affect current practice include local availability of equipment, fluids and costs.

CRRT is applied either in the arteriovenous (driving force is patient's blood pressure and flow) or venovenous mode (driving force is external pump). Advantages of the arteriovenous therapies include ease of set-up and operation and low extracorporeal blood volumes. Disadvantages of arteriovenous therapies include the prolonged arterial cannulation, the requirement of a MAP of >60 mm Hg to maintain circuit blood flow, and the low blood flows that can be achieved. Advantages of the venovenous therapies are the decreased risk of vascular damage as compared to the arteriovenous therapies, the ability to maintain blood flow independent of MAP, the ability to achieve higher blood flow rates and clearances (level III) [46,47]. The higher clearances associated with better survival [26] cannot be achieved without the introduction of a blood pump. The use of blood pumps has increased the complexity

of CRRT systems, but in clinical practice this disadvantage does not counterbalance the advantages, and there is general consensus that venovenous systems are the modality of choice [46-49].

CRRT vs conventional IHD

One of the most pressing clinical questions regarding the use of CRRT is whether CRRT offers an important advantage over IHD, regarding survival and/or recovery of renal function. The effects of IHD versus CRRT on survival and/or recovery of renal function were reported in five prospective RCTs [50-54] and two meta-analyses [55,56].

1. In a large multicenter RCT (n=160) CVVHDF showed no survival (ICU and hospital) advantage compared with alternate day IHD after adjustment for severity of illness (level I) [52]. However, CRRT was associated with a significantly higher rate of complete renal recovery in surviving patients who received an adequate trial of therapy, without crossover to IHD (CRRT 92.3% vs IHD 59.4%, $p < .01$). Of notice, in this study patients were excluded when MAP was <70 mm Hg in the 8 hours preceding randomization. Furthermore, significant baseline differences in severity of illness existed between groups and the delivered dialysis dose per group was not reported, making comparison difficult.
2. In a large multicenter RCT (n=224) septic patients were randomized to receive either IHD or CVVHDF with the same polyacrylonitrile membrane and bicarbonate buffer [54]. The 60-day survival was 23,5% in the CVVHDF group and 28,6% in the IHD group ($p=0.23$) (level I)
3. In a single-center RCT (n=125) patients were randomized into CVVHDF or daily IHD treatment [53]. IHD was started gently with a low blood flow and small hemofilter and removing small amounts of fluid, to avoid haemodynamic instability. The treatment doses were comparable between groups. Hospital mortality was 47% in the CVVHDF group and 51% in the IHD group ($p = 0.72$). Unfortunately, the study was underpowered due to the pre-terminal end and the smaller than expected number of patients included (level II).
4. A single-center RCT (n=80) that compared CVVHD with alternate day IHD showed no survival or renal recovery advantages between groups, despite a significant decrease in MAP for patients on IHD therapy not seen in those on CVVHD therapy (level II) [50]. However, the study was not sufficiently powered for survival as an endpoint.
5. A single-center RCT (n=104) showed no differences in survival or MAP between patients receiving CVVH and patients treated with daily IHD (level II) [51]. Again, this study was not adequately powered to detect small differences between modalities. Furthermore, the majority of patients (n=33) in the CVVH group were treated with low-volume CVVH (18 mL/kg/h) and this may also have adversely affected the outcome in the CVVH group.
6. Kellum et al. [55] performed a metaanalysis, including 13 studies (n=1400) comparing CRRT with IHD, and did not find a statistically significant impact of dialysis modality on survival and renal recovery in haemodynamic stable patients (level I).

7. Tonelli et al. [56] included six studies in their metaanalysis (n=624) and concluded that in unselected critically ill patients with ARF, CRRT does not improve survival or renal recovery (level I).
8. In a large (n=839) prospective, multicenter cohort study mortality was comparable between the patients undergoing IHD and the patients undergoing CRRT, however patients undergoing IHD had lower Logistic Organ Dysfunction Scores (level III) [57].
9. Likewise, in another large (n=587) observational prospective multicenter study RRT was not found to have any prognostic value [58]; however, patients selected for CRRT had a higher number of organ dysfunction at admission and at the time of ARF (level III).
10. Two smaller observational studies [59,60] reported improved survival with CRRT, even though CRRT patients were sicker at baseline (level III).
11. Two retrospective studies [61,62] in critically ill patients with ARF showed comparable mortality between the IHD group and the CRRT group, but patients with severe illness were preferentially selected for CRRT (level IV).

Discussion

None of the level I or level II studies showed a survival advantage for CRRT as compared with conventional IHD [50-56]. However, the largest RCT [52] suggest that CRRT is associated with increased complete renal recovery (level I). Although most of the studies did not report on the delivered treatment dose per group, none of the studies seem to have achieved the higher dose associated with a better survival in the CRRT studies [26,32]. The study of Mehta et al. [52], suggests that there is a physician's bias for CRRT being the treatment of choice for patients in shock and this was also suggested in numerous prospective observational and retrospective studies [57-62]. Indeed, beneficial effects on cardiovascular stability, cerebral edema and intestinal acidosis have been reported during CRRT therapy in comparison with conventional IHD [50;63-67] (level II). On the other hand, the study of Uehlinger et al. [53], suggests that haemodynamic instability during IHD can be avoided even in unstable patients, as long as gentle IHD is applied (daily sessions using low blood flow, small surface filter and discrete fluid removal).

FINAL RECOMMENDATIONS

Because of the quality of the studies recommendation grades are low. Comparison among the studies is complicated by the use of various definitions of ARF. Furthermore, strategies of timing, dose and RRT mode are likely to interact. However, most of the studies only investigate one of these items and do not report on the others, making it difficult to draw firm conclusions.

The below recommendations concern critically ill patients with ARF

- It is recommended to define ARF according to the RIFLE classification system into ARF_{risk}, ARF_{injury} and ARF_{failure}.
- It is recommended to base the decision when to start RRT not only on the severity of ARF, but also on the severity of other organ failure (Grade E). Initiation of RRT is to be considered in oliguric patients (RIFLE_{risk-oliguria} or RIFLE_{injury-oliguria}), despite adequate fluid resuscitation, and/or a persisting steep rise in serum creatinine, in addition to persisting shock (Grade E). RRT may be postponed when the underlying disease is improving, other organ failure recovering and the slope in the serum creatinine rise declines, in order to see if renal function is also recovering (Grade E).
- It is recommended to continue RRT as long as the criteria defining severe oliguric ARF (RIFLE_{failure-oliguria}) are present (grade E). If the clinical condition improves, it may be considered to wait before connecting a new circuit to see whether renal function recovers. RRT should be restarted in case of clinical or metabolic deterioration.
- The recommended delivered (not prescribed) ultrafiltrate (dialysate) flow during CVVH(D) is 35 mL/kg/h in postdilution (Grade A). A higher dose applied for a short period may be considered in sepsis/SIRS (grade E). The dose needs to be adjusted for predilution using the dilution factor, and for filter down time.
- In non-shock patients, continuous and intermittent treatments are equivalent regarding survival (level I). However, CRRT is recommended over IHD for patients with ARF who have, or are at risk for, cerebral oedema (Grade C). CRRT is preferred in the management of patients with ARF and shock (Grade E).
- CRRT should be applied in the venovenous mode (Grade B)

HF in patients with sepsis or SIRS without ARF is not supported by enough evidence to be recommended in daily clinical practice.

SAMENVATTING AANBEVELINGEN

De aanbevelingen hebben betrekking op de ernstig zieke IC patiënt met acute nierinsufficiëntie.

- Het advies is om acute nierinsufficiëntie volgens het RIFLE classificatie system te definiëren in de categorieën ARF_{risk}, ARF_{injury} and ARF_{failure}
- Het advies is om de beslissing om met nierfunctie vervangende therapie (NVT) te beginnen niet alleen te laten afhangen van de ernst van het acute nierfalen maar ook van de ernst van het overig orgaanfalen (niveau E). Starten van RRT kan worden overwogen bij oligure patiënten (RIFLE_{risk-oliguria} of RIFLE_{injury-oliguria}), en/of bij patiënten met een aanhoudende snelle stijging in het kreatinine gehalte in combinatie met aanhoudende shock (niveau E). Uitstel van NVT kan worden overwogen indien de onderliggende ziekte aan het verbeteren is, overig orgaan falen herstellende en het kreatinine gehalte aan het aftoppen is, om te zien of de nierfunctie ook herstellende is (niveau E).
- Het advies is om de NVT voort te zetten zolang er voldaan wordt aan de ernstige oligurie criteria (RIFLE_{failure-oliguria}) (niveau E). Men kan overwegen het aansluiten van een nieuw circuit uit te stellen indien de klinische conditie aan het verbeteren is om te beoordelen of de nierfunctie ook aan het herstellen is.
- Het advies is om tijdens CVVH(D) in postdilutie daadwerkelijk een ultrafiltraat (dialysaat) flow van 35 mL/kg/h te geven (niveau A). Bij sepsis/SIRS kan men overwegen gedurende korte tijd te behandelen met een hogere ultrafiltraat flow (Niveau E). De dosis moet worden gecorrigeerd voor predilutie met de verdunnings factor en voor de uren dat de filtratie (dialyse) niet loopt.
- Bij patiënten zonder shock is geen verschil in overleving aangetoond tussen continue en intermitterend behandeling (level I). Echter, bij patiënten met hersenoedeem of een verhoogd risico hierop wordt CRRT aanbevolen (niveau C). Continue behandelingen verdienen de voorkeur bij patiënten met shock (niveau E).
- Voor continue behandelingen moeten venoveneuze technieken worden toegepast (niveau D)

Er bestaat onvoldoende bewijs om HF te adviseren bij patiënten met sepsis of SIRS zonder acute nierinsufficiëntie.

List of abbreviations.

ARF ADQI: acute dialysis initiative
APACHE: acute physiology and chronic health evaluation
ARF: acute renal failure
BUN: blood urea nitrogen
CAVH: continuous arteriovenous haemofiltration
CRRT: continuous renal replacement therapy
CVVH: continuous venovenous haemofiltration
CVVHD: continuous venovenous haemodialysis
CVVHDF: continuous venovenous haemodiafiltration
ESRD: end stage renal disease
ICU: intensive care unit
IHD: intermittent haemodialysis
Kt/V: fractional clearance (K=clearance, t=time, V=volume)
MAP: mean arterial pressure
RCT: randomized controlled trial
RIFLE: Risk Injury Failure Loss End stage kidney disease
RRT: renal replacement therapy
SAPS: simplified acute physiology score
SIRS: systemic inflammatory response syndrome

Appendix

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Table 1. The guidelines of Evidence-Based medicine's rating system for strength of recommendation and quality of evidence [7].

Rating system for references	
Level I	Large randomized trials with clear-cut results; low false positive (α) or false negative (β) error. Meta-analysis with low false positive (α) or false negative (β) error.
Level II	Small, randomized trials with uncertain results; high false positive (α) or negative (β) error. Meta-analysis with high false positive (α) or false negative (β) error.
Level III	Nonrandomized, contemporaneous control.
Level IV	Nonrandomized, historical controls.
Level V	Case series, uncontrolled studies and expert opinion.
Rating system for recommendations	
Grade A	Supported by at least two 'level I' investigations.
Grade B	Supported by only one 'level I' investigation.
Grade C	Supported by 'level II' investigations only.
Grade D	Supported by at least one 'level III' investigation.
Grade E	Supported by 'level IV' or 'level V' investigations only.

Table 2. Clinical studies evaluating the timing of initiation of CRRT in critically ill patients

	Study design [no.patients]	Clinical setting	Definition of timing	Confounding CRRT factors	Survival advantage early group	Level of evidence
Bouman [12]	RCT [105]	oliguric ARF and MOF	Early: < 12 h after onset oliguria (<180 mL in 6 h) Late: urea > 40 mmol/L or severe pulmonary edema ^{a)}	no	no	II
Jiang [13]	RCT [37]	Severe pancreatitis	Early: < 48 h after onset abdominal pain. Late: > 96 h after onset abdominal pain	no	yes	II
Gettings [16]	Retrospective [100]	Post trauma	Early: urea of <60 mg/dl ^{b)} Late: urea of ≥60 mg/dl	Dose not reported	yes	III
Piccini [17]	Retrospective [80]	Sepsis with oliguric ARF and ALI	Early: < 12 h after ICU admission. Late: urea >35 mmol/L, sCr >600 µmol/L	Dose early >> dose late	yes	IV
Elahi [15]	Retrospective [64]	ARF after cardiac surgery	Early: oliguria (<100 mL in 8 h) Late: urea >30 mmol/L, sCr >250 µmol/L,	Dose not reported	yes	IV
Demirkilic [14]	Retrospective [61]	ARF after cardiac surgery	Early: oliguria (<100 mL in 8 h) Late: SCr > 5 mg/dL ^{c)}	Dose not reported	yes	IV
Honore [18]	Cohort [20]	Severe septic shock	Early: refractory septic shock	HF, 35 L in 4 h	yes	IV

CRRT continuous renal replacement therapy; ARF, Acute renal failure; ALI, acute lung injury; sCr, serum creatinine; HF hemofiltration;

^{a)} pO₂/FiO₂ < 150 mm Hg and 10 PEEP cm H₂O; ^{b)} 21 mmol/L; ^{c)} 420 µmol/L.

Table 3. Comparison of randomized controlled trials on the effect of renal replacement dose on mortality and recovery of renal function

Study [Ref]	Randomization (number of patients)	Mean Delivered dose		Survival (%)	p	ARF in days (mean)	p	Evidence Level
		mL/kg/h	Kt/V per week					
				<i>Day 14 after end IHD</i>				
Schiffli [27]	Alternate day IHD (72) Daily IHD (74)		3.0 5.8	46 28	0.01	16 9	.001	I
				<i>Day 15 after end CVVH</i>				
Ronco [26]	CVVH 20 mL/kg/h (146) CVVH 35 mL/kg/h (139) CVVH 45 mL/kg/h (140)	19 34 42	5.3 9.5 11.8	41 57 58	0.008	11 13 12	N.S.	I
				<i>Day 28 after inclusion</i>				
Saudan [32]	CVVH 25 mL/kg/h (102) CVVHDF 42 mL/kg/h (104)	22 34	6.2 9.4	39 59	0.03	Not reported		I
				<i>Day 28 after inclusion</i>				
Bouman [12]	ELV 1,5 L/h (35) LLV 1,5 L/h (35) EHV 4 L/h (36)	20 19 48	5.6 5.3 13.4	69 75 74	0,8	8,6 11,6 8,6	.55	II
				<i>ICU survival</i>				
Phu [25]	PD (36) CVVH 25 L/day (34)		<< 5,5 5,5	53 85	0.005	Not reported		II
				<i>Day 14 after start CVVH</i>				
Jiang [13]	ELV 1 L/h (9) LLV 1 L/h (10) EHV 4 L/h (9) LHV 4 L/h (9)	Not reported		HV 68 LV 89 E 84 L 74	<0.01 <0.05	Not reported		II

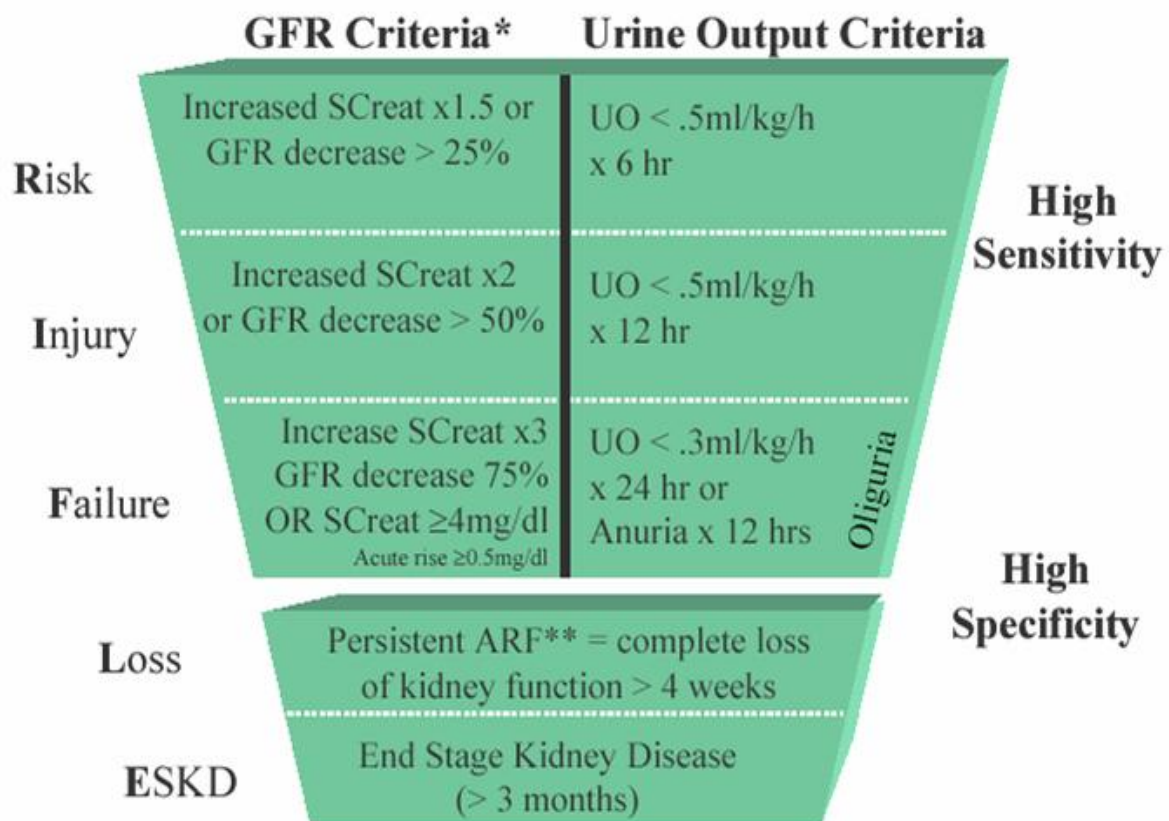
IHD, intermittent hemodialysis; CVVH, continuous venovenous hemofiltration; CVVHDF, continuous venovenous hemodiafiltration; ELV, early low-volume hemofiltration, LLV, late low-volume hemofiltration; EHV, early high volume hemofiltration; LHV, late high-volume hemofiltration; Kt/V, clearance times duration of treatment divided by volume of distribution; ARF acute renal failure; HV, high volume; LV, low volume; E. early; L, late.

Table 4. Modes of CRRT

	Solute transport	Blood flow (mL/min)	Ultrafiltrate flow (mL/min)	Dialysate flow (mL/min)	Clearance (L/24h)
Slow continuous ultrafiltration	No	50 – 100	1 - 2	No	no
Continuous arteriovenous or venovenous hemofiltration (CAVH or CVVH)	Convection	50 -200	8 - 66	No	12 - 96
Continuous arteriovenous or venovenous hemodialysis (CAVHD or CVVHD)	Diffusion	50 -200	2 - 3	10 - 20	14 - 36
Continuous arteriovenous hemodiafiltration or venovenous hemodiafiltration (CAVHDF or CVVHDF)	Convection and diffusion	50 -200	8 - 12	10 - 20	20 - 40
Continuous arteriovenous or venovenous high flux dialysis (HDF)	Convection and diffusion	50 -200	2 - 8	50 - 200	40 - 60

Figure 1.

The RIFLE Classification for acute renal failure [6]. (With approval of the ADQI)



SCreat, serum creatinine (4 mg/dL = 354 mmol/L, 0.5 mg/dL = 44 mmol/L);
GFR, glomerular filtration rate; UO, urine output; ARF, acute renal failure;
ESKD, end stage kidney disease;

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