ESC European Society of Cardiology

European Heart Journal: Acute Cardiovascular Care (2025) **00**, 1–13
https://doi.org/10.1093/ehjacc/zuaf084

REVIEW
Heart Failure and Cardiomyopathies

Severe acute kidney injury in the intensive care unit: step-to-step management

Mauro Riccardi [1,2], Matteo Pagnesi [1], Carlo M. Lombardi[1,2], and Marco Metra [1]*

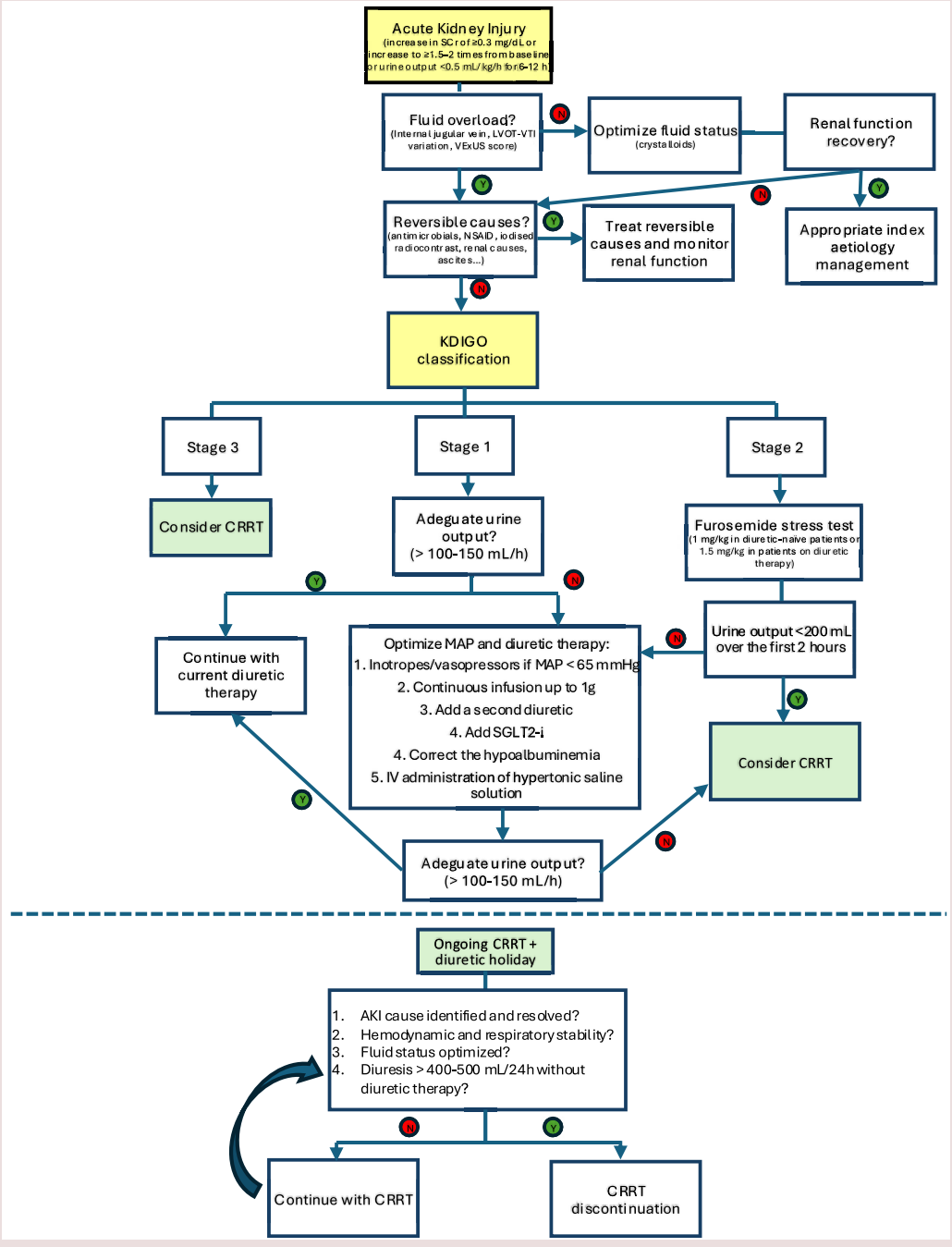
[1]Institute of Cardiology, Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Spedali Civili di Brescia, Piazzale Spedali Civili 1, 25123 Brescia, Italy; and [2]Division of Cardiology, Cremona Hospital, Viale Concordia 1, 26100 Cremona, Italy

Received 5 March 2025; revised 22 May 2025; accepted 16 June 2025; online publish-ahead-of-print 28 June 2025

Acute kidney injury (AKI) is a sudden loss of renal function limited to 7 days with increased basal serum creatinine levels and/or decreased urinary production. AKI is a frequent condition in the intensive care unit (ICU) ranging from 13% to 36% in patients hospitalized with acute heart failure, up to 80% in patients with cardiogenic shock (CS). AKI requiring dialysis is also common (5% to 8%) and can exceed 13% in patients with CS. AKI is consistently associated with increased mortality in both the short-term, especially when dialysis is needed, and the long-term. The aim of this review is to provide an update on step-by-step management, from pharmacological treatment to renal replacement therapy, in patients with severe AKI in ICU patients with fluid overload.

* Corresponding author. Tel: +393356460581, Email: metramarco@libero.it

Graphical Abstract



Step-to-step management of patients with severe AKI in ICU. The figure illustrates the multi-step approach to be performed in a patient with severe AKI in ICU. First, we need to confirm a fluid overload (distension of internal jugular vein, no response to a fluid challenge and VExUS score ≥ 1). The next step is an attempt at drug management. The cornerstone of pharmacological therapy is the use of diuretics. Inotropes or vasopressors may be considered to maintain a MAP ≥ 65 mmHg by promoting nephron perfusion. In case of failure of medical therapy, the next step is the initiation of CRRT. AKI, acute kidney injury; CRRT, continuous renal replacement therapy; CVP, central venous pressure; CVVH, continuous venovenous; CVVHD, continuous venovenous haemodialysis; CVVHDF, continuous venovenous hemodiafiltration; ICU, cardiac intensive care unit; LVOT-VTI, left ventricular outflow tract—velocity time integral; MAP, mean arterial pressure; SGLT2-I, sodium-glucose cotransporter 2 inhibitors.

Keywords AKI • ICU • Diuretic therapy • CRRT

Introduction

Acute kidney injury (AKI) is a sudden loss of renal function occurring in 7 days with increased baseline serum creatinine levels (SCr) and/or decreased urinary output.[1] The 2012 KDIGO guideline defined standard criteria for AKI, which classify it into progressive stages based on changes in SCr and urinary output over hours to days in patients with fluid overload or after proper volemic filling (*Table 1*).[2] A consensus statement published in 2020 has complemented this definition with the use of biomarkers.[3]

The most common cause of AKI in patients hospitalized with acute HF is type 1 cardiorenal syndrome.[4] The pathophysiology of AKI is complex and not yet completely understood because it is likely that distinct but overlapping causes may contribute, ranging from a simple decrease in estimated glomerular filtration rate (eGFR) mediated purely by systemic or local haemodynamic abnormalities (e.g. reduced arterial perfusion or venous congestion) with reversible tubular stress/injury up to frank tubular necrosis secondary to inflammatory, ischaemic and nephrotoxic causes.[5] An abrupt and primary worsening of kidney function may also lead to acute cardiac dysfunction but this situation, named type 3 renocardial syndrome, appears less common than type 1.[4] Several factors may favour AKI development in intensive care unit (ICU).[6–8] The degree of chronic kidney disease (CKD) is one of the strongest risk factors for AKI, reflecting reduced renal reserve and impaired ability of the kidneys to respond to stress.[7] Other risk factors include advanced age, hypertension, diabetes mellitus, and ICU admission diagnosis. Finally, the use of iodinated radiocontrast material during cardiovascular interventional procedures is an important modifiable risk factor for AKI, with contrast-associated AKI occurring in about 15% of patients with acute coronary syndrome undergoing percutaneous coronary intervention.[9]

AKI is constantly associated with increased short-term mortality, especially when dialysis is needed.[10] In addition to early death, but the severity of AKI also extends beyond the acute phase affecting progression to CKD, increasing the risk of cardiovascular complications, recurrent episodes of AKI and long-term mortality.[5]

The aim of the present review is to provide an update on the management of severe AKI in ICU patients with fluid overload.

Initial approach and confirmation of fluid overload

Any acute increase in SCr and/or decrease in urine output should be promptly evaluated to identify and treat reversible causes (*Graphical abstract*).

Point-of-care ultrasonography

Ultrasound is an important diagnostic tool in AKI evaluation. A renal ultrasound can assess kidneys size and echogenicity to rule out renal causes of AKI. Bladder retention, as cause of decrease urine output, must be also excluded. In addition, ultrasound allows the assessment of filling pressures (degree of congestion) and forward flow (degree of perfusion) ensuring the optimisation of haemodynamic and fluid balance.[11] Internal jugular vein ultrasound had moderate sensitivity and specificity for the diagnosis of hypervolemia and hypovolemia but could be utilized as first approach.[12]

The left ventricular outflow tract—velocity time integral assessment can be useful to identify patients' response to volemic filling[13] while a combined classification of inferior vena cava, hepatic vein and portal vein (VExUS score) reliably demonstrates venous congestion and helps in the clinical decision to perform fluid removal.[14] In recent studies, VExUS score ≥1 was significantly associated with AKI,[15] higher use of diuretics in the following 48 h than patients with a VExUS score ≤1,[16] and poorer prognosis.[17] However, compared with the evaluation of the inferior vena cava and the internal jugular vein, it requires a minimum of anatomical knowledge and familiarity with Doppler techniques.[18] Among the various components of the VExUS grading system, portal vein Doppler could be more effective in monitoring real-time decongestion in patients undergoing haemodialysis.[19]

Reassessment of ongoing therapy

The use of potential nephrotoxic drugs (some antimicrobials, especially aminoglycosides, non-steroidal anti-inflammatory drugs and others) should be promptly discontinued and/or recent use of iodized radiocontrast must be excluded. Mineralocorticoid receptor antagonists may reduce the rate of eGFR but, considering the potential beneficial effects in patients with cardiovascular disease, their continuation may initially be reasonable during mild AKI, but caution should be taken with an early termination in case of progressive deterioration of renal function or development of hyperkaliemia.[20] The same applies to sodium-glucose cotransporter-2 (SGLT2) inhibitors and angiotensin receptor-neprilysin inhibitor (ARNI).[21] A recent analysis of the patients who developed severe kidney dysfunction, defined as eGFR < 25 mL/min, in DAPA-HF (Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction) trial and in DELIVER (Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction) trial showed the persistence of the beneficial effects of dapagliflozin vs. placebo also in these patients.[22] Similarly, an analysis of the patients showing a deterioration of kidney function in PARADIGM-HF and PARAGON-HF clinical trials and a meta-analysis including 2494 patients with concomitant HF and end-stage kidney disease undergoing dialysis showed persistence of the clinical benefits of ARNI on the risk of death and HF hospitalisations without an increase of adverse events, including severe hyperkalaemia and symptomatic hypotension.[23]

These data suggest that the prosecution of SGLT2 inhibitors and ARNI may be advised also in patients who develop a deterioration of kidney function shown by an eGFR < 30 mL/min/m^2.

Ultrafiltration vs. pharmacological treatment as first-line strategy

Randomized clinical trials compared renal replacement therapy (RRT) vs. intravenous diuretic treatment as first-line strategy in patients with HF and AKI (*Table 2*). The CARRESS-HF (Cardiorenal Rescue Study in Acute Decompensated Heart Failure) trial compared ultrafiltration with an aggressive, urine output-guided pharmacological protocol of diuretic therapy. The main analysis of the trial results suggested a neutral effect of ultrafiltration on outcome with a higher incidence of adverse events, including worsening renal function, in the RRT arm.[24] However, the high drop-out rate and crossover rate between the two treatment groups may have had a major role (*Table 2*).[29,30] A subsequent per-protocol analysis showed that ultrafiltration was associated with highly significant cumulative fluid loss, net fluid loss and relative reduction in weight, but also with higher SCr and blood urea nitrogen by 72 h, lower serum sodium at 48 h and increased plasma renin activity at 96 h, whereas the pharmacological arm was associated with higher serum bicarbonate after 24 h. A lack of differences in 60-day outcomes between the ultrafiltration and pharmacological arms was confirmed also in this analysis.[25] The earlier UNLOAD (Ultrafiltration Versus Intravenous Diuretics Decompensated Heart Failure) trial showed a greater body weight decrease and fluid loss and fewer 90-day HF hospitalisation in the ultrafiltration group ($P = 0.037$).[26] Similarly, the ultrafiltration group had a lower incidence of HF hospitalisations at 1 year than those undergoing standard care in the CUORE (Continuous Ultrafiltration for Congestive Heart Failure) trial.[27] Finally, patients in the ultrafiltration group had a non-statistically significant trend to longer time to first HF event than

Table 1 Standard KDIGO classification for AKI using SCr and urine output[2] and new proposed definition[3]

KDIGO	SCr	Urine output
Stage 1	Increase in SCr to 1.5–1.9 times baseline or ≥0.3 mg/dL increase;	<0.5 mL/kg/h for 6–12 h
Stage 2	Increase in SCr to 2.0–2.9 times baseline;	<0.5 mL/kg/h for ≥12h
Stage 3	Increase in SCr to 3.0 times baseline, increase in SCr to ≥4.0 mg/dL, or initiation of RRT	<0.3 mL/kg/h for ≥24 h or anuria ≥12h

KDIGO update	SCr and urine output	Biomarkers (cystatin C and NGAL)
1S	No change or sCr increase < 0.3 mg/dL and no urinary output criteria	Positive biomarkers
1A	Increase of sCr by ≥0.3 mg/dL for ≤48 h or ≥150% for ≤7 days and/or urinary output <0.5 mL/kg/h for >6 h	Negative biomarkers
1B	Increase of sCr by ≥0.3 mg/dL for ≤48 h or ≥150% for ≤7 days and/or urinary output <0.5 mL/kg/h for >6 h	Positive biomarkers
2A	Increase of sCr by >200% and/or urinary output <0.5 mL/kg/h for >12 h	Negative biomarkers
2B	Increase of sCr by >200% and/or urinary output <0.5 mL/kg/h for >12 h	Positive biomarkers
3A	Increase of sCr by >300% (≥4.0 mg/dL with an acute increase of ≥0.5 mg/dL) and/or urinary output <0.3 mL/kg/h for >24 h or anuria >12 h and/or acute RRT	Negative biomarkers
3B	Increase of sCr by >300% (≥4.0 mg/dL with an acute increase of ≥0.5 mg/dL) and/or urinary output <0.3 mL/kg/h for >24 h or anuria >12 h and/or acute RRT	Positive biomarkers

GFR, glomerular filtration rate; NGAL, neutrophil gelatinase–associated lipocalin, RRT, renal replacement therapy; SCr, serum creatinine.

patients in the diuretic therapy group but significantly fewer HF and cardiovascular events at 30 days in the AVOID-HF (Aquapheresis vs. Intravenous Diuretics and Hospitalisation for Heart Failure).[28] These trials highlight the difficulty in showing a clear benefit of ultrafiltration on outcome in randomized controlled trials. Consequently, we have no strong data to support the use of ultrafiltration as a first-line therapy for decompensated acute HF, and an initial attempt with drug therapy remains the preferred strategy to date.

Pharmacological treatment

No specific vasoactive drugs have been shown to prevent or treat severe AKI in ICU, including inotropes or vasodilators.[11,31,32] Low-dose or 'renal' dose dopamine has been advocated in the past for its action of DA1 receptors causing dilation of the renal and splanchnic arteries. However, there are data showing that in critical patients, low-dose dopamine may even worsen renal perfusion.[33] In particular, the ROSE (Renal Optimisation Strategies Evaluation) trial evaluated if the addition of low-dose dopamine (2 μg/kg/min) to diuretic therapy could improve decongestion and preserve renal function in patients with acute HF and renal dysfunction, without demonstrating any significant benefit.[34] A meta-analysis has concluded that 'renal-dose' dopamine has no benefit in either preventing or improving AKI in critical patients, and therefore it is not recommended.[35] Levosimendan may reduce AKI, but studies are limited at patients after cardiac surgery.[36]

It has been calculated that the nephron, in order to function properly, needs at least 40.7 mmHg of perfusion pressure [= mean arterial pressure (MAP)—intra-abdominal pressure—central venous pressure (CVP)—airway pressure].[37] Therefore, in a patient with reduced urine output, it is possible to act by increasing the MAP or reducing the CVP. The use of inotropes or vasopressors to maintain appropriate MAP values (> 65 mmHg) may therefore be considered. A higher MAP (>80–85 mmHg) was associated with increased cardiac output, although with no difference in urine output or creatinine clearance.[38]

Conversely, loop diuretics may reduce the blood volume and CVP, improving renal perfusion and therefore diuresis.[32,39] Although diuretics have not been demonstrated to reduce mortality or prevent the need for dialysis in patients with AKI, patients who respond to diuretics appear to have better outcomes.[40] The DOSE (Diuretic Strategies in Patients with Acute Decompensated Heart Failure) trial reported no significant difference in symptoms or change in the SCr level between bolus infusion vs. continuous infusion strategy. Moreover, a high-dose strategy was associated with greater diuresis and more favourable outcomes but also with transient worsening of renal function.[41] A meta-analysis showed that continuous loop diuretic infusion compared with intravenous bolus strategy at equivalent doses was associated with a greater body weight reduction and potential increase in 24-h urine output but no differences in all-cause mortality and length of hospitalisation.[42] However, in ICU, continuous infusion may be beneficial for selected patients, such as those with haemodynamic instability who may not tolerate repeated bolus administration, or those requiring accurate titration or high doses. Importantly, when opting for continuous infusion, an initial intravenous bolus should be administered to reach the threshold concentration necessary to initiate effective diuresis. It may be appropriate, when starting intravenous diuretic treatment, to use low doses and assess the diuretic response with urine output and, in case of bolus administration, also natriuresis; the dose should be increased if the response is insufficient.[43–45]

Lastly, intra-abdominal hypertension (IAH) is an increasingly recognized contributor to AKI in critically ill patients.[46] Among its reversible causes, ascites plays a central role. In cases of tense ascites, therapeutic paracentesis has been shown to significantly reduce IAP, thereby improving renal perfusion and facilitating diuresis.[47] IAP is most commonly measured indirectly via bladder pressure monitoring, a simple and minimally invasive bedside method.[48] The measurement is taken at end-expiration, with normal values typically <12 mmHg. So, early recognition and prompt drainage in the context of ascitic IAH may represent a pivotal, reversible step in the management of AKI.

Table 2 Major randomized trial that compared ultrafiltration vs. diuretic therapy in patients with AKI and HF

Trial	N of patients	Treatment	Results	Comments
CARRESS-HF[24]	$n = 188$	UF vs. Diuretic	At 96 h: • Higher percentage of WRF in the UF group ($P = 0.003$) • No significant differences in weight loss ($P = 0.58$) • Higher percentage of AEs in the UF group (72% vs. 57%, $P = 0.03$) • The 60-day estimated mortality was lower in UF group (17% vs. 13%, $P = 0.47$) • No significant difference in the composite rate of death or rehospitalization for HF (38% vs. 35%, $P = 0.96$)	• Rate of fluid removal was mandated to be 200 mL/h • 90% was not sufficiently decongested • High crossover rate
CARRESS-HF, per-protocol analysis[25]	$n = 188$	UF vs. Diuretic	At 96 h: • Higher cumulative fluid loss ($P = 0.003$), net fluid loss ($P = 0.001$), and relative reduction in weight ($P = 0.02$) in UF group. • Higher percentage of WRF ($P < 0.001$). • No differences in 60-day outcomes (death, HF hospitalisation, or unscheduled emergency department or clinic visit)	Not powered to determine long-term clinical outcomes
UNLOAD[26]	$n = 200$	UF vs. Diuretic	• At 48 h, weight and fluid loss were greater in UF group (both $P = 0.001$) • At 90 days, HF hospitalisation was lower in UF group ($P = 0.037$)	/
CUORE[27]	$n = 56$	UF vs. Diuretic	• Similar weight reduction ($P = 0.75$) • Lower incidence of HF hospitalisation during the following year ($P = 0.002$) • Renal function remained unchanged	• Small sample • Older age (75 ± 8) may limit generalizability
AVOID-HF[28]	$n = 110$	UF vs. Diuretic	• Estimated days to first HF event was 62 in the UF group vs. 34 in diuretic (log-rank $P = 0.106$) • UF group had greater total amount of fluid removed ($P = 0.015$) without significant difference in weight loss ($P = 0.343$) • At 30 days, patients in UF group had fewer HF hospitalisation ($P = 0.034$), and fewer hospitalisation due to a CV event ($P = 0.037$) • At 90 days, there were no differences in mortality ($P = 0.827$)	• Untimely termination by the sponsor. • 60% was not sufficiently decongested

AEs, adverse events; CV, cardiovascular; HF, heart failure; UF, ultrafiltration; WRF, worsening renal function.

Diuretic resistance

Diuretic resistance may have multiple causes.[49] A first cause is gut malabsorption, caused by gut congestion, and this may be easily overcome by intravenous or, more recently, subcutaneous furosemide administration.[50,51] Second, hypotension and low cardiac output may impair loop diuretics delivery to the nephron. However, these pre-renal mechanisms appear as less important in patients with HF than the intrarenal ones.[49] Loop diuretic agents are organic anions that circulate tightly bound to albumin (>90%). Thus, their volume of distribution is low, except during extreme hypoalbuminemia. Evidence suggest that albumin infusion may enhances natriuretic efficacy in presence of albumin < 2 g/L.[52] Other pharmacokinetic aspects may also be important. To gain access to the tubular fluid and therefore to their sites of activity, they must be secreted across the proximal tubule. Peritubular uptake is mediated by the organic anion transporters OAT1 and OAT3.[49] Therefore, increased plasma levels of other organic anions and metabolic acidosis, a characteristic of AKI, may contribute to diuretic resistance, compromising the achievement of active site in the nephron.[53] A pH correction with sodium bicarbonate infusion may improve the delivery and action of furosemide in this setting. However, induction of a hypochloremic metabolic alkalosis must be avoided because it reduces diuretic response by impairing chloride-dependent sodium transport in the nephron, which is essential for loop diuretics to exert their effect.[54] Ethacrynic acid may be useful in the presence of acidosis in case of furosemide failure.[55] Then, after peritubular uptake, diuretic secretion into the tubular lumen is necessary and this step could be compromised in CKD, requiring higher diuretic doses.[49] Increased sodium retention in other sites that the ascending loop of Henle has, however, the most important role in diuretic resistance and this is the basis for sequential nephron blockade in the treatment of congestion refractory to loop diuretics administration alone.[56,57]

Solutions to overcome diuretic resistance

Current HF guidelines recommend starting treatment of congestion with 40 mg intravenous furosemide in diuretic naïve patients or with 1–2 the home oral dose administered intravenously in those on oral therapy. Urine output and/or natriuresis must be reassessed after 2–6 h with doubling of loop diuretic dose, eventually followed by combined diuretic treatment if the diuretic response is insufficient. Conversely, other authors have considered a 'furosemide stress test' in patients with fluid overload and AKI stage I-II by measuring the urine output after a intravenous furosemide dose of 1.0 mg/kg, in diuretic-naïve patients, or 1.5 mg/kg, in patients already on high loop diuretic doses.[58–60] Patients who have a urine output <200 mL over the first 2 h are at increased risk of progressive AKI and potential need for RRT; a 6-h urine output <600 mL is predictive of the need for RRT in patients with stage III AKI (*Graphical abstract*).

Intravenous furosemide doses up to about 1 g can occasionally produce diuresis in patients with severe AKI who fail to respond to a standard furosemide challenge. However, the kidney is both the site of action and the major site of metabolism of furosemide. Increase dose combined with the reduction in metabolism leads to an increase in furosemide plasma concentrations with the risk of adverse events.[53]

The addition of a second diuretic, frequently a thiazide-type diuretic, to ongoing loop diuretic therapy can potentially overcome diuretic resistance and increase urine output.[57,61,62] In the CLOROTIC study, the addition of hydrochlorothiazide to an intravenous furosemide regimen resulted in increased diuresis within 24 h and increased weight loss within 72 h.[57] Oral metolazone was non-inferior to intravenous chlorothiazide for enhancing net urine output and weight loss in patients with acute decompensated HF and loop diuretic resistance.[63–65] Close monitoring of electrolytes and renal function is warranted when using combination diuretic therapy due to the elevated risk of electrolyte disturbances and worsening renal function. More recently, there have been demonstrations of efficacy of combination therapy also with acetazolamide and SGLT2 inhibitors.[66–69] Regarding acetazolamide, in the ADVOR trial its addition to loop diuretic therapy resulted in a greater incidence of successful decongestion[66] and the treatment response was magnified in patients with baseline or loop diuretic-induced elevated HCO3 (marker of proximal nephron NaHCO3 retention).[70] Regarding SGLT2 inhibitors, a randomized trial showed that dapagliflozin was not more effective at relieving congestion than metolazone. Moreover, patients assigned to dapagliflozin received a larger cumulative dose of furosemide.[71] It is well known that SGLT2 inhibitors lead to substantially lower natriuresis compared with thiazide.[72,73] For this reason, it is preferable to consider SGLT2 inhibitors more as disease-modifying drugs with some diuretic action rather than a drug to be used primarily to overcome diuretic resistance. In the last few years, hypertonic saline solution (HSS) with furosemide has sparked renewed interest in the management of HF with volume overload and diuretic resistance. Several studies have suggested the superiority of this approach in increasing urine output and weight loss, improving renal function, and decreasing the incidence of HF rehospitalization.[74–84] The underlying mechanism of this approach is attributed to the osmotic properties of HSS, which may facilitate fluid mobilisation from the interstitial space into the intravascular compartment and by augmenting sodium and chloride delivery to Henle's loop, potentially enhancing furosemide action. However, most of these studies were open-label, and evidence in a double-blind fashion is scarce. Recently, the SALT-HF (Efficacy and Safety of Hypertonic Saline Therapy in Ambulatory Patients with Heart Failure) trial, a multicentre, double-blind, randomized study, showed that a single infusion of intravenous furosemide combined with HSS did not improve 3 h diuresis, congestion parameters or the incidence of death from any cause or HF hospitalisation in patients with ambulatory worsening HF compared with intravenous furosemide alone.[85] A post-hoc analysis stratified with baseline serum chloride showed benefit on diuresis and 30-day HF events in patients with lower chloride levels.[86] Further evidence is necessary to better evaluate this possible strategy in HF patients with diuretic resistance.

To provide practical guidance for clinicians, we propose a stepwise algorithm for the management of diuretic resistance in critically ill patients, summarising the escalation of therapy from loop diuretics to more advanced interventions (*Figure 1*).

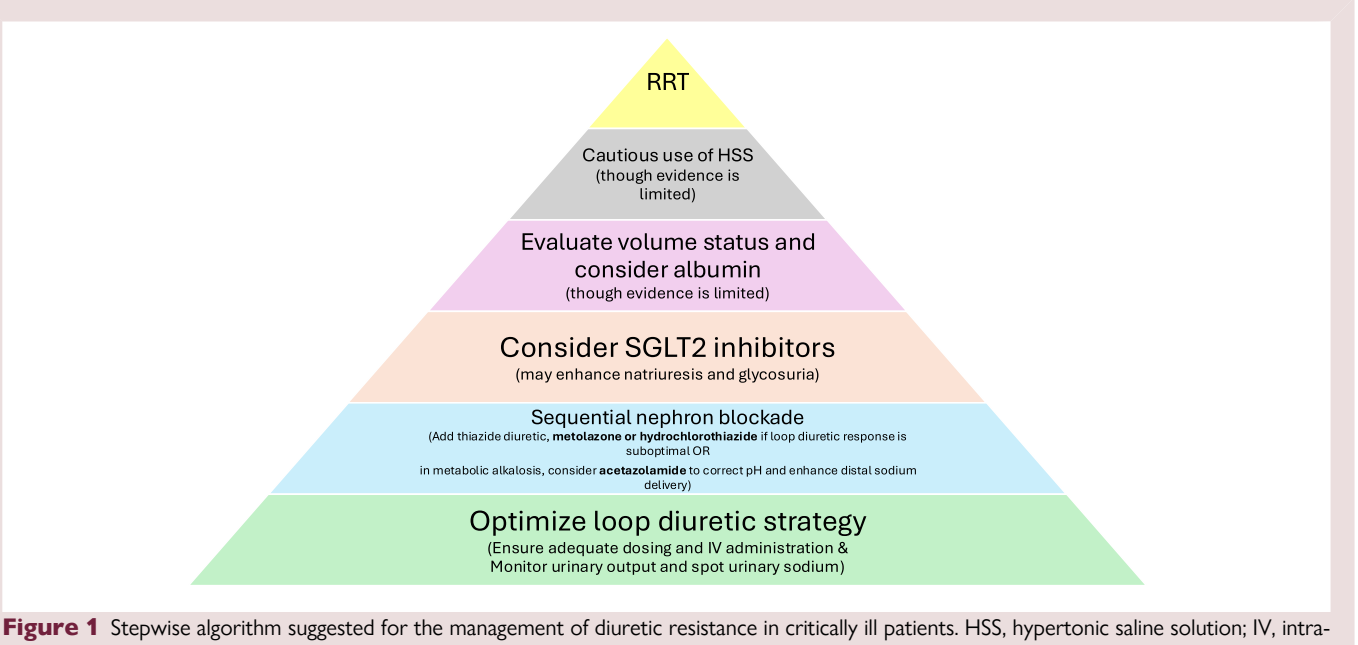


Figure 1 Stepwise algorithm suggested for the management of diuretic resistance in critically ill patients. HSS, hypertonic saline solution; IV, intravenous; RRT, renal replacement therapy; SGLT2, sodium-glucose cotransporter-2.

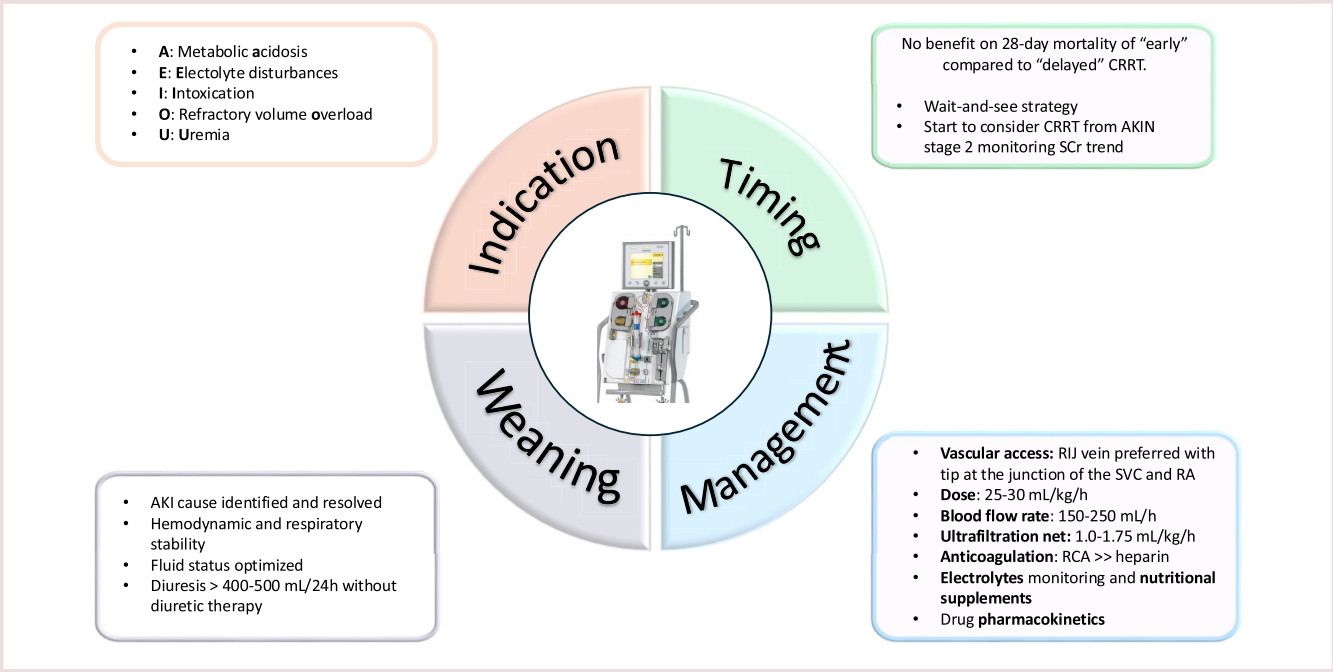


Figure 2 Indication to CRRT, start timing, management of CRRT and indications at weaning. AKI, acute kidney injury; AKIN, acute kidney injury network; CRRT, continuous renal replacement therapy; RCA, regional citrate anticoagulation; SCr, serum creatinine.

Renal replacement therapy

Traditionally, the decision to initiate urgent RRT in critically ill patients with AKI is based on the standard 'AEIOU' indications (*Figure 2*): Acidosis, electrolyte derangements, intoxications, volume overload, and uraemia.[87] Among these, the most common indication in ICU is medically refractory volume overload with haemodynamic instability (65%).[88]

RRT removes metabolic wastes and excess water, balances electrolytes and fills buffers in patients with severe AKI.[89] The RRT apparatus consists of a semi-permeable membrane dialyzer, that allows bidirectional exchange (for diffusion or convection) of solutes and fluids between the patient's blood and dialysate without loss of high molecular weight substances or cells, dialysate (dialysis solution), sterile tubes for blood and dialysate transport and a machine to power and control the procedure by sensors and alarms.[10]

The haemodynamic instability and the poor ability to control fluid balance observed with intermittent haemodialysis (IHD) explains its lower use in ICUs in favour of continuous RRT (CRRT), at least until the patient stabilizes,[90] despite data about mortality differences in randomized trials are contradictory.[91,92] Three CRRT techniques are available in the ICU (*Table 3*): continuous venovenous hemofiltration (CVVH) based on convective therapy, continuous venovenous haemodialysis (CVVHD) based on diffusive therapy, and continuous venovenous hemodiafiltration (CVVHDF) using both convective and diffusive therapy. All the three CRRT techniques provide both solute clearance and volume removal. Despite differences in the type of dialysis, there is no convincing evidence to prefer a type of CRRT.[93]

Timing of CRRT

There is no clear evidence on the best timing for starting CRRT.[94] In a meta-analysis of 9 studies including 1879 patients, early CRRT initiation did not influence death at 28 days compared with an initial wait-and-see strategy in severe AKI.[95] Similarly, in a larger meta-analysis including 5086 patients, early initiation of CRRT did not decrease 28-day all-cause mortality compared with delayed CRRT in critically ill patients with AKI. In addition, early initiation of CRRT led to unnecessary CRRT exposure in some patients and was associated with a higher incidence of hypotension and CRRT-associated infection events.[96] Therefore, only patients with a clear and strong indication could benefit from an early initiation of CRRT. The other patients can be initially observed, even in the presence of oliguria (i.e. urine output < 400–500 mL/day). The development of a refractory symptomatic fluid overload or other clear indications for RRT should lead to consideration of CRRT. However, to avoid any harmful delays, it is recommended to evaluate the patients for potential CRRT indications already in the presence of AKI stage II (*Figure 2*). SCr trend can help to assess the correct timing of CRRT start: in a patient whose SCr values, although high, have started to decrease, it might be considered to perform close monitoring and wait for CRRT initiation; on the contrary, where values are constantly increasing, a more aggressive initial approach may be justified.

CRRT management: tips and tricks

Vascular access

The initiation of CRRT requires a proper venous vascular access, which is usually established by positioning a large diameter double lumen catheter sufficient to support blood flows from 200 to 300 mL/min. The cannulation of the internal jugular vein is the site of choice, with the right internal jugular vein preferred to the left, given the straightest course from the right side to the right atrium (*Figure 2*). The femoral vein or axillary are two possible alternative targets.[97,98]

CRRT dose, blood flow rate and net ultrafiltration

Regarding the optimal dose of CRRT, in order to ensure an adequate dose supplied, KDIGO guidelines suggest prescribing 25–30 mL/kg/h (*Figure 2*).[2] Prospective data to guide CRRT dosing in severe obesity are poor.[99–101] Reasonable approaches in this setting include a dose

Table 3 Comparison among CRRT modalities

CRRT modality	Mechanisms of clearance	Blood flow (mL/min)	Ultrafiltration Rate (mL/h)	Advantages	Disadvantages
CVVHD	Diffusion	100–200	80–200	No replacement fluid request	Lesser volume removal
CVVH	Convection	200–400	1000–4000	Aggressive volume control	Replacement fluid required
CVVHDF	Convection and diffusion	100–200	1000–2000	Balance between volume control and solute removal	High cost

CRRT, continuous renal replacement therapy; CVVH, continuous venovenous; CVVHD, continuous venovenous haemodialysis; CVVHDF, continuous venovenous hemodiafiltration.

based on effective body weight (but the total dose should not exceed 5000 mL/h), then decreasing the dose based on daily body weight.

Blood flow rate is typically set to 150–250 mL/min in adults, because low blood flow rates promote haemostasis and filter coagulation, while high blood flow rates may lead to a higher risk of hypotension, pressure alarms and CRRT interruption (*Figure 2*).[102,103]

There is little data to guide the volume removal prescription (net ultrafiltration). The choice of ultrafiltration rate requires a careful multidisciplinary evaluation considering the objective to be achieved (decongestion) and patient tolerance as the main modifiable risk factor for hypotension during CRRT, with possible need for vasopressor support.[104,105]

The relationship between net ultrafiltration and mortality has a U-shaped curve, with the lowest mortality associated with net ultrafiltration rates of 1.0–1.75 mL/kg/h (*Figure 2*).[106,107]

Anticoagulation

Blood is exposed to thrombogenic surfaces as it passes through the dialysis and CRRT circuits. Clotting in the dialyzer or blood filter may impair the efficiency of CRRT. Regional citrate anticoagulation (RCA), by inhibiting multiple calcium dependent phases in the coagulation cascade, is the first anticoagulation choice because it is associated with better permeability of the circuits, lower risk of bleeding and avoidance of heparin-induced thrombocytopenia (HIT) (*Figure 2*).[2,108–110] Importantly, RCA can be used even in patients requiring systemic anticoagulation for other indications to increase filter lifespan, especially in the scenario of previous premature loss of filter despite anticoagulation. Target blood citrate concentration is 3–4 mmol/L, corresponding to ionized calcium between 0.25 and 0.4 mmol/L. Complication during RCA infusion are described in Electrolyte disorders and nutrient deficiencies. A systemic calcium infusion is necessary to replace the calcium loss.[108] Patients with liver failure and profound shock cannot effectively eliminate citrate and may require lower doses of citrate to avoid toxicity.[111] In alternative to citrate, unfractionated heparin (UFH) can be used either systemically, in patients with indication for anticoagulant therapy, or regionally. Advantages of UFH are that it is inexpensive, has a relatively short half-life, and is readily reversed with protamine. Disadvantages include the unpredictable pharmacokinetics resulting in dosing variability, heparin resistance due to low anti-thrombin levels, the development of HIT, and the increased risk of bleeding.[108]

Electrolytes monitoring and nutritional supplements

In addition to total and ionized calcium during RCA infusion, other electrolytes should be monitored every 6–12 h, including phosphorus and magnesium. Critically ill patients with AKI are in a catabolic state, which often requires additional proteins. Therefore, an international consensus recommended protein supplementation (*Figure 2*).[108]

Effects of CRRT on drug pharmacokinetics

Multiple factors can alter the clearance of a drug during CRRT including an increased volume of distribution due to fluid overload, the ability of the drug to pass through the filter, blood flow rate, dialysate flow and ultrafiltration rate.[112,113] Therefore, for drugs with renal excretion, dosing should be adjusted when initiating or discontinuing CRRT (*Figure 2*).

The main drugs used in CICU as inotropes, vasopressors and vasodilators are not substantially cleared by CRRT[10] except for milrinone, which accumulates during AKI, with a half-life of up to 20 h in patients in RRT, leading to a drug accumulation and toxicity.[114] The half-life of the metabolites of levosimendan is prolonged by 1.5 times during CRRT with a maximum concentration that can be increased up to 2 times. Therefore, levosimendan should be used with caution, at reduced dosage, and closely monitoring the patient.[115] Antimicrobial agents usually require altered dosing in patients with AKI-D are typically with higher and/or more frequent doses for patients on CRRT than patients without CRRT.[112,116,117]

Assessment of renal recovery and CRRT discontinuation

Rates of successful weaning from CRRT vary from 21% to 60% among ICU patients[118,119] and weaning failure is associated with increased mortality.[118,120]

The international KDIGO recommendations suggest weaning patients from CRRT when it is no longer necessary because of sufficient renal recovery or because it is no longer consistent with the goal of care.[2] However, there are currently no widely accepted specific criteria to guide renal function recovery assessment for the discontinuation of CRRT. A pooled analysis showed that CKD, CRRT duration, and urine output at the cessation of CRRT were predictors for short-term successful weaning from CRRT.[121]

Increase in diuresis is the most frequently reason for weaning with an optimal threshold of 436 mL/24 h without diuretics and 2330 mL/24 h with diuretics.[118] However, weaning based on urine volume alone is no guarantee of success.[122] Low SCr and low serum urea could be considered positive weaning predictors.[123]

Diuretics should be used primarily to improve urine output after discontinuation of CRRT as there is no evidence that may favour a renal recovery.[124] Discontinuation of diuretic therapy during CRRT may be a reasonable option ('diuretic holiday') with the possibility to maintain a dose of 5–10 mg/hour only in patients on chronic baseline diuretic therapy. It is also possible to make small suspension windows from CRRT, preferably at the same time as the filter runs out, with concomitant initiation of continuous diuretic infusion (at variable dosage based on the patient's profile) to evaluate the diuretic response.

Of note, among the causes of CRRT interruption there are also complications and other unplanned or undesired conditions including low

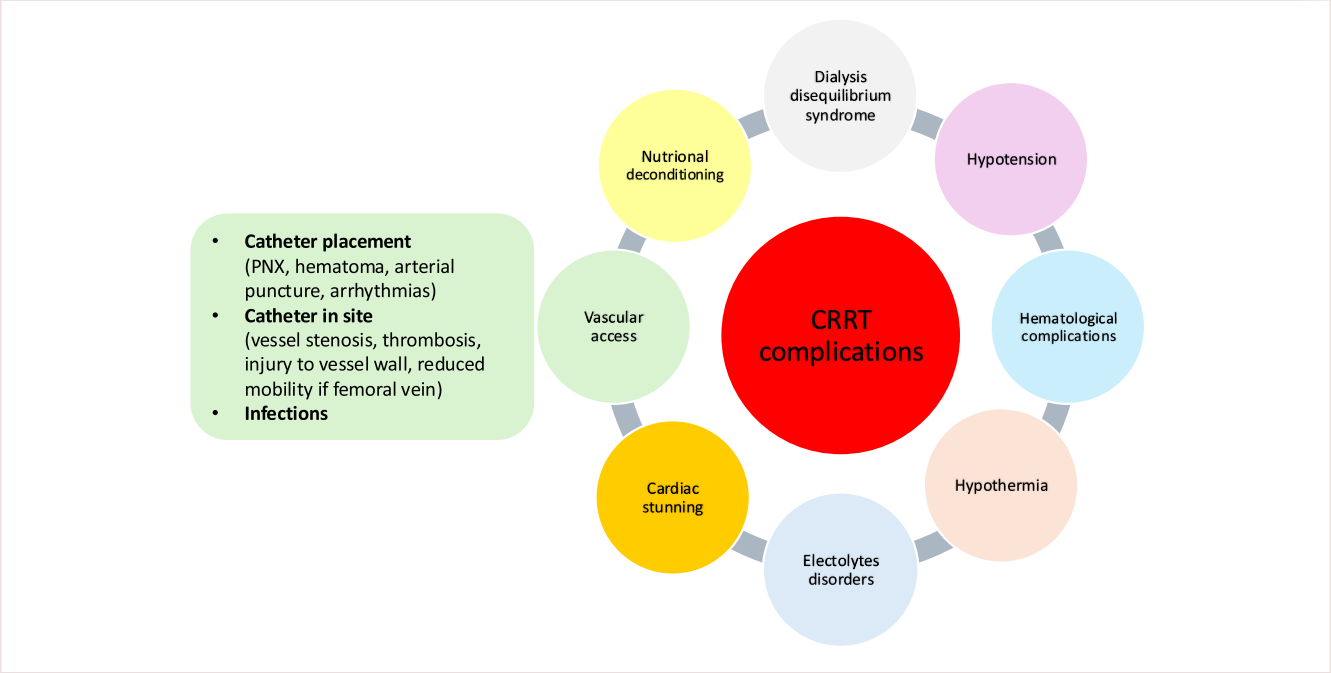


Figure 3 CRRT-associated complications. The following figure illustrates the complications that may occur during CRRT treatment. CRRT, continuous renal replacement therapy.

Table 4 Future research

Setting	Gaps in evidence
Pharmacological therapy	Correct multi-step approach
Modality of CRRT	Advantage of using a modality over the others
Timing for CRRT	• Early start vs. 'wait and see' strategy with concomitant maximum optimisation of medical therapy • Role of the biomarkers in risk stratification (cystatin C, NGAL, IL-18, IL-6, and serum osteopontin)
CRRT dose, blood flow rate and net ultrafiltration	• Correct dose in obesity • Correct net ultrafiltration rate • Hypotension values that can be tolerated or managed with vasopressor therapy
CRRT discontinuation	• Correct strategy to properly discontinue CRRT • Switch to intermittent dialysis • Diuretic holiday vs. continuing diuretic therapy • Role of the biomarkers (cystatin C, NGAL, IL-18, IL-6, and serum osteopontin)
CRRT complications	• Strategies to avoid cardiac stunning • Strategies to encourage early mobilisation during the CRRT

CRRT, continuous renal replacement therapy; IL, interleukin, NGAL, Neutrophil gelatinase-associated lipocalin

MAP, agitation, inability to use any anticoagulant therapy, and lack of dedicated care.[125]

5.3 Complications of CRRT

CRRT use is associated with the risk of developing specific complications.[126] (*Figure 3*).

Vascular complications

Vascular access is the lifeline of CRRT. Vascular access complications may arise during placement or maintenance of the vascular access.[127] To reduce placement complications, guided ultrasound techniques are recommended. Infectious complications are also possible.[127] Although access placement at the level of the jugular veins involves an area at lower risk for infection, no clinically relevant benefit of catheterisation of the jugular site compared with femoral catheterisation has been found in a previous study.[128]

5.3.2 Hypotension and hypothermia

Hypotension during CRRT is another common complication, occurring in more than one third of patients, but it is most often unrelated to the CRRT procedure *per se*.[129,130] When hypotension is associated with

volume depletion, it should be treated with volume reinfusion and adjustment in ultrafiltration targets; alternative aetiologies should be considered and managed.[97] Modest thermal losses during CRRT cause vasoconstriction and are believed to contribute to increased haemodynamic stability, but may mask the onset of fever. If thermal losses are more substantial, significant hypothermia may ensue, necessitating aggressive external warming.[127]

Electrolyte disorders and nutrient deficiencies

Electrolyte abnormalities are common during CRRT. Hypophosphataemia may result from continuous removal in the extracorporeal circuit and can be avoided by pre-emptive enteral or parenteral phosphate supplementation or by the use of phosphate-containing dialysate or replacement fluids.[131] Other electrolyte abnormalities are less common, although hyponatremia or hypernatremia and hyperkalaemia have resulted from compounding errors in custom manufactured dialysate and replacement fluids.[132] Hypocalcaemia, hypernatriemia and metabolic alkalosis are also the side effects of using RCA.[109,133] In addition, the most serious adverse effect with RCA is the citrate toxicity (increased need for calcium infusion to maintain adequate levels of ionized calcium or ratio of total systemic calcium to ionized calcium > 2.5) and, in this case, RCA must be suspended or discontinued. Nutritional losses represent a significant concern for patients on CRRT. Careful administration of calories and nutrients in close coordination with the nutritionist would be desirable.

Circuit clotting and haematological disorders

Another common complication during CRRT is circuit clotting, often due to inadequate catheter function. In this case, prompt catheter replacement may be necessary. Excessive filtration fraction may lead to haemoconcentration within the haemofilter, also contributing to filter clotting.[97] Blood exposure to the extracorporeal circuit may trigger immediate allergic or delayed immunologic reactions secondary to cytokine activation.[134]

Haematologic complications are among the most underrecognized complications observed during CRRT and often related to UFH used, as HIT and anaemia.[127]

Other complications

In critically ill patients, initiation of CRRT has been associated with cardiac stunning.[135] Dialysis disequilibrium syndrome (DDS) is another of the complications that can occur after initiating patients on IHD due to rapid shifts of solutes. Although CRRT has been postulated to have slower clearance of solutes, thus decreasing the risks of DDS, there have been a few case reports of DDS occurring in patients receiving CRRT.[136]

Conclusions

Severe AKI is a common complication among patients in ICU and is strongly associated with poor outcomes with few effective treatments available. A multi-step drug therapy centred on the use of loop diuretics is the first approach in patients with AKI after confirming fluid overload. Patients requiring CRRT represent a growing subset of ICU patients who are at progressively higher risk of mortality and post-discharge dialysis dependence. Future research (*Table 4*) is urgently needed to assess the optimal pharmacological approach in patients with refractory AKI-D and CRS, including possible new therapies and improved strategies for starting CRRT, its management and eventual transition to a long-term dialysis.

Acknowledgements

None declared.

Author contributions

Mauro Riccardi [MD (Conceptualisation: Lead; Writing—original draft: Lead; Writing—review & editing: Lead)], Matteo Pagnesi [MD PhD (Conceptualisation: Equal; Writing—original draft: Equal; Writing—review & editing: Equal)], Carlo M. Lombardi [MD (Writing—review & editing: Supporting)], and Marco Metra [MD (Conceptualisation: Equal; Writing—review & editing: Equal)]

Funding

None declared.

Conflict of interest: M.P. has received personal fees from Abbott Laboratories, AstraZeneca, Boehringer Ingelheim, and Vifor Pharma (all unrelated to this study). M.M. has received consulting fees in the past 3 years from Abbott Structural Heart, AstraZeneca, Bayer, Boehringer Ingelheim, Edwards Lifesciences, and Roche Diagnostics. Dr Geisler has received speaker honoraria and research grants from AstraZeneca, Bayer, Bristol Myers Squibb/Pfizer, Ferrer/Chiesi, Medtronic, and Edwards Lifesciences (all unrelated to this study). M.R. and C.M.L. have nothing to disclose.

Data availability

No new data were generated or analysed in support of this research.

References

1. Kellum JA, Romagnani P, Ashuntantang G, Ronco C, Zarbock A, Anders HJ. Acute kidney injury. *Nat Rev Dis Primers* 2021;**7**:52.
2. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract* 2012;**120**:c179–c184.
3. Ostermann M, Zarbock A, Goldstein S, Kashani K, Macedo E, Murugan R, *et al.* Recommendations on acute kidney injury biomarkers from the acute disease quality initiative consensus conference: a consensus statement. *JAMA Netw Open* 2020;**3**:e2019209.
4. Ronco C, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal syndrome. *J Am Coll Cardiol* 2008;**52**:1527–1539.
5. Pickkers P, Darmon M, Hoste E, Joannidis M, Legrand M, Ostermann M, *et al.* Acute kidney injury in the critically ill: an updated review on pathophysiology and management. *Intensive Care Med* 2021;**47**:835–850.
6. Hoste EA, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, *et al.* Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. *Intensive Care Med* 2015;**41**:1411–1423.
7. Cartin-Ceba R, Kashiouris M, Plataki M, Kor DJ, Gajic O, Casey ET. Risk factors for development of acute kidney injury in critically ill patients: a systematic review and meta-analysis of observational studies. *Crit Care Res Pract* 2012;**2012**:691013.
8. Sun Y-B, Liu B-C, Zou Y, Pan J-R, Tao Y, Yang M. Risk factors of acute kidney injury after acute myocardial infarction. *Ren Fail* 2016;**38**:1353–1358.
9. Yang Y, George KC, Luo R, Cheng Y, Shang W, Ge S, *et al.* Contrast-induced acute kidney injury and adverse clinical outcomes risk in acute coronary syndrome patients undergoing percutaneous coronary intervention: a meta-analysis. *BMC Nephrol* 2018;**19**:374.
10. Jentzer JC, Bihorac A, Brusca SB, Del Rio-Pertuz G, Kashani K, Kazory A, *et al.* Contemporary management of severe acute kidney injury and refractory cardiorenal syndrome: JACC council perspectives. *J Am Coll Cardiol* 2020;**76**:1084–1101.
11. Jentzer JC, Chawla LS. A clinical approach to the acute cardiorenal syndrome. *Crit Care Clin* 2015;**31**:685–703.
12. Wang MK, Piticaru J, Kappel C, Mikhaeil M, Mbuagbaw L, Rochwerg B. Internal jugular vein ultrasound for the diagnosis of hypovolemia and hypervolemia in acutely ill adults: a systematic review and meta-analysis. *Intern Emerg Med* 2022;**17**:1521–1532.
13. Riccardi M, Cani DS, Pagnesi M, Lombardi CM, Metra M, Inciardi RM. Assessing aortic flow with Doppler echocardiography in cardiogenic shock: a crucial diagnostic tool. *Echocardiography* 2024;**41**:e15901.
14. Bhardwaj V, Vikneswaran G, Rola P, Raju S, Bhat RS, Jayakumar A, *et al.* Combination of Inferior vena Cava diameter, hepatic venous flow, and portal vein pulsatility Index: Venous Excess Ultrasound score (VEXUS score) in predicting acute kidney injury in patients with cardiorenal syndrome: a prospective cohort study. *Indian J Crit Care Med* 2020;**24**:783–789.
15. Viana-Rojas JA, Argaiz E, Robles-Ledesma M, Arias-Mendoza A, Nájera-Rojas NA, Alonso-Bringas AP, *et al.* Venous excess ultrasound score and acute kidney injury in

patients with acute coronary syndrome. *Eur Heart J Acute Cardiovasc Care* 2023;**12**: 413–419.
16. Rihl MF, Pellegrini JAS, Boniatti MM. VExUS score in the management of patients with acute kidney injury in the intensive care unit: AKIVEX study. *J Ultrasound Med* 2023;**42**: 2547–2556.
17. Anastasiou V, Peteinidou E, Moysidis DV, Daios S, Gogos C, Liatsos AC, *et al.* Multiorgan congestion assessment by venous excess ultrasound score in acute heart failure. *J Am Soc Echocardiogr* 2024;**37**:923–933.
18. Koratala A, Romero-González G, Soliman-Aboumarie H, Kazory A. Unlocking the potential of VExUS in assessing venous congestion: the art of doing it right. *Cardiorenal Med* 2024;**14**:350–374.
19. Tonelli MM, Argaiz ER, Pare JR, Hooker E, Kurniawan H, Muruganandan KM, *et al.* Portal vein Doppler is a sensitive marker for evaluating venous congestion in End-stage kidney disease. *Cardiorenal Med* 2024;**14**:375–384.
20. Matsumoto S, Henderson AD, Shen L, Yang M, Swedberg K, Vaduganathan M, *et al.* Mineralocorticoid receptor antagonists in patients with heart failure and impaired renal function. *J Am Coll Cardiol* 2024;**83**:2426–2436.
21. Mullens W, Damman K, Testani JM, Martens P, Mueller C, Lassus J, *et al.* Evaluation of kidney function throughout the heart failure trajectory—a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2020; **22**:584–603.
22. Chatur S, Vaduganathan M, Claggett BL, Mc Causland FR, Desai AS, Jhund PS, *et al.* Dapagliflozin in patients with heart failure and deterioration in renal function. *J Am Coll Cardiol* 2023;**82**:1854–1863.
23. Nguyen DV, Le TN, Truong BQ, Nguyen HTT. Efficacy and safety of angiotensin receptor-neprilysin inhibition in heart failure patients with end-stage kidney disease on maintenance dialysis: a systematic review and meta-analysis. *Eur J Heart Fail* 2025; **27**:72–84.
24. Bart BA, Goldsmith SR, Lee KL, Givertz MM, O'Connor CM, Bull DA, *et al.* Ultrafiltration in decompensated heart failure with cardiorenal syndrome. *N Engl J Med* 2012;**367**:2296–2304.
25. Grodin JL, Carter S, Bart BA, Goldsmith SR, Drazner MH, Tang WHW, *et al.* Direct comparison of ultrafiltration to pharmacological decongestion in heart failure: a per-protocol analysis of CARRESS-HF. *Eur J Heart Fail* 2018;**20**:1148–1156.
26. Costanzo MR, Guglin ME, Saltzberg MT, Jessup ML, Bart BA, Teerlink JR, *et al.* Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. *J Am Coll Cardiol* 2007;**49**:675–683.
27. Marenzi G, Muratori M, Cosentino ER, Rinaldi ER, Donghi V, Milazzo V, *et al.* Continuous ultrafiltration for congestive heart failure: the CUORE trial. *J Card Fail* 2014;**20**:9–17.
28. Costanzo MR, Negoianu D, Jaski BE, Bart BA, Heywood JT, Anand IS, *et al.* Aquapheresis versus intravenous diuretics and hospitalizations for heart failure. *JACC Heart Fail* 2016;**4**:95–105.
29. Costanzo MR, Ronco C, Abraham WT, Agostoni P, Barasch J, Fonarow GC, *et al.* Extracorporeal ultrafiltration for fluid overload in heart failure. *J Am Coll Cardiol* 2017;**69**:2428–2445.
30. Costanzo MR, Kazory A. Better late than never: the true results of CARRESS-HF. *Eur J Heart Fail* 2018;**20**:1157–1159.
31. Ronco C, Bellomo R, Kellum JA. Acute kidney injury. *Lancet* 2019;**394**:1949–1964.
32. Rangaswami J, Bhalla V, Blair JEA, Chang TI, Costa S, Lentine KL, *et al.* Cardiorenal syndrome: classification, pathophysiology, diagnosis, and treatment strategies: a scientific statement from the American Heart Association. *Circulation* 2019;**139**:e840–e878.
33. Lauschke A, Teichgräber UKM, Frei U, Eckardt K-U. Low-dose' dopamine worsens renal perfusion in patients with acute renal failure. *Kidney Int* 2006;**69**:1669–1674.
34. Chen HH, Anstrom KJ, Givertz MM, Stevenson LW, Semigran MJ, Goldsmith SR, *et al.* Low-dose dopamine or low-dose nesiritide in acute heart failure with renal dysfunction: the ROSE acute heart failure randomized trial. *JAMA* 2013;**310**:2533–2543.
35. Joannidis M, Druml W, Forni LG, Groeneveld ABJ, Honore PM, Hoste E, *et al.* Prevention of acute kidney injury and protection of renal function in the intensive care unit: update 2017: expert opinion of the working group on prevention, AKI section, European Society of Intensive Care Medicine. *Intensive Care Med* 2017;**43**: 730–749.
36. Niu Z-Z, Wu S-M, Sun W-Y, Hou W-M, Chi Y-F. Perioperative levosimendan therapy is associated with a lower incidence of acute kidney injury after cardiac surgery: a meta-analysis. *J Cardiovasc Pharmacol* 2014;**63**:107–112.
37. Suarez J, Busse LW. New strategies to optimize renal haemodynamics. *Curr Opin Crit Care* 2020;**26**:536–542.
38. Bourgoin A, Leone M, Delmas A, Garnier F, Albanèse J, Martin C. Increasing mean arterial pressure in patients with septic shock: effects on oxygen variables and renal function. *Crit Care Med* 2005;**33**:780–786.
39. Teixeira C, Garzotto F, Piccinni P, Brienza N, Iannuzzi M, Gramaticopolo S, *et al.* Fluid balance and urine volume are independent predictors of mortality in acute kidney injury. *Crit Care* 2013;**17**:R14.
40. Bove T, Belletti A, Putzu A, Pappacena S, Denaro G, Landoni G, *et al.* Intermittent furosemide administration in patients with or at risk for acute kidney injury: meta-analysis of randomized trials. *PLoS One* 2018;**13**:e0196088.
41. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, *et al.* Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med* 2011;**364**: 797–805.
42. Kuriyama A, Urushidani S. Continuous versus intermittent administration of furosemide in acute decompensated heart failure: a systematic review and meta-analysis. *Heart Fail Rev* 2019;**24**:31–39.
43. ter Maaten JM, Beldhuis IE, van der Meer P, Krikken JA, Postmus D, Coster JE, *et al.* Natriuresis-guided diuretic therapy in acute heart failure: a pragmatic randomized trial. *Nat Med* 2023;**29**:2625–2632.
44. Dauw J, Charaya K, Lelonek M, Zegri-Reiriz I, Nasr S, Paredes-Paucar CP, *et al.* Protocolized natriuresis-guided decongestion improves diuretic response: the multicenter ENACT-HF study. *Circ Heart Fail* 2024;**17**:e011105.
45. Authors/Task Force Members; McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, *et al.* 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2022;**24**:4–131.
46. Muğlu H, İnan Kahraman E, Sünger E, Murt A, Bilici A, Görgülü N, *et al.* Acute kidney injury secondary to abdominal compartment syndrome: biomarkers, pressure variability, and clinical outcomes. *Medicina (Kaunas)* 2025;**61**:383.
47. Cullaro G, Kanduri SR, Velez JCQ. Acute kidney injury in patients with liver disease. *Clin J Am Soc Nephrol* 2022;**17**:1674–1684.
48. Sugrue M, De Waele JJ, De Keulenaer BL, Roberts DJ, Malbrain MLNG. A user's guide to intra-abdominal pressure measurement. *Anaesthesiol Intensive Ther* 2015;**47**: 241–251.
49. Felker GM, Ellison DH, Mullens W, Cox ZL, Testani JM. Diuretic therapy for patients with heart failure: JACC state-of-the-art review. *J Am Coll Cardiol* 2020;**75**:1178–1195.
50. Keshvani N, Rizvi S, Segar MW, Miller JW, Coellar JD, Patel KV, *et al.* Diuretic efficiency of a single dose of subcutaneous versus oral furosemide after heart failure hospitalization across diuretic resistance strata: a pilot randomized controlled trial. *Eur J Heart Fail* 2025;**27**:347–352.
51. Osmanska J, Petrie MC, Docherty KF, Lee MMY, McMurray JJV, Campbell RT. Subcutaneous furosemide in heart failure: a systematic review. *Eur Heart J Cardiovasc Pharmacother* 2025;**11**:94–104.
52. Lee TH, Kuo G, Chang C-H, Huang YT, Yen CL, Lee C-C, *et al.* Diuretic effect of co-administration of furosemide and albumin in comparison to furosemide therapy alone: an updated systematic review and meta-analysis. *PLoS One* 2021;**16**:e0260312.
53. Wilcox CS. New insights into diuretic use in patients with chronic renal disease. *J Am Soc Nephrol* 2002;**13**:798–805.
54. Hanberg JS, Rao V, Ter Maaten JM, Laur O, Brisco MA, Perry Wilson F, *et al.* Hypochloremia and diuretic resistance in heart failure: mechanistic insights. *Circ Heart Fail* 2016;**9**:10.1161/CIRCHEARTFAILURE.116.003180 e003180.
55. Kim KE, Onesti G, Moyer JH, Swartz C. Ethacrynic acid and furosemide. Diuretic and hemodynamic effects and clinical uses. *Am J Cardiol* 1971;**27**:407–415.
56. Meekers E, Dauw J, Martens P, Dhont S, Verbrugge FH, Nijst P, *et al.* Renal function and decongestion with Acetazolamide in acute decompensated heart failure: the ADVOR trial. *Eur Heart J* 2023;**44**:3672–3682.
57. Trullàs JC, Morales-Rull JL, Casado J, Carrera-Izquierdo M, Sánchez-Marteles M, Conde-Martel A, *et al.* Combining loop with thiazide diuretics for decompensated heart failure: the CLOROTIC trial. *Eur Heart J* 2023;**44**:411–421.
58. Sakhuja A, Bandak G, Barreto EF, Vallabhajosyula S, Jentzer J, Albright R, *et al.* Role of loop diuretic challenge in stage 3 acute kidney injury. *Mayo Clin Proc* 2019;**94**: 1509–1515.
59. Lumlertgul N, Peerapornratana S, Trakarnvanich T, Pongsittisak W, Surasit K, Chuasuwan A, *et al.* Early versus standard initiation of renal replacement therapy in furosemide stress test non-responsive acute kidney injury patients (the FST trial). *Crit Care* 2018;**22**:101.
60. Chawla LS, Davison DL, Brasha-Mitchell E, Koyner JL, Arthur JM, Shaw AD, *et al.* Development and standardization of a furosemide stress test to predict the severity of acute kidney injury. *Crit Care* 2013;**17**:R207.
61. Cox ZL, Hung R, Lenihan DJ, Testani JM. Diuretic strategies for loop diuretic resistance in acute heart failure: the 3T trial. *JACC Heart Fail* 2020;**8**:157–168.
62. Jentzer JC, DeWald TA, Hernandez AF. Combination of loop diuretics with thiazide-type diuretics in heart failure. *J Am Coll Cardiol* 2010;**56**:1527–1534.
63. Shulenberger CE, Jiang A, Devabhakthuni S, Ivaturi V, Liu T, Reed BN. Efficacy and safety of intravenous chlorothiazide versus oral metolazone in patients with acute decompensated heart failure and loop diuretic resistance. *Pharmacotherapy* 2016;**36**: 852–860.
64. Gibson CM, Beard MM, Escano AK, Good BL, Potter TG, Truong AM, *et al.* Metolazone versus chlorothiazide in acute heart failure patients with diuretic

resistance and renal dysfunction: a retrospective cohort study. *J Cardiovasc Pharmacol* 2024;**84**:451–456.
65. Moranville MP, Choi S, Hogg J, Anderson AS, Rich JD. Comparison of metolazone versus chlorothiazide in acute decompensated heart failure with diuretic resistance. *Cardiovasc Ther* 2015;**33**:42–49.
66. Mullens W, Dauw J, Martens P, Verbrugge FH, Nijst P, Meekers E, *et al.* Acetazolamide in acute decompensated heart failure with volume overload. *N Engl J Med* 2022;**387**:1185–1195.
67. Biegus J, Voors AA, Collins SP, Kosiborod MN, Teerlink JR, Angermann CE, *et al.* Impact of empagliflozin on decongestion in acute heart failure: the EMPULSE trial. *Eur Heart J* 2023;**44**:41–50.
68. Cox ZL, Collins SP, Hernandez GA, McRae AT, Davidson BT, Adams K, *et al.* Efficacy and safety of dapagliflozin in patients with acute heart failure. *J Am Coll Cardiol* 2024;**83**:1295–1306.
69. Schulze PC, Bogoviku J, Westphal J, Aftanski P, Haertel F, Grund S, *et al.* Effects of Early Empagliflozin Initiation on Diuresis and Kidney Function in Patients With Acute Decompensated Heart Failure (EMPAG-HF). *Circulation* 2022;**146**:289–298.
70. Martens P, Verbrugge FH, Dauw J, Nijst P, Meekers E, Augusto SN, *et al.* Pre-treatment bicarbonate levels and decongestion by Acetazolamide: the ADVOR trial. *Eur Heart J* 2023;**44**:1995–2005.
71. Yeoh SE, Osmanska J, Petrie MC, Brooksbank KJM, Clark AL, Docherty KF, *et al.* Dapagliflozin vs. metolazone in heart failure resistant to loop diuretics. *Eur Heart J* 2023;**44**:2966–2977.
72. Mordi NA, Mordi IR, Singh JS, McCrimmon RJ, Struthers AD, Lang CC. Renal and cardiovascular effects of SGLT2 inhibition in combination with loop diuretics in patients with type 2 diabetes and chronic heart failure. *Circulation* 2020;**142**:1713–1724.
73. Scholtes RA, Muskiet MHA, van Baar MJB, Hesp AC, Greasley PJ, Karlsson C, *et al.* Natriuretic effect of two weeks of dapagliflozin treatment in patients with type 2 diabetes and preserved kidney function during standardized sodium intake: results of the DAPASALT trial. *Diabetes Care* 2021;**44**:440–447.
74. Covic A, Copur S, Tapoi L, Afsar B, Ureche C, Siriopol D, *et al.* Efficiency of hypertonic saline in the management of decompensated heart failure: a systematic review and meta-analysis of clinical studies. *Am J Cardiovasc Drugs* 2021;**21**:331–347.
75. Tuttolomondo A, Pinto A, Parrinello G, Licata G. Intravenous high-dose furosemide and hypertonic saline solutions for refractory heart failure and ascites. *Semin Nephrol* 2011;**31**:513–522.
76. Paterna S, Di Gaudio F, La Rocca V, Balistreri F, Greco M, Torres D, *et al.* Hypertonic saline in conjunction with high-dose furosemide improves dose-response curves in worsening refractory congestive heart failure. *Adv Ther* 2015;**32**:971–982.
77. Gandhi S, Mosleh W, Myers RBH. Hypertonic saline with furosemide for the treatment of acute congestive heart failure: a systematic review and meta-analysis. *Int J Cardiol* 2014;**173**:139–145.
78. De Vecchis R, Esposito C, Ariano C, Cantatrione S. Hypertonic saline plus i.v. Furosemide improve renal safety profile and clinical outcomes in acute decompensated heart failure: a meta-analysis of the literature. *Herz* 2015;**40**:423–435.
79. Griffin M, Soufer A, Goljo E, Colna M, Rao VS, Jeon S, *et al.* Real world use of hypertonic saline in refractory acute decompensated heart failure: a U.S. Center's experience. *JACC Heart Fail* 2020;**8**:199–208.
80. Lafrenière G, Béliveau P, Bégin J-Y, Simonyan D, Côté S, Gaudreault V, *et al.* Effects of hypertonic saline solution on body weight and serum creatinine in patients with acute decompensated heart failure. *World J Cardiol* 2017;**9**:685–692.
81. Issa VS, Andrade L, Ayub-Ferreira SM, Bacal F, de Bragança AC, Guimarães GV, *et al.* Hypertonic saline solution for prevention of renal dysfunction in patients with decompensated heart failure. *Int J Cardiol* 2013;**167**:34–40.
82. Wan Y, Li L, Niu H, Ma X, Yang J, Yuan C, *et al.* Impact of compound hypertonic saline solution on decompensated heart failure. *Int Heart J* 2017;**58**:601–607.
83. Licata G, Di Pasquale P, Parrinello G, Cardinale A, Scandurra A, Follone G, *et al.* Effects of high-dose furosemide and small-volume hypertonic saline solution infusion in comparison with a high dose of furosemide as bolus in refractory congestive heart failure: long-term effects. *Am Heart J* 2003;**145**:459–466.
84. Paterna S, Fasullo S, Parrinello G, Vitrano G, Terrazzino G, Maringhini G, *et al.* Short-term effects of hypertonic saline solution in acute heart failure and long-term effects of a moderate sodium restriction in patients with compensated heart failure with New York Heart Association class III (class C) (SMAC-HF study). *Am J Med Sci* 2011;**342**:27–37.
85. Cobo Marcos M, de la Espriella R, Comín-Colet J, Zegrí-Reiriz I, Rubio Gracia J, Morales-Rull JL, *et al.* Efficacy and safety of hypertonic saline therapy in ambulatory patients with heart failure: the SALT-HF trial. *Eur J Heart Fail* 2024;**26**:2118–2128.
86. Núñez J, Miñana G, de la Espriella R, Zegrí-Reiriz I, Comín-Colet J, Rubio Gracia J, *et al.* Salt repletion and diuretic response: the role of serum chloride. A post-hoc analysis of the SALT-HF trial on furosemide and hypertonic saline solution administration in ambulatory patients with worsening heart failure. *Eur J Heart Fail* 2025; doi:10.1002/ejhf.3597. Published online ahead of print.
87. Tamargo C, Hanouneh M, Cervantes CE. Treatment of acute kidney injury: a review of current approaches and emerging innovations. *J Clin Med* 2024;**13**:2455.
88. Keleshian V, Kashani KB, Kompotiatis P, Barsness GW, Jentzer JC. Short, and long-term mortality among cardiac intensive care unit patients started on continuous renal replacement therapy. *J Crit Care* 2020;**55**:64–72.
89. Summary of recommendation statements. *Kidney Int Suppl (2011)* 2012;**2**:8–12.
90. Bonnassieux M, Duclos A, Schneider AG, Schmidt A, Bénard S, Cancalon C, *et al.* Renal replacement therapy modality in the ICU and renal recovery at hospital discharge. *Crit Care Med* 2018;**46**:e102–e110.
91. Wald R, Gaudry S, da Costa BR, Adhikari NKJ, Bellomo R, Du B, *et al.* Initiation of continuous renal replacement therapy versus intermittent hemodialysis in critically ill patients with severe acute kidney injury: a secondary analysis of STARRT-AKI trial. *Intensive Care Med* 2023;**49**:1305–1316.
92. Nash DM, Przech S, Wald R, O'Reilly D. Systematic review and meta-analysis of renal replacement therapy modalities for acute kidney injury in the intensive care unit. *J Crit Care* 2017;**41**:138–144.
93. Friedrich JO, Wald R, Bagshaw SM, Burns KEA, Adhikari NKJ. Hemofiltration compared to hemodialysis for acute kidney injury: systematic review and meta-analysis. *Crit Care* 2012;**16**:R146.
94. Pan H-C, Chen Y-Y, Tsai I-J, Shiao C-C, Huang T-M, Chan C-K, *et al.* Accelerated versus standard initiation of renal replacement therapy for critically ill patients with acute kidney injury: a systematic review and meta-analysis of RCT studies. *Crit Care* 2021;**25**:5.
95. Gaudry S, Hajage D, Benichou N, Chaïbi K, Barbar S, Zarbock A, *et al.* Delayed versus early initiation of renal replacement therapy for severe acute kidney injury: a systematic review and individual patient data meta-analysis of randomised clinical trials. *Lancet* 2020;**395**:1506–1515.
96. Li X, Liu C, Mao Z, Li Q, Zhou F. Timing of renal replacement therapy initiation for acute kidney injury in critically ill patients: a systematic review of randomized clinical trials with meta-analysis and trial sequential analysis. *Crit Care* 2021;**25**:15.
97. Tandukar S, Palevsky PM. Continuous renal replacement therapy: who, when, why, and how. *Chest* 2019;**155**:626–638.
98. Karkar A, Ronco C. Prescription of CRRT: a pathway to optimize therapy. *Ann Intensive Care* 2020;**10**:32.
99. VA/NIH Acute Renal Failure Trial Network; Palevsky PM, Zhang JH, O'Connor TZ, Chertow GM, Crowley ST, *et al.* Intensity of renal support in critically ill patients with acute kidney injury. *N Engl J Med* 2008;**359**:7–20.
100. RENAL Replacement Therapy Study Investigators; Bellomo R, Cass A, Cole L, Finfer S, Gallagher M, *et al.* Intensity of continuous renal-replacement therapy in critically ill patients. *N Engl J Med* 2009;**361**:1627–1638.
101. Uchino S, Toki N, Takeda K, Ohnuma T, Namba Y, Katayama S, *et al.* Validity of low-intensity continuous renal replacement therapy*. *Crit Care Med* 2013;**41**:2584–2591.
102. Leypoldt JK, Kamerath CD, Gilson JF, Friederichs G. Dialyzer clearances and mass transfer-area coefficients for small solutes at low dialysate flow rates. *ASAIO J* 2006;**52**:404–409.
103. Clark WR, Turk JE, Kraus MA, Gao D. Dose determinants in continuous renal replacement therapy. *Artif Organs* 2003;**27**:815–820.
104. Bitker L, Bayle F, Yonis H, Gobert F, Leray V, Taponnier R, *et al.* Prevalence and risk factors of hypotension associated with preload-dependence during intermittent hemodialysis in critically ill patients. *Crit Care* 2016;**20**:44.
105. Douvris A, Zeid K, Hiremath S, Bagshaw SM, Wald R, Beaubien-Souligny W, *et al.* Mechanisms for hemodynamic instability related to renal replacement therapy: a narrative review. *Intensive Care Med* 2019;**45**:1333–1346.
106. Murugan R, Bellomo R, Palevsky PM, Kellum JA. Ultrafiltration in critically ill patients treated with kidney replacement therapy. *Nat Rev Nephrol* 2021;**17**:262–276.
107. Murugan R, Kerti SJ, Chang CH, Gallagher M, Clermont G, Palevsky PM, *et al.* Association of net ultrafiltration rate with mortality among critically ill adults with acute kidney injury receiving continuous venovenous hemodiafiltration: a secondary analysis of the Randomized Evaluation of Normal vs Augmented Level (RENAL) of renal replacement therapy trial. *JAMA Netw Open* 2019;**2**:e195418.
108. Legrand M, Tolwani A. Anticoagulation strategies in continuous renal replacement therapy. *Semin Dial* 2021;**34**:416–422.
109. Zarbock A, Küllmar M, Kindgen-Milles D, Wempe C, Gerss J, Brandenburger T, *et al.* Effect of regional citrate anticoagulation vs systemic heparin anticoagulation during continuous kidney replacement therapy on dialysis filter life span and mortality among critically ill patients with acute kidney injury: a randomized clinical trial. *JAMA* 2020;**324**:1629–1639.
110. Bai M, Zhou M, He L, Ma F, Li Y, Yu Y, *et al.* Citrate versus heparin anticoagulation for continuous renal replacement therapy: an updated meta-analysis of RCTs. *Intensive Care Med* 2015;**41**:2098–2110.
111. Slowinski T, Morgera S, Joannidis M, Henneberg T, Stocker R, Helset E, *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.
112. Moriyama B, Henning SA, Neuhauser MM, Danner RL, Walsh TJ. Continuous-infusion beta-lactam antibiotics during continuous venovenous hemofiltration for the treatment of resistant gram-negative bacteria. *Ann Pharmacother* 2009;**43**:1324–1337.

113. Schetz M. Drug dosing in continuous renal replacement therapy: general rules. *Curr Opin Crit Care* 2007;**13**:645–651.
114. Taniguchi T, Shibata K, Saito S, Matsumoto H, Okeie K. Pharmacokinetics of milrinone in patients with congestive heart failure during continuous venovenous hemofiltration. *Intensive Care Med* 2000;**26**:1089–1093.
115. Puttonen J, Kantele S, Kivikko M, Häkkinen S, Harjola VP, Koskinen P, *et al.* Effect of severe renal failure and haemodialysis on the pharmacokinetics of levosimendan and its metabolites. *Clin Pharmacokinet* 2007;**46**:235–246.
116. Pistolesi V, Morabito S, Di Mario F, Regolisti G, Cantarelli C, Fiaccadori E, *et al.* A guide to understanding antimicrobial drug dosing in critically ill patients on renal replacement therapy. *Antimicrob Agents Chemother* 2019;**63**:e00583-19.
117. Kanji S, Roger C, Taccone FS, Muller L. Practical considerations for individualizing drug dosing in critically ill adults receiving renal replacement therapy. *Pharmacotherapy* 2023; **43**:1194–1205.
118. Uchino S, Bellomo R, Morimatsu H, Morgera S, Schetz M, Tan I, *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.
119. Jeon J, Kim DH, Baeg SI, Lee EJ, Chung CR, Jeon K, *et al.* Association between diuretics and successful discontinuation of continuous renal replacement therapy in critically ill patients with acute kidney injury. *Crit Care* 2018;**22**:255.
120. Chen X, Chen Z, Wei T, Li P, Zhang L, Fu P. The effect of Serum neutrophil gelatinase-associated lipocalin on the discontinuation of continuous renal replacement therapy in critically ill patients with acute kidney injury. *Blood Purif* 2019;**48**:10–17.
121. Li Y, Deng X, Feng J, Xu B, Chen Y, Li Z, *et al.* Predictors for short-term successful weaning from continuous renal replacement therapy: a systematic review and meta-analysis. *Ren Fail* 2023;**45**:2176170.
122. Katulka RJ, Al Saadon A, Sebastianski M, Featherstone R, Vandermeer B, Silver SA, *et al.* Determining the optimal time for liberation from renal replacement therapy in critically ill patients: a systematic review and meta-analysis (DOnE RRT). *Crit Care* 2020;**24**:50.
123. Klouche K, Brunot V, Larcher R, Lautrette A. Weaning from kidney replacement therapy in the critically ill patient with acute kidney injury. *J Clin Med* 2024;**13**:579.
124. van der Voort PHJ, Boerma EC, Koopmans M, Zandberg M, de Ruiter J, Gerritsen RT, *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.
125. Zeng Z, Shen Y, Wan L, Yang X, Liang Z, He M. Risk factors for unplanned weaning of continuous renal replacement therapy in ICU patients: a meta-analysis. *Ren Fail* 2024; **46**:2387431.
126. Finkel KW, Podoll AS. Complications of continuous renal replacement therapy. *Semin Dial* 2009;**22**:155–159.
127. Gautam SC, Lim J, Jaar BG. Complications associated with continuous RRT. *Kidney360* 2022;**3**:1980–1990.
128. Parienti J-J, Thirion M, Mégarbane B, Souweine B, Ouchikhe A, Polito A, *et al.* Femoral vs jugular venous catheterization and risk of nosocomial events in adults requiring acute renal replacement therapy. *JAMA* 2008;**299**:2413.
129. Akhoundi A, Singh B, Vela M, Chaudhary S, Monaghan M, Wilson GA, *et al.* Incidence of adverse events during continuous renal replacement therapy. *Blood Purif* 2015;**39**: 333–339.
130. Sigwalt F, Bouteleux A, Dambricourt F, Asselborn T, Moriceau F, Rimmelé T. Clinical complications of continuous renal replacement therapy. *Contrib Nephrol* 2018;**194**: 109–117.
131. Troyanov S, Geadah D, Ghannoum M, Cardinal J, Leblanc M. Phosphate addition to hemodiafiltration solutions during continuous renal replacement therapy. *Intensive Care Med* 2004;**30**:1662–1665.
132. Culley CM, Bernardo JF, Gross PR, Guttendorf S, Whiteman KA, Kowiatek JG, *et al.* Implementing a standardized safety procedure for continuous renal replacement therapy solutions. *Am J Health Syst Pharm* 2006;**63**:756–763.
133. Wu M-Y, Hsu Y-H, Bai C-H, Lin Y-F, Wu C-H, Tam K-W. Regional citrate versus heparin anticoagulation for continuous renal replacement therapy: a meta-analysis of randomized controlled trials. *Am J Kidney Dis* 2012;**59**:810–818.
134. Ebo DG, Bosmans JL, Couttenye MM, Stevens WJ. Haemodialysis-associated anaphylactic and anaphylactoid reactions. *Allergy* 2006;**61**:211–220.
135. Slessarev M, Salerno F, Ball IM, McIntyre CW. Continuous renal replacement therapy is associated with acute cardiac stunning in critically ill patients. *Hemodial Int* 2019;**23**: 325–332.
136. Tuchman S, Khademian ZP, Mistry K. Dialysis disequilibrium syndrome occurring during continuous renal replacement therapy. *Clin Kidney J* 2013;**6**:526–529.