Renal replacement therapy in critically ill patients: who, when, why, and how

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Purpose of review
The increasing incidence of acute kidney injury has the immediate effect of a growing need for renal replacement therapy (RRT). Shedding light on the questions of who, when, why, and how RRT should be performed is difficult to accomplish because of ambiguous study results, poor quality evidence, and low standardization.

Recent findings
Critically ill patients are exposed to multiple factors known to deteriorate kidney function. Especially severe fluid overload is strongly associated with worse outcome and may be considered as a trigger for initiating RRT. In the absence of life-threatening complications, a strategy of early initiation of RRT might be most advantageous keeping in mind the potential adverse effects of RRT. By providing better hemodynamic stability and superior control of fluid balance continuous RRT is the first choice therapeutic tool as compared with intermittent techniques. The femoral and jugular veins are the preferred insertion sites for temporary catheters. Although data are still weak, there is some preliminary evidence that regional citrate anticoagulation is superior to systemic heparinization.

Summary
The best management of RRT is still a subject of controversy. Continuous RRT with regional citrate anticoagulation via a temporary catheter in a jugular vein is the recommended first choice treatment option in critically ill patients with acute kidney injury.

Keywords
acute kidney injury, anticoagulation, critically ill patients, initiation, kidney disease: improving global outcomes guidelines, renal replacement therapy

INTRODUCTION

Acute kidney injury (AKI) has increasingly been diagnosed over the last two decades [1]. Approximately, 22–57% of critically ill patients develop AKI during their hospitalization [1,2]. The high incidence can be attributed to an ever ageing population, associated multimorbidity, high illness acuity, and a growing number of highly invasive medical procedures, whether they are surgical or interventional. The rising need for renal replacement therapy (RRT) further underlines the significance to optimize the quality and reliability of this technique [3–5]. The kidney disease: improving global outcomes (KDIGO) guidelines for AKI, which were published in 2012, diagnose AKI through serum creatinine elevations and decrease in urine output over a certain period of time and give concrete suggestions on how to manage RRT [6], but evidence remains limited and inconclusive because of a lack of large high-quality randomized controlled trials (RCTs) resulting in a wide variability of clinical practice patterns.

The purpose of this review is to outline current knowledge and discuss recent advances aimed at managing RRT in critically ill patients with AKI.

WHO

In critically ill patients, the development of AKI exacerbates the clinical disease course resulting in worse short and long-term patient-centered outcomes, including chronic kidney disease [7–10], sepsis [11,12], gastrointestinal bleeding [13], cardiovascular events [14,15], stroke [16], malignancy [17], fractures

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KEY POINTS

- Severe fluid overload is strongly associated with mortality and is the most important trigger to initiate RRT.
- Early initiation of RRT may reduce mortality.
- There is no evidence that a higher dose of RRT improves survival.
- In hemodynamically compromised patients CRRT is the preferred technique to deliver RRT.
- Jugular and femoral sites are the preferred localizations for the placement of temporary dialysis catheters.
- Evidence is low whether RCA outperforms SHA with regard to patient-centered outcomes.

[18], and death [2,8,19,20]. Typically, AKI is a consequence of multiple etiologic factors. Comorbidities (e.g., higher age, chronic kidney disease, diabetes) and acute clinical conditions (sepsis, major surgeries, mechanical assist devices, positive pressure ventilation, vasopressor therapy) facilitate the development of AKI [21▪▪]. Additionally, critically ill patients are often exposed to nephrotoxic agents (aminoglycosides, vancomycin, contrast agents, and hypnotics), further increasing the likelihood of AKI [6,22].

RRT is still the gold standard for treating patients suffering from severe AKI, and beyond, it is the only reliable therapeutic option. Apart from its detoxification function, the primary goals of RRT are the achievement and maintenance of electrolyte, acid–base, and fluid balance. In particular, the deleterious effects of fluid overload have become apparent over the last two decades. The association of the degree of fluid overload at the time of RRT initiation and mortality has first been characterized in pediatric patients [23]. This association could also be demonstrated in critically ill adults in a variety of settings [24,25▪▪,26–28]. A fluid accumulation of more than 10% of the body weight during the ICU admission was strongly associated with higher mortality rates [28]. Moreover, fluid accumulation has been shown to worsen oxygenation during mechanical ventilation [29]. The extent of fluid overload appears as a reasonable criterion for the initiation of RRT.

WHEN

Initiation of renal replacement therapy

The KDIGO guidelines recommend to start RRT emergently in case of life-threatening complications such as severe changes in fluid, electrolyte, and acid–base balance, or in case of progressive decline of renal function and concurrent serious worsening of the patients' clinical condition [6]. In fact, this can be read the other way: In the absence of life-threatening complications, the decision when to initiate RRT remains at the discretion of the attending intensivist and is subject to his individual experiences and preferences. The controversial issue of an early vs. late initiation strategy of RRT has recently attracted much attention. Theoretically, both conflicting views, early and late, have their pros and cons. The tight control of fluid balance, electrolyte, and acid–base homeostasis requires early initiation as imbalances are strongly associated with worse outcome [27,28]. However, RRT is not without complications (catheter-related bloodstream infections, catheter insertion complications, hemodynamic instability) and represents a tremendous therapeutic escalation.

Just recently, the early versus late initiation of renal replacement therapy in critically ill patients with acute kidney injury trial (ELAIN) [30▪▪] and the artificial kidney initiation in kidney injury trial (AKIKI) [31] trial have been performed to more explicitly analyze the effect of early vs. late initiation of RRT. The ELAIN trial compared initiation of RRT at KDIGO stage 2 (early group) vs. initiation at KDIGO stage 3 (late group). The authors implemented an inclusion strategy which combined clinical criteria of AKI progression and a biomarker model to reduce the danger to include patients, who would recover spontaneously without RRT from AKI. In the ELAIN trial, the early group showed both improved survival and better renal recovery rates as compared with the late group. The AKIKI trial compared a strategy of initiation of RRT at KDIGO stage 3 (early) with KDIGO stage 3 and clinical indication (late) and did not demonstrate a difference in mortality. But, only 51% of the patients in the late group received RRT. That means that 49% of the patients in the late group spontaneously recovered from AKI without requiring RRT. If the patients in the late group, who received RRT, were analyzed separately, mortality in the late group was significantly higher than in the early group. Recently, Park *et al.* performed a multicenter cohort study in 607 patients and divided early and late groups based on the median 6-h urine output immediately prior to RRT initiation (early: urinary output $\geq$0.24 ml/kg/h), late: urinary output $<$0.24 ml/kg/h) [32]. The results showed a significantly improved survival in the early group ($P < 0.01$). Several meta-analyses on this issue remained contradictory [33,34]. Anyhow, because of the various definitions of early and late, included studies show a high heterogeneity and limited interpretability of the results. Two large RCTs

(NCT01682590 and NCT02568722) are currently underway. The Initiation of Dialysis EArly Versus deLayed-ICU trial compares a strategy of early initiation of RRT (within 12 h after diagnosing AKI stage 'F' according to the risk, injury, failure, loss, end-stage (RIFLE) classification) with deferred initiation of RRT (48–60 h after the diagnosis of RIFLE 'F') with mortality as the primary outcome. The Standard vs. Accelerated Initiation of RRT-AKI trial compares standard (guided by the presence of one or more predefined clinical indications) and accelerated RRT initiation strategies (within 12 h after modified KDIGO stage 2). Hopefully, these large trials will add further important insights to address this knowledge gap. It would be helpful, if the design of future studies would integrate the measurement of newly developed biomarkers. Such an approach allows a more effective prognostication of AKI progression and better prediction of dialysis-dependent renal failure [35,36].

Discontinuation of renal replacement therapy

Data on the optimal timing of RRT discontinuation are scarce. Wu *et al.* [37] performed a retrospective observational case–control trial aiming to identify risk factors for redialysis in patients with postoperative AKI. The authors found larger declines in sequential organ failure assessment score and increases in urine output in patients with successful RRT cessation [37]. Uchino *et al.* [38] performed a post hoc analysis and found significantly lower hospital mortality rates in patients with successful RRT discontinuation. The predictive ability of urine output was negatively affected by the use of diuretics. Receiver operating characteristic analysis revealed that a urine output of 400 ml/d without the use of diuretics was equivalent to an output of 2.330 ml with diuretics with respect to the sensitivity and specificity of successful RRT termination. Daily urea excretion and 2 and 24 h creatinine clearance correlated in other studies with the success rate of RRT weaning [39▪,40,41].

The perspective that furosemide might improve renal recovery after RRT received a strong damper by Van der Voort *et al.* [42] who conducted a RCT. The authors were unable to demonstrate differences in renal recovery or duration of AKI. As already mentioned a strategy based on urinary biomarkers might be an option to more accurately define the optimal timing of RRT discontinuation in forthcoming studies.

WHY

The primary goals of RRT in AKI are usually fluid and solute removal. The dose on the basis of urea kinetics is typically used to measure the efficacy of RRT in AKI. For intermittent techniques, urea clearance is expressed via fractional urea clearance (Kt/V_{urea} = a dimensionless index of dialysis dose in which K is the urea clearance of the dialyzer, t is the duration of dialysis and V is the volume of distribution of urea). For continuous techniques, the clearance of small solutes corresponds to the delivered effluent rate: ultrafiltrate in continuous venovenous hemofiltration, consumed dialysate in continuous venovenous hemodialysis and the sum of ultrafiltrate, and consumed dialysate in continuous venovenous hemodiafiltration.

Based on findings in patients receiving treatment with chronic hemodialysis, it has been suggested that the delivery of higher doses of RRT is associated with better outcomes in patients suffering from AKI [43]. The results from initial prospective trials have confirmed this suggestion and demonstrated an improved survival with high-dose dialysis [43,44]. These observations could not be confirmed by rigorous multicenter RCTs [45–47]. In the large multicenter acute renal failure trial a strategy of intensive (intermittent technique, six times/week or continuous techniques with prescribed effluent rate of 35 ml/kg/h) vs. less intensive RRT (intermittent technique, three times/week or continuous techniques with prescribed effluent rate of 20 ml/kg/h) was compared [45]. Hemodynamically compromised patients were treated with continuous (CRRT) or prolonged intermittent RRT (PIRRT). Patients who were hemodynamically stable received intermittent hemodialysis (IHD). The results showed no differences in all-cause mortality, rate of renal recovery, duration of RRT, or development of nonrenal organ failure between both study groups. However, the study did not make a formal distinction between the different RRT techniques, and treatment intensities were assigned independent of the particular approach. Another study, the randomized evaluation of normal versus augmented level trial, compared two intensities of CRRT: higher intensity (prescribed effluent volume of 40 ml/kg/h) vs. lower intensity (prescribed effluent volume of 25 ml/kg/h) [46]. The results showed no differences in mortality, renal recovery, or in the occurrence of nonrenal organ failure. This was also confirmed by the DOse REsponse Multicentre International trial study group which compared three groups of CRRT intensities (least intensive (<20 ml/kg/h) vs. less intensive (21–34 ml/kg/h) vs. higher intensive dose treatment (≥35 ml/kg/h)) and found no differences regarding mortality [47]. However, in all the three trials the actually delivered dose was markedly lower than the prescribed dose. On the basis of these findings, the KDIGO guidelines

suggest a prescribed dose of 35 ml/kg/h for the management of CRRT to ensure that a target dose of 20–25 ml/kg/h is consistently delivered [6].

HOW

Modalities

RRT modalities in the ICU include IHD, hybrid techniques (e.g., PIRRT) and CRRT.

Originally, IHD was implemented in critically ill patients for the treatment of AKI. After the introduction of CRRT, the latter technique evolved as the standard for the treatment of AKI in many countries. The restrictive use of IHD in critically ill patients is mainly explained by the hemodynamic variations caused by high dialysate flows which are inevitable in view of a fast removal of toxins. In contrast, CRRT requires continuous anticoagulation, and makes mobilization and rehabilitation more difficult. Overall, it can be concluded that both techniques have specific advantages and disadvantages and consequently need to be considered as complementary therapies. This claim is supported by the fact that there is no clear evidence for a survival benefit of either technique [6,48–50]. To choose the optimal RRT modality, clinical circumstances, especially patient-specific characteristics, need to be considered.

In the setting of severe critical illness with hemodynamic instability and fluid accumulation, CRRT offers better control of volume homeostasis [51]. Yet, meta-analyses evaluating the effect of the different RRT modalities have shown heterogeneous results [48,52]. A Cochrane data analysis disclosed significantly higher mean arterial pressures during CRRT as compared with IHD [median difference, 5.35; 95% confidence interval (CI), 1.41–9.29; $P < 0.05$] [52]. However, the occurrence of hypotensive episodes was not different (relative risk (RR), 0.48; 95% CI, 0.10–2.28; $P > 0.05$). Bagshaw *et al.* [48] found significantly fewer episodes of hemodynamic instability in patients treated with CRRT as compared with IHD (OR, O.66; 95% CI, 0.45–0.96; $P = 0.03$). As a result of the low evidence, the KDIGO guidelines suggest the use of CRRT in patients not tolerating electrolyte imbalances (e.g., brain injuries where rapid blood osmolality shifts may contribute to increases in intracranial pressure) [6].

Intermittent techniques may be the preferred modality in hemodynamically stable patients whose therapeutic priority is mobilization and rehabilitation. Data comparing PIRRT and CRRT showed no significant difference between extended daily dialysis and CRRT with respect to mortality, renal recovery, fluid removal, and episodes of vasopressor escalation [49]. But yet, to this date there is no consensus regarding the optimal mode of RRT. On the other hand, there is some evidence that initial therapy with CRRT in critically ill patients with AKI reduces the likelihood of chronic dialysis as compared with IRRT [53,54]. Liang *et al.* [55] analyzed retrospective data and found improved renal recovery at 90 days in patients initially treated with CRRT. However, the long-term data were not consistent and no difference was found after 1 year.

In summary, it can be said that critically ill patients who are hemodynamically compromised, should initially be treated with CRRT [6]. Transition from CRRT to IRRT can be considered in case the patient is hemodynamically stable and ready for mobilization and accelerated rehabilitation.

Catheters

For the insertion of temporary dialysis catheters, different target vessels are available. The femoral and jugular sites are the preferred localizations [6]. Subclavian sites should be avoided because of a predisposition to venous stenosis. The recently performed three-sites trial demonstrated a significantly higher risk of deep vein thrombosis when the jugular site was chosen as compared with the subclavian site (hazard ratio, 2.1; 95% CI, 1.0–4.3; $P = 0.04$) [56]. As AKI is strongly associated with end-stage kidney disease and consequently with the need for permanent vascular access, it is recommended to preserve the subclavian sites [6].

Complications of temporary catheters include catheter-related bloodstream infections (CRBSI) and catheter-tip colonization. As the risk is correlated to exposure time, daily reassessment of RRT–catheter is crucial. The occurrence differs between the different catheter localizations. Arvaniti *et al.* [57] found that subclavian and jugular sites have a similar risk for the development of CRBSI. Parienti looked in closer detail to CRBSI in jugular vs. subclavian central catheterization and found higher rates at the jugular site (RR, 1.80; 95% CI, 1.01–3.20; $P = 0.05$) [58]. Moreover, patients with higher BMI showed higher incidence of catheter-tip colonization in the femoral position and patients with lower BMI in the jugular position [59]. There was no difference in CRBSI. Catheter dysfunction was not different between the femoral and jugular position. In the femoral location, catheters shorter than 25 cm or with lower flow capacity may predispose to catheter dysfunction [59,60]. In the jugular location, access via the left internal jugular vein is be related to a higher degree of catheter dysfunction because of anatomical reasons [59].

Independent of the localization, ultrasound guidance should be used for the insertion of RRT catheters [6]. Ultrasound reduces the risk of placement failure, arterial puncture, and rates of complication [61]. Dual lumen, step tip catheters with the venous port 2–3 cm distal to the arterial port may be the preferred type of catheter. These catheters reduce the amount of recirculation and ensure maximal RRT performance.

Anticoagulation

One of the disadvantages of CRRT is the need for anticoagulation to prevent circuit clotting, prolong filter life time and avoid thromboembolic complications. The KDIGO guidelines suggest to use regional citrate anticoagulation (RCA) in patients without contraindications rather than systemic heparin anticoagulation (SHA) [6]. And yet, this recommendation is based on low evidence.

In some countries, practitioners do not use any anticoagulation for CRRT at all, although it has been shown that anticoagulation prolongs filter life time [62]. The use of anticoagulants is not without complications. Systemic heparin may increase the risk of bleeding, especially in surgical patients, the need for blood transfusion, and the likelihood of heparin-induced thrombocytopenia. As an alternative anticoagulant, citrate may lead to severe metabolic imbalances and citrate accumulation [63]. As citrate is mainly eliminated through the liver, liver disease was suggested as a relative contraindication to RCA [6]. But there is new evidence that RCA can safely be used in patients with liver failure [64▪] and after liver transplant [65].

As the publication of the latest KDIGO guidelines, three new RCTs have been published, which analyze the effects of RCA vs. SHA. These trials uniformly disclose superior filter life spans and fewer adverse events for RCA [66–68]. A difference in survival between RCA and SHA could not be detected [66,67]. This might be explained by the fact that both studies were not powered for the detection of a survival difference, and one study was prematurely terminated because of a slow randomization process [67]. Currently, there is one large RCT ongoing which is powered for the two primary outcomes filter life span and all-cause mortality after 90 days (NCT 02669589). Hopefully, the results will be conclusive to definitely answer the question.

CONCLUSION

The question how to manage RRT remains unanswered at least in large parts. Since the publication of the KDIGO guidelines in 2012, many research efforts have been undertaken, but the results are contradictory and unclear. Critically ill patients are predisposed for the development of AKI because of the complex nature of the disease. In the face of life-threatening complications, the decision of when to initiate RRT is self-evident. In the absence of such complications, severe fluid overload is a reasonable trigger for the initiation of RRT. In certain circumstances, early initiation of RRT is superior to a more delayed start. Considering the technique, a continuous strategy is recommended in hemodynamically compromised patients. Anticoagulation with citrate is the first choice in patients without contraindications although evidence is low. Ongoing trials regarding optimal timing and anticoagulation of RRT will hopefully bring new insights to improve the practice of RRT.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

1. Siew ED, Davenport A. The growth of acute kidney injury: a rising tide or just closer attention to detail? Kidney Int 2015; 87:46–61.
2. Hoste EA, Bagshaw SM, Bellomo R, *et al.* Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive Care Med 2015; 41:1411–1423.
3. Wald R, McArthur E, Adhikari NK, *et al.* Changing incidence and outcomes following dialysis-requiring acute kidney injury among critically ill adults: a population-based cohort study. Am J Kidney Dis 2015; 65: 870–877.
4. Hsu RK, McCulloch CE, Dudley RA, *et al.* Temporal changes in incidence of dialysis-requiring AKI. J Am Soc Nephrol 2013; 24:37–42.
5. Kolhe NV, Muirhead AW, Wilkes SR, *et al.* National trends in acute kidney injury requiring dialysis in England between 1998 and 2013. Kidney Int 2015; 88:1161–1169.
6. Kellum JA, Norbert Lameire, Aspelin P, *et al.* KDIGO Clinical Practice Guideline for Acte Kidney Injury 2012. Kidney Int Suppl 2012; 2:1–138.
7. Chawla LS, Amdur RL, Amodeo S, *et al.* The severity of acute kidney injury predicts progression to chronic kidney disease. Kidney Int 2011; 79: 1361–1369.
8. Uchino S, Kellum JA, Bellomo R, *et al.* Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA 2005; 294:813–818.
9. Basile DP, Bonventre JV, Mehta R, *et al.* Progression after AKI: understanding maladaptive repair processes to predict and identify therapeutic treatments. J Am Soc Nephrol 2016; 27:687–697.

10. Coca SG, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. Kidney Int 2012; 81:442–448.
11. Mehta RL, Bouchard J, Soroko SB, *et al.,* Program to Improve Care in Acute Renal Disease (PICARD) Study Group. Sepsis as a cause and consequence of acute kidney injury: program to improve care in acute renal disease. Intensive Care Med 2011; 37:241–248.
12. Lai TS, Wang CY, Pan SC, *et al.* Risk of developing severe sepsis after acute kidney injury: a population-based cohort study. Crit Care 2013; 17:R231.
13. Wu PC, Wu CJ, Lin CJ, *et al.* Long-term risk of upper gastrointestinal hemorrhage after advanced AKI. Clin J Am Soc Nephrol 2015; 10:353–362.
14. Chawla LS, Amdur RL, Shaw AD, *et al.* Association between AKI and long-term renal and cardiovascular outcomes in United States veterans. Clin J Am Soc Nephrol 2014; 9:448–456.
15. Wu VC, Wu CH, Huang TM, *et al.* Long-term risk of coronary events after AKI. J Am Soc Nephrol 2014; 25:595–605.
16. Wu VC, Wu PC, Wu CH, *et al.* The impact of acute kidney injury on the long-term risk of stroke. J Am Heart Assoc 2014; 3:.
17. Chao CT, Wang CY, Lai CF, *et al.* Dialysis-requiring acute kidney injury increases risk of long-term malignancy: a population-based study. J Cancer Res Clin Oncol 2014; 140:613–621.
18. Vaara ST, Pettila V, Kaukonen KM, *et al.* The attributable mortality of acute kidney injury: a sequentially matched analysis. Crit Care Med 2014; 42: 878–885.
19. Liborio AB, Leite TT, Neves FM, *et al.* AKI complications in critically ill patients: association with mortality rates and RRT. Clin J Am Soc Nephrol 2015; 10:21–28.
20. Chertow GM, Burdick E, Honour M, *et al.* Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. J Am Soc Nephrol 2005; 16:3365–3370.
21. ■■ Meersch M, Schmidt C, Hoffmeier A, *et al.* Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers: the PrevAKI randomized controlled trial. Intensive Care Med 2017; 43:1551–1561.

That is the first work demonstrating that the implementation of the KDIGO bundles reduce the occurrence of AKI in high-risk patients undergoing cardiac surgery.

22. Leite TT, Macedo E, Martins Ida S, *et al.* Renal outcomes in critically ill patients receiving propofol or midazolam. Clin J Am Soc Nephrol 2015; 10:1937–1945.
23. Goldstein SL, Currier H, Graf C, *et al.* Outcome in children receiving continuous venovenous hemofiltration. Pediatrics 2001; 107:1309–1312.
24. Teixeira C, Garzotto F, Piccinni P, *et al.* Fluid balance and urine volume are independent predictors of mortality in acute kidney injury. Crit Care 2013; 17:R14.
25. ■■ Garzotto F, Ostermann M, Martin-Langerwerf D, *et al.* The Dose Response Multicentre Investigation on Fluid Assessment (DoReMIFA) in critically ill patients. Crit Care 2016; 20:196.

The important work shows that fluid overload is associated with worse outcome and the elucidates the different types of fluid playing a role in the development of AKI.

26. Selewski DT, Cornell TT, Lombel RM, *et al.* Weight-based determination of fluid overload status and mortality in pediatric intensive care unit patients requiring continuous renal replacement therapy. Intensive Care Med 2011; 37:1166–1173.
27. Payen D, de Pont AC, Sakr Y, *et al.* A positive fluid balance is associated with a worse outcome in patients with acute renal failure. Crit Care 2008; 12:R74.
28. Wang N, Jiang L, Zhu B, *et al.* Fluid balance and mortality in critically ill patients with acute kidney injury: a multicenter prospective epidemiological study. Crit Care 2015; 19:371.
29. Selewski DT, Cornell TT, Blatt NB, *et al.* Fluid overload and fluid removal in pediatric patients on extracorporeal membrane oxygenation requiring continuous renal replacement therapy. Crit Care Med 2012; 40:2694–2699.
30. ■■ Zarbock A, Kellum JA, Schmidt C, *et al.* Effect of early vs delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury: the ELAIN Randomized Clinical Trial. JAMA 2016; 315:2190–2199.

Large randomized trial analyzing that a strategy of early implementation of RRT defined as initiation at KDIGO stage 2 in critically ill patients at high risk for the progression of AKI is associated with an improved survival.

31. Gaudry S, Hajage D, Schortgen F, *et al.* Initiation strategies for renal-replacement therapy in the intensive care unit. N Engl J Med 2016; 375: 122–133.
32. Park JY, An JN, Jhee JH, *et al.* Early initiation of continuous renal replacement therapy improves survival of elderly patients with acute kidney injury: a multicenter prospective cohort study. Critical care 2016; 20:260.
33. Zou H, Hong Q, Xu G. Early versus late initiation of renal replacement therapy impacts mortality in patients with acute kidney injury post cardiac surgery: a meta-analysis. Crit Care 2017; 21:150.
34. Yang XM, Tu GW, Zheng JL, *et al.* A comparison of early versus late initiation of renal replacement therapy for acute kidney injury in critically ill patients: an updated systematic review and meta-analysis of randomized controlled trials. BMC Nephrol 2017; 18:264.
35. Cruz DN, Bagshaw SM, Maisel A, *et al.* Use of biomarkers to assess prognosis and guide management of patients with acute kidney injury. Contrib Nephrol 2013; 182:45–64.
36. Cruz DN, de Geus HR, Bagshaw SM. Biomarker strategies to predict need for renal replacement therapy in acute kidney injury. Semin Dial 2011; 24: 124–131.
37. Wu VC, Ko WJ, Chang HW, *et al.* Risk factors of early redialysis after weaning from postoperative acute renal replacement therapy. Intensive Care Med 2008; 34:101–108.
38. Uchino S, Bellomo R, Morimatsu H, *et al.* Discontinuation of continuous renal replacement therapy: a post hoc analysis of a prospective multicenter observational study. Crit Care Med 2009; 37:2576–2582.
39. ■ Viallet N, Brunot V, Kuster N, *et al.* Daily urinary creatinine predicts the weaning of renal replacement therapy in ICU acute kidney injury patients. Ann Intensive Care 2016; 6:71.

Recently performed trial showing that daily urine output correlates with successful discontinuation from RRT.

40. Frohlich S, Donnelly A, Solymos O, Conlon N. Use of 2-h creatinine clearance to guide cessation of continuous renal replacement therapy. J Crit Care 2012; 27:744 e1–744 e5.
41. Aniort J, Ait Hssain A, Pereira B, *et al.* Daily urinary urea excretion to guide intermittent hemodialysis weaning in critically ill patients. Crit Care 2016; 20:43.
42. van der Voort PH, Boerma EC, Koopmans M, *et al.* Furosemide does not improve renal recovery after hemofiltration for acute renal failure in critically ill patients: a double blind randomized controlled trial. Crit Care Med 2009; 37:533–538.
43. Ronco C, Bellomo R, Homel P, *et al.* Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomised trial. Lancet 2000; 356:26–30.
44. Saudan P, Niederberger M, De Seigneux S, *et al.* Adding a dialysis dose to continuous hemofiltration increases survival in patients with acute renal failure. Kidney Int 2006; 70:1312–1317.
45. VA/NIH Acute Renal Failure Trial Network. Palevsky PM, Zhang JH, *et al.* O'Connor TZ. Intensity of renal support in critically ill patients with acute kidney injury. N Engl J Med 2008; 359:7–20.
46. RENAL Replacement Therapy Study Investigators. Bellomo R, Cass A, *et al.* Cole L. Intensity of continuous renal-replacement therapy in critically ill patients. N Engl J Med 2009; 361:1627–1638.
47. Vesconi S, Cruz DN, Fumagalli R, *et al.* Delivered dose of renal replacement therapy and mortality in critically ill patients with acute kidney injury. Crit Care 2009; 13:R57.
48. Bagshaw SM, Berthiaume LR, Delaney A, Bellomo R. Continuous versus intermittent renal replacement therapy for critically ill patients with acute kidney injury: a meta-analysis. Crit Care Med 2008; 36: 610–617.
49. Zhang L, Yang J, Eastwood GM, *et al.* Extended daily dialysis versus continuous renal replacement therapy for acute kidney injury: a meta-analysis. Am J Kidney Dis 2015; 66:322–330.
50. Truche AS, Darmon M, Bailly S, *et al.* Continuous renal replacement therapy versus intermittent hemodialysis in intensive care patients: impact on mortality and renal recovery. Intensive Care Med 2016; 42: 1408–1417.
51. Truche AS, Darmon M, Bailly S, *et al.,* OUTCOMEREA Study Group. Continuous renal replacement therapy versus intermittent hemodialysis in intensive care patients: impact on mortality and renal recovery. Intensive Care Med 2016; 42:1408–1417.
52. Rabindranath K, Adams J, Macleod AM, *et al.* Intermittent versus continuous renal replacement therapy for acute renal failure in adults. Cochrane Databa Sys Rev 2007; CD003773.
53. Wald R, Shariff SZ, Adhikari NK, *et al.* The association between renal replacement therapy modality and long-term outcomes among critically ill adults with acute kidney injury: a retrospective cohort study*. Critical Care Med 2014; 42:868–877.
54. Schneider AG, Bellomo R, Bagshaw SM, *et al.* Choice of renal replacement therapy modality and dialysis dependence after acute kidney injury: a systematic review and meta-analysis. Intensive Care Med 2013; 39: 987–997.
55. Liang KV, Sileanu FE, Clermont G, *et al.* Modality of RRT and recovery of kidney function after AKI in patients surviving to hospital discharge. Clin J Am Soc Nephrol 2016; 11:30–38.
56. Parienti JJ, Mongardon N, Megarbane B, *et al.* Intravascular complications of central venous catheterization by insertion site. N Engl J Med 2015; 373:1220–1229.
57. Arvaniti K, Lathyris D, Blot S, *et al.* Cumulative evidence of randomized controlled and observational studies on catheter-related infection risk of central venous catheter insertion site in ICU patients: a pairwise and network meta-analysis. Critical Care Med 2017; 45:e437–e448.
58. Parienti JJ. Catheter-related bloodstream infection in jugular versus subclavian central catheterization. Crit Care Med 2017; 45:e734–e735.
59. Parienti JJ, Megarbane B, Fischer MO, *et al.* Catheter dysfunction and dialysis performance according to vascular access among 736 critically ill adults requiring renal replacement therapy: a randomized controlled study. Crit Care Med 2010; 38:1118–1125.
60. Bellomo R, Martensson J, Lo S, *et al.* Femoral access and delivery of continuous renal replacement therapy dose. Blood Purif 2016; 41: 11–17.

61. Rabindranath KS, Kumar E, Shail R, *et al.* Use of real-time ultrasound guidance for the placement of hemodialysis catheters: a systematic review and meta-analysis of randomized controlled trials. Am J Kidney Dis 2011; 58:964–970.
62. Thompson A, Li F, Gross AK. Considerations for medication management and anticoagulation during continuous renal replacement therapy. Adv Crit Care 2017; 28:51–63.
63. Khadzhynov D, Dahlinger A, Schelter C, *et al.* Hyperlactatemia, lactate kinetics and prediction of citrate accumulation in critically ill patients undergoing continuous renal replacement therapy with regional citrate anticoagulation. Crit Care Med 2017; 45:e941–e946.
64. Slowinski T, Morgera S, Joannidis M, *et al.* Safety and efficacy of regional
■ citrate anticoagulation in continuous venovenous hemodialysis in the presence of liver failure: the Liver Citrate Anticoagulation Threshold (L-CAT) observational study. Crit Care 2015; 19:349.
Interesting and important work showing that citrate can safely be used in patients with liver failure.
65. Sponholz C, Settmacher U, Bauer M, *et al.* Regional citrate anticoagulation for continuous renal replacement therapy in the perioperative care of liver transplant recipients: a single center experience. Therap Aph Dial 2015; 19:8–15.
66. Hetzel GR, Schmitz M, Wissing H, *et al.* Regional citrate versus systemic heparin for anticoagulation in critically ill patients on continuous venovenous haemofiltration: a prospective randomized multicentre trial. Nephrol Dial Transplant 2011; 26:232–239.
67. Schilder L, Nurmohamed SA, Bosch FH, *et al.* Citrate anticoagulation versus systemic heparinisation in continuous venovenous hemofiltration in critically ill patients with acute kidney injury: a multicenter randomized clinical trial. Crit Care 2014; 18:472.
68. Gattas DJ, Rajbhandari D, Bradford C, *et al.* A randomized controlled trial of regional citrate versus regional heparin anticoagulation for continuous renal replacement therapy in critically ill adults. Crit Care Med 2015; 43: 1622–1629.