CRRT for sepsis-induced acute kidney injury

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Purpose of review
Sepsis-induced acute kidney injury (SI-AKI) represents the first cause of AKI in ICUs, and renal replacement therapy (RRT) is frequently applied in advanced AKI stages. The debate between 'rescue' indications for RRT start in patients with severe AKI (acidosis, hyperkalemia, uremia, oliguria/anuria, volume overload) and a proactive RRT initiation is still ongoing. In addition, current SI-AKI pathophysiologic theory has identified the toxic effects of soluble middle-molecules released during sepsis and inflammation (pathogen and damaged associated molecular patterns).
The purpose of the present review is to summarize the recent literature on RRT for patients with SI-AKI. Supportive or replacement measures for severe stages of renal dysfunction and blood purification techniques for sepsis syndrome will be reviewed.

Recent findings
Anticipated RRT for SI-AKI does not seem to improve survival or renal recovery. There is no clinical advantage by delivering continuous RRT at high doses for blood purification purposes. Similarly, specific applications with dedicated devices and membranes have yielded no clinical benefit in these patients, so far.

Summary
In the present review, the recent insights and results from large randomized and nonrandomized trials in the area of RRT applied both as supportive measures for kidney failure and blood purification techniques are described.

Keywords
acute kidney injury, high-cutoff membranes, high-volume hemofiltration, renal replacement therapy, sepsis

INTRODUCTION

Sepsis-induced acute kidney injury (SI-AKI) is currently accounted as the first cause of AKI in the ICU [1]. SI-AKI affects almost 50% of critically ill septic patients [1] with 15–20% of them requiring renal replacement therapy (RRT) [2▪,3]. SI-AKI is linked with short and long-term adverse outcomes including the development of chronic kidney disease and increased risk of death [4]. SI-AKI associated mortality rates remain remarkably high, with 50–60% of ICU patients receiving RRT not surviving their hospital admission [5]. In a recently published substudy of the Intensive Care Over Nations audit, a multicenter worldwide audit, conducted on 4727 adult critically ill patients with AKI [6] (1318, 68%, with SI-AKI), mortality rate was higher in patients receiving RRT (40%) compared to those without RRT (22%) with no difference between hemofiltration versus hemodialysis [3].

The present review will summarize current literature on RRT for patients with SI-AKI as a supportive measure for severe stages of AKI. RRT has also been applied for the treatment of sepsis syndrome (clearance of inflammatory mediators) as blood purification therapy. These studies will be listed and critically reviewed.

PATHOPHYSIOLOGY OF SEPSIS-INDUCED ACUTE KIDNEY INJURY AND RATIONAL FOR BLOOD PURIFICATION

SI-AKI is a specific 'endotype' of AKI, distinct from nonseptic AKI [7▪▪,8]. The mechanisms of SI-AKI associated kidney damage come from blood flow

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KEY POINTS

- Sepsis is the first cause of AKI in the ICU. It is associated with short and long-term adverse outcomes and increased risk of death. Globally, 15–20% of patients with SI-AKI develop severe stages of renal insufficiency and need RRT.
- Preemptively commencing RRT for SI-AKI does not seem to improve survival or renal recovery.
- No clinical advantage has been demonstrated by providing CRRT doses beyond 25 ml/kg/h. Although there is a clear biologic rationale for blood purification techniques in septic patients, high-volume hemofiltration and special membranes have yielded no clinical benefit in SI-AKI patients.

redistribution and toxic and/or immunologic causes [9,10]. Toxins causing tubular injury are grouped in the class of Pathogen Associated Molecular Patterns (e.g., lipopolysaccharide), Damage Associated Molecular Patterns, endogenous molecules released by injured or necrotic cells, inflammatory cytokines and chemokines (e.g., IL-6, IL-8, IL-18, tumor necrosis factor) and complement fragments [9,10]. These medium-sized molecules [11▪▪] may reach the tubules through glomerular filtration and by acting on endothelial cells located in the peritubular capillaries causing derangement of tubular function at the basolateral compartment and biologic alterations, loss of cell polarity, apoptosis, enhanced senescence, and differentiations of tubular epithelial cells to fibroblasts [12,13]. Based on the 'humoral pathogenesis' of SI-AKI, RRT has been used as a specific treatment to protect and improve renal function, other than replace it in the phase of oligo-anuria.

TIMING FOR RENAL REPLACEMENT THERAPY IN SEPSIS-INDUCED ACUTE KIDNEY INJURY

The optimal time to start RRT in the setting of SI-AKI is still undefined. The conventional indications for commencing RRT in patients with AKI (refractory acidosis, severe hyperkalemia, uremia, oliguria/anuria, and volume overload unresponsive to diuretic therapy) have long been recognized and universally accepted by nephrologists and intensive care physicians [14]. However, it is widely known that such life-threatening complications may reach very different clinical consequences in different patients. Volume overload, electrolyte and acid–base derangements, and increment in inflammatory cytokines commonly occur in patients with sepsis even without advanced stages of AKI. These insults may potentially cause further damage to the kidney and lessen the chance of renal recovery [15]. Commencing RRT early in the patients with SI-AKI could limit fluid overload, organ injury, and, theoretically, contribute to manage the abnormal host response to infection [16▪▪,17]. On the other side, to start RRT proactively, when renal function is still adequate or before a clear understanding of its eventual rapid recovery, may expose patients to the risks of unnecessary extracorporeal blood circulation (e.g., contact with nonbiocompatible surfaces, anticoagulation, immobilization, and so on) with additional undesired loss of antibiotics or other solutes (immunosuppressant drugs, phosphate, so on) [18]. Recently, three randomized controlled trials (RCTs) have explored this issue, although not in the specific context of SI-AKI: Wald *et al.* [19▪] conducted a randomized open-label pilot trial comparing accelerated (12 h or less once fulfilling the criteria for KDIGO stage 2 AKI) to standard RRT initiation in critically ill adults. The investigators found no significant difference in 90-day survival or RRT-related complications between groups even if this feasibility pilot trial was underpowered to detect differences in mortality. In early 2016, Zarbock *et al.* [20▪▪] published a RCT (the ELAIN trial) on early versus delayed RRT strategy showing a significant reduction in 90-day mortality in the early group. Almost contemporary, Gaudry *et al.* [21▪▪] published an apparently similar RCT (the AKIKI trial) that failed to reach the benefit in 60-day mortality. Table 1 summarizes the similarities and differences of these studies. In spite of controversial results of the two RCTs, significant differences in study design, population, and choice of RRT modality should be taken into consideration in the attempt to appraising any conclusion about RRT timing (Table 1) [22]. Furthermore, beyond isolated variables, such as the number of hours needed to start or a specific metabolic parameter or AKI stage, a more personalized good-sense approach should guide our clinical decisions [23]. Although in specialized centers, it seems well tolerated to proactively start an early treatment, the final decision should take into account a number of clinical data including state of fluid balance, catabolic conditions, need for nephrotoxic drugs, parenteral nutrition or blood products, coagulation disorders, hemodynamic instability, vascular access, and finally, the 50% possibility of a timely spontaneous urine flow recovery. Two further ongoing trials will hopefully better clarify the issue of timing in the next future: 'The Standard versus Accelerated Initiation of Renal Replacement Therapy in Acute Kidney Injury (STARRT-AKI, NCT02568722)' trial and the 'Initiation of Dialysis Early versus

Table 1. Recent randomized controlled trials on renal replacement therapy timing

	ELAIN trial [20▪▪]	**AKIKI trial [21▪▪]**
Primary outcome	90-day mortality	Survival at 60 day
Secondary outcomes	28 and 60-day mortality Clinical evidence of organ dysfunction Recovery of renal function Requirement of RRT after day 90 Duration of renal support ICU and hospital LoS Markers of inflammation (IL-6, IL-8, IL-10, IL-18, MIF)	Receipt of RRT at least once with the delayed strategy Numbers of RRT-free days Dialysis catheter-free days MV-free days Vasopressor therapy-free days SOFA score at day 3 and day 7 Vital status at day 28 ICU and hospital LoS Proportion of patients with treatment limitations Occurrence of nosocomial infections or complications potentially related to AKI or RRT
Study design	**Single-center randomized clinical trial**	**Multicenter randomized trial**
Setting and patients	General adult ICU. Many post (cardiac) surgical patients Early: within 8 h of diagnosis of KDIGO stage 2 Delayed: within 12 h of diagnosis of KDIGO stage 3 or no initiation	General adult ICU (not postsurgical) Early: immediately after randomization (KDIGO stage 3+ MV, or catecholamines, or both)[a] Delayed: if one of the following: Severe hyperkalaemia Metabolic acidosis Pulmonary edema BUN >112 mg/dl Anuria or oliguria >72 h after randomization
Results/patients	231 (early: 112; delayed: 119) Received RRT (early: 112; 100%; delayed: 108; 91%) Timing (RRT start) Early: 6.0 h (Q1, Q3: 4.0, 7.0) Delayed: 25.5 h (Q1, Q3: 18.8, 40.3)	619 (early: 311; delayed: 308) Received RRT (early: 305; 98%; delayed: 157; 51%) Timing (RRT start) Early: median of 2.0 h (IQR, 1–3) Delayed: median 57 h (IQR, 25–83)
Primary endpoint 90-day mortality	Early: 39.3% Delayed: 54.7% ($P=0.03$)	Early: 58.5% Delayed: 49.7% ($P=0.79$)
Secondary endpoints	Duration of RRT Early: 9 days (Q1, Q3: 4, 44) for the early group; delayed: 25 days (Q1, Q3: 7, >90); $P=0.04$ Enhanced recovery of renal function at day 90 Early: 53.6%; Delayed: 38.7%; $P=0.02$ MV Early: 125.5 h (Q1, Q3: 41, 203); delayed: 81.0 days (Q1, Q3: 65, 413); $P=0.002$ LoS (hospital) Early: 51 days (Q1, Q3: 31, 74); delayed 82 days (Q1, Q3: 67, >90) for the delayed group; $P<0.001$ LoS (ICU) Early: 19 days (Q1, Q3: 9, 29); delayed: 22 days (Q1, Q3: 12, 36) in the delayed group; $P=0.33$ Requirement of RRT on day 90 Early: 13.4%; delayed: 15.1%; $P=0.80$ CK (IL-6) Early: 399.4 pg/ml; delayed: 989.3 pg/ml; $P=0.02$ CK (IL-8) Early: 65.7 pg/ml; delayed: 215.5 pg/ml; $P=0.001$ MIF, IL-10, and IL-18 did not differ between groups	In the delayed-strategy group, 61% of the 155 who were alive at day 60 had not received RRT Dependence on RRT at day 28 Early: 12%; delayed: 10%; $P=0.51$ Dependence on RRT at day 60 Early: 12%; delayed: 10%; $P=0.12$ Catheter-related bloodstream infections Early: 10%; delayed: 5%; $P=0.03$ Hypophosphatemia Early: 22%; delayed: 15%; $P=0.03$ Other secondary outcomes did not differ significantly between the two study groups Adequate diuresis together with no need for RRT were observed earlier in the delayed-strategy group than in the early strategy group ($P<0.001$)
Summary of findings	Early RRT compared to delayed initiation of RRT reduced mortality over the first 90 days	No significant difference with regard to mortality between an early and a delayed strategy for the initiation of RRT. A delayed strategy averted the need for RRT in an appreciable number of patients

AKI, acute kidney injury; BUN, blood urea nitrogen; CK, cytokine; IQR, interquartile range; KDIGO, Kidney Disease Improving Global Outcome; LoS, length of stay; MIF, macrophage migration inhibitory factor; MV, mechanical ventilation; Q, quartile; RRT, renal replacement therapy; SOFA, sequential organ failure assessment.
[a]Without life-threatening conditions related to renal failure. AKI compatible with a diagnosis of acute tubular necrosis in the context of ischemic or toxic injury.

Delayed in the Intensive Care Unit (IDEAL-ICU, NCT01682590)'.

INTENSITY OF RENAL REPLACEMENT THERAPY WITH STANDARD FILTERS IN SEPSIS-INDUCED ACUTE KIDNEY INJURY

The optimal intensity (clearance × time) [24] of RRT in critically ill patients with SI-AKI remains controversial. The application of convective modality in SI-AKI is attracting as the inflammatory mediators, medium-sized (8–60 kDa) water soluble and free of binding to the plasma proteins molecules, can be cleared with the hemofilters. Several large RCTs have attempted to prove this concept by investigating clinical outcomes, in intensive/higher volume hemofiltration or hemodiafiltration versus less-intensive doses in septic patients. The first single center landmark RCT by Ronco *et al.* [25] showed a significant survival benefit with effluent rates of 35–45 ml/kg/h compared to 20 ml/kg/h. Subsequent controlled studies, that addressed the dose of RRT applied to patients with severe AKI, the Randomized Evaluation of Normal versus Augmented Level of RRT in ICU and The Veteran Affairs/National Institute of Health Acute Renal Failure Trail Network Study (ATN), failed to replicate this result [26,27]. Currently, KDIGO guidelines recommend a 'standard' intensity of 20–25 ml/kg/h [14]. However, it has been demonstrated that the actual delivered dose is frequently lower than the prescribed one (downtime effect) [28▪▪]. Thus, prescribing a 30–35 ml/kg/h dose may be more appropriate when commencing continuous renal replacement therapy (CRRT), especially in SI-AKI.

Owing to the possibility to clear inflammatory mediators from the bloodstream with conventional hemofilters (high flux membranes with ultrafiltration coefficient (K_{UF}) > 25 ml/h/mmHg/m^2) [24], many studies have explored the potential benefits of prescribing 'high dose' CRRT in order to cope with the elevated generation rate of such molecules in septic patients [29]. Continuous treatments with a dose greater than 35 and 45 ml/kg/h identify high-volume hemofiltration (HVHF) and very HVHF modalities, respectively [29]. Five RCTs on RRT, performed with standard high flux membranes, have been performed in septic patients with AKI (Table 2). None of these studies showed any significant benefit in terms of improvement of primary or secondary outcomes by the high intensity prescription. In 2017, a Cochrane on HVHF for sepsis was published [35▪▪]. The analysis included four studies and 201 patients. Investigators reported no adverse effects of HVHF, but they concluded that new large RCTs are necessary to investigate HVHF in patients with sepsis. Possible reasons for lack of HVHF benefit could be an increased clearance of antimicrobials leading to inadvertent and potentially harmful sub-therapeutic levels, increase in electrolytes disturbances (e.g., hypokalemia, hypophosphatemia), depletion of micronutrients, and ineffective at providing adequate mediators clearance at the cellular level rather than in the circulation. Therapeutic drug monitoring is crucial for patient under RRT for septic AKI as antibiotics are the mainstay of sepsis treatment and substantial changes in pharmacokinetic parameters occur in these patients, including increased volume of distribution, hypoalbuminemia, the presence of other extracorporeal circuits (i.e., extracorporeal membrane oxygenation), unnecessarily high RRT dose prescriptions and changes in renal and nonrenal clearances. It recently became clearer that in critically ill patients, these aspects may exceed the reduced antibiotic clearance secondary to renal dysfunction [36]. In general, careful dose adjustments should be provided [37▪]. In addition, excessive fear of antibiotic toxicity (especially nephrotoxicity) and limited drug dosing resources may contribute to detrimental suboptimal antibiotic therapy whose clinical relevance may have been overlooked.

SPECIAL MEMBRANES AND MODALITIES: HIGH CUTOFF AND ADSORPTION

Owing to the apparent inefficacy of increasing dialysis intensity, filters specifically dedicated to septic patients have been designed [38,49,40▪▪]. High cut-off (HCO) membranes have been proposed for septic patients to enhance the clearance of inflammatory mediators [17]. Currently available membranes achieve effective removal of substances in the range of 20–60 kDa: larger molecules are retained, although pores size ranges nominally reach larger values because of secondary layer formation and membrane fouling [39]. So far, 10 small clinical studies, recently summarized in a review article, with variable results on HCO treatment application have been published (Table 3) [39]. Very recently, Atan *et al.* [11▪▪] have published a phase II double-blind randomized study comparing continuous veno-venous hemofiltration-standard (CVVH-Std) with continuous veno-venous hemofiltration-HCO (CVVH-HCO) in critically ill patients with SI-AKI requiring vasopressor support. The primary end-point was hemodynamic impact of CVVHCO, expressed as hours of norepinephrine-free time within the first week of treatment. The investigators randomized patients to receive either CVVH-Std or CVVH-HCO within 12 h of a decision to commence hemofiltration. Patients who underwent CVVH-Std

Table 2. Randomized studies on renal replacement therapy in septic patients at different intensity and modalities

Authors	Year	Setting and patients	RRT filter	Prescription	Main findings
Payen *et al.* [30]	2009	Sepsis: CVVH (39 patients) versus Standard therapy (39 patients)	Polysulfone membrane Molecular weight cutoff 30 kDa	24.7 ml/kg/h (96 h)	Study interrupted prematurely. Number and severity of organ failures significantly higher in the CVVH group ($P < 0.05$) No modifications in plasma CK levels
Zhang *et al.* [31]	2012	Severe sepsis: CVVH–HVHF (139 patients) versus EHVHF (141 patients)	Polysulfone membrane	49.99 ml/kg/h (8.88 days) versus 87.54 ml/kg/h (9.38 days)	No difference in mortality: At 28 days: 58.3% in HVHF and 57.4% in EHVHF At 60 days: 62.6% in HVHF and 59.6% in EHVHF At 90 days: 63.3% in HVHF and 59.6% in EHVHF (P = NS) No effect on survival at any time point in the subgroup analysis of septic shock patients
(IVOIRE) Joannes-Boyau *et al.* [32▪]	2013	Septic shock: CVVH HVHF (66 patients) versus SVHF (77 patients)	Polyethersulfone filter Molecular weight cutoff 35 kDa	65.6 ml/kg/h (HVHF) (96 h) versus 33.2 ml/kg/h (SVHF) (96 h)	No difference in mortality at 28 days: HVHF 37.9% SVHF 40.8% No differences in secondary endpoints
Quenot *et al.* [33]	2015	Septic shock: CVVH very HVHF (29 patients) versus Usual care (31 patients)	Cascade system[a]	120 ml/kg/h (48 h)	No difference in catecholamine-free days No difference in mechanical ventilation-free days By multivariate analysis, the number of RRT-free days was significantly higher in the HVHF group No difference in mortality at 7, 28, or 90 days
(HICORES) Park *et al.* [34]	2016	Sepsis-induced AKI (>injury according to RIFLE grading) CVVHDF 40 ml/kg/h (107 patients) CVVHDF 80 ml/kg/h (105 patients)	Polyacrylonitrile AN 69 membrane	34.3 ml/kg/h (5.4 days) (conventional dose) versus 75.1 ml/kg/h (6.2 days) (high dose)	No difference in mortality: At 28 days: 64.5% in standard dose group and 65.7% in high dose group At 90 days: 74.8% in standard dose group and 78.1% in high dose group (P = NS) No difference in lengths of ICU stay or total hospital stay among survivors No differences in recovery of kidney function at 28 or 90 days after randomization No difference in the occurrence of adverse events No difference in IL-6, IL-8, IL-1b, and IL-10 levels measured at the dialyzer inlet or outlet Different CK levels between dialyzer inlet and outlet only in high dose group No difference in serum CK levels measured at baseline or 24 h after CVVHDF initiation Serum IL-6 and IL-8 levels between baseline and after 24 h of CVVHDF were significantly decreased at 24 h only in high-dose group

CK, cytokines; CVVH, continuous veno-venous hemofiltration; EHVHF, extra-high volume hemofiltration; HVHF, high volume hemofiltration; NS, nonsignificant; RIFLE, risk, injury, failure, loss, end-stage renal disease; RRT, renal replacement therapy; SVHF, standard volume hemofiltration.
[a]Two hemofilters with different cutoffs: (1) hemofilter filters blood through a conventional membrane (cutoff 30–40 kDa); (2) This first ultrafiltrate is refiltered through a second membrane with a lower cutoff (15 kDa). This second ultrafiltrate is reinjected into the blood circuit upstream of the first hemofilter. High and middle molecular weight molecules are retained by the second membrane and are concentrated in a limited volume of fluid effluent [33].

Table 3. Human studies performed with high cutoff membranes for renal replacement therapy

Authors	Year	Setting and patients	RRT filters and modalities	Prescription	Endpoint	Main findings
Morgera *et al.* [41]	2003	RCT 28 septic patients with acute renal failure (14:14:3)	High-flux polyamide hemofilter (P2SH, surface area 0.6 m^2) HCO-CVVH (12 h) alternated to C-HF (12 h) versus C-HF for 60 h (versus short HCO and C-HF in 3 healthy volunteers)	1 l/h, postdilution (both)	PBMCs function restoration by HCO	None
Morgera *et al.* [42]	2003	Observational 16 patients with septic shock and MOF	High-flux polyamide hemofilter (P2SH, surface area 0.6 m^2) HCO-CVVH (12 h) alternated to C-HF (12 h) for 5 days	1 l/h, postdilution (both)	IL-6 K: 12–17 ml/min TNFα K: negligible	Insignificant improvement in SOFA score
Morgera *et al.* [43]	2003	24 patients with MOD because of septic shock (6:6:6:6)	High-flux polyamide hemofilter (P2SH, surface area 1.1 m^2) Group 1: CVVH 1 l/h Group 2: CVVH 2.5 l/h Group 3: CVVHD 1 l/h Group 4: CVVHD 2.5 l/h	1 or 2.5 l/h postdilution hemofiltration versus 1 or 2.5 hemodialysis for 72 h	IL-1ra K: 18–26 ml/min IL-6 K: 16–20 ml/min	No differences between groups in different severity scores
Morgera *et al.* [44]	2004	RCT 28 septic patients with acute renal failure (14:14:2)	High-flux polyamide hemofilter (P2SH, surface area 0.6 m^2) HCO-CVVH (12 h) alternated to C-HF (12 h) versus C-HF for 60 h (vs. short HCO and C-HF in 2 healthy volunteers)	1 l/h, postdilution (both)	The PML phagocytosis rate measured at the end of the third HCO session was significantly decreased compared to baseline values	None
Morgera *et al.*[45]	2006	RCT 30 patients with sepsis-induced acute renal failure (20:10) 2 HCO patients subsequently excluded	High-flux polyamide hemofilter (P2SH, surface area 1.1 m^2) HCO-CVVH versus C-HF for 48 h	2.5 l/h, postdilution (both)	IL-1ra K: 39 ml/min IL-6 K: 36–40 ml/min	Slight reduction of SAPS score in the HCO group; significant reduction of adjusted norepinephrine dose
Haase *et al.* [46]	2007	Double-blind, crossover, RCT 10 septic patients with acute renal failure	PAES surface area of 1.1 m^2; custom-made 4 h of HCO-IHD and 4 h of standard HF-IHD in random order with 4 h wash-out (no treatment)	Blood flow at 200 ml/min and dialysate flow at 300 ml/min in both groups	IL-6 K: 9.6–14.1 ml/min; reduction of plasma levels of IL-6, IL-8, and IL-10	Insignificant greater reduction on norepinephrine dose in HCO group

Table 3 (*Continued*)

Authors	Year	Setting and patients	RRT filters and modalities	Prescription	Endpoint	Main findings
Kade *et al.* [47]	2016	Retrospective 28 patients with septic shock	PAES membrane (Septex) HCO-CVVHDF	Blood flow 150 ml/min, dialysis flow 1200 ml/h. Predilution fluid 250 ml/h	IL-6 K: 59–75 ml/min	None
Chelazzi *et al.* [48]	2016	Retrospective 24 septic patients with MDR gram-negative infection (16:8)	PAES membrane (Septex) HCO-CVVHD versus CVVHDF	HCO: 35 ml/kg/h versus CVVHDF 45 ml/kg/h	None	HCO group lower ICU-LOS, days Ventilation days/ICU-LOS, vasopressor days/ICU-LOS, ICU mortality
Atan *et al.* [49]	2016	Double-blind RCT 14 patients with AKI and underlying shock requiring vasopressor infusion (6:8) A nested cohort of patients within a larger double-blind, randomized, parallel group, controlled trial	Polyethersulfone filters, surface area of 1.1 m^2 HCO-CVVH versus CVVH	Blood flow 250 ml/min, 25 ml/kg/h predilution both groups	IL-6 K: 36 ml/min IL-8 K: 26 ml/min IL-10 K: 9.66 ml/min	None
Villa *et al.* [50]	2017	Prospective, multicenter 38 patients with septic shock and AKI	PAES membrane (Septex) HCO-CVVHD	35 ml/kg/h for 72 h (any KDIGO stage >0)	Decrease of IL-6, IL-10, and TNFα especially in survivors	Survivors quick SOFA decrease. KDIGO stage and lactates associated with mortality
Atan *et al.* [11▪▪]	2018	>50% for each group with septic shock Single-center double-blind RCT	CVVH with custom manufactured polyethersulfone standard hemofilters (CVVH-Std) Polyethersulfone HCO filters (CVVH-HCO) (P2SH filters, 1.12 m^2; Gambro, Hechingen, Germany)	25 ml/kg/h	Hours of norepinephrine-free time within the first week of treatment Change in the levels of IL-1, IL-6, and IL-10, the percentage change in serum albumin levels, the total amount of albumin administered to each patient over the first 7 days, the filter life, the maximum rate of vasopressor infusion per day, and duration of hemofiltration	No difference in primary and secondary outcome Overall combined CK levels had fallen to 62.2% of baseline at 72 h for CVVH-HCO ($P < 0.0001$) and to 75.9% of baseline with CVVH-Std ($P = 0.008$) there were no between group differences

AKI, acute kidney injury; C-HF, conventional hemofiltration; CK, cytokine; CVVH, continuous veno-venous hemofiltration; CVVHD, continuous veno-venous hemodialysis; CVVHDF, continuous veno-venous hemodiafiltration; HCO, high cutoff; IHD, intermittent hemodialysis; K, clearance; KDIGO, Kidney Disease Improving Global Outcome; LOS, length of stay; MDR, multidrug resistant; MOD, multiorgan dysfunction; MOF, multiorgan failure; PAES, polyarylethersulfone; PBMC; peripheral blood mononuclear cell; PML, polymorphonuclear leukocytes; RCT, randomized controlled trial; RRT, renal replacement therapy; SOFA, sequential organ failure assessment; TNF, tumor necrosis factor.

were treated with custom manufactured polyethersulfone standard hemofilters (nominal cutoff point of 30 kDa) or polyethersulfone HCO filters (nominal cutoff point of 100 kDa). Overall, 38 patients were assigned to each group. Median HCO filter life was 9 h (4–17 h) versus 10 h (5.5–19.8 h) in CVVH-Std ($P = 0.21$). Median cumulative norepinephrine-free time and the maximum noradrenaline rates of infusion per day were similar for both groups. Changes in serum albumin levels within the first 7 days were not significantly different between the two groups. There was no difference in time to permanent cessation of hemofiltration. Interestingly, at 20 days about 70% patients in the CVVH-Std versus 50% in the HCO-CVVH were surviving ($P = 0.052$). Changes in cytokines levels was shown in a previous publication in which no significant between group differences in plasma levels for each cytokine over the 72 h treatment period were present. For all cytokines combined, however, the median sieving coefficient was higher for CVVH-HCO as was the mass removal rate by ultrafiltration. This study unfortunately appears as a further confirmation that either our understanding of SI-AKI syndrome and sepsis pathogenesis in general is inadequate or the means so far utilized in order to control it are not efficient.

In the same context appears to be the technique known as coupled-plasma filtration adsorption (CPFA). During CPFA, plasma, separated from blood by a plasma-filter, is run through a synthetic resin cartridge (with adsorption capacity for inflammatory mediators) and then returned to the blood circuit in which a hemofilter removes excess fluid and allows renal replacement [51]. CPFA is a sorbent technology based on RRT for removal of inflammatory mediators. Two multicenter, randomized trials comparing CPFA versus standard therapy, the COMPACT (COMbining Plasma-filtration and Adsorption Clinical Trial) study and the COMPACT2, were completed [52]. The first study did not find any statistical difference in hospital mortality, or in secondary endpoints, whereas the COMPACT2 was prematurely terminated because of a higher early mortality rates in septic shock patients treated with CPFA. After this ad interim analysis an urgent field safety notice was delivered (http://www.hsa.gov.sg/content/dam/HSA/HPRG/Medical_Devices/Updates_and_Safety_reporting/Field_Safety_Corrective_Action/FSN/2018/April%202018/HSA%206004101-046-18-04_46%20FSN_Redacted.pdf).

During the last years, other new membranes have been conceived with the specific aim of providing renal support combined with the attempt to treat SI-AKI. These membranes cope with the enhanced clearance on middle-to-high molecular weight solutes of super-high-flux membranes with a particularly elevated adsorptive capacity. Adsorption implies the retention of specific proteins (e.g., inflammatory mediators, cytokines) within the membrane fibers after the interaction with variable polarity ionic charges. For instance, the AN69 and the AN69 surface-treated (AN69ST) membranes have a highly hydrophilic hydrogel structure. Yumoto *et al.* [53] by comparing four different membranes showed that the AN69ST had the highest efficiency of High-Mobility Group Box 1 Protein removal. Lastly, the oXiris is a recently manufactured hemofilter membrane representing then the evolution of AN69 and AN69ST that incorporates some interesting properties as cytokines and endotoxin adsorbing activity and, interestingly, low thrombogenicity [54]. Whether cytokine/endotoxin-adsorbing hemofilters will be recognized as adjunctive effective treatment of sepsis, septic shock and SI-AKI in the near future, is actually unknown and dedicated RCTs are warranted.

NET ULTRAFILTRATION AND FLUID BALANCE

Retrospective and prospective studies have clearly shown that patients with AKI have higher mortality if they have a positive fluid balance [55]. The DoReMIFA study included a total of 991 patients (23.35% with sepsis on admission) and showed that the odds ratio for hospital mortality increased by 1.075 (95% confidence interval 1.055–1.095) with every 1% increase of maximum fluid overload (peak value of fluid overload observed during the entire ICU stay). This phenomenon was a continuum and independent of thresholds as previously reported; the speed of fluid accumulation was independently associated with ICU mortality; and fluid accumulation increased significantly in the 3-day period prior to the diagnosis of AKI and peaked 3 days later. These clear associations between fluid accumulation and mortality should encourage careful consideration on net ultrafiltration (fluid removal applied to patients during RRT) prescription and support the avoidance of accumulating positive fluid balance. Interestingly, a post hoc analysis of the Randomized Evaluation of Normal versus Augmented Level trial, initially conceived for the evaluation of different RRT intensities, clearly showed that the rapid (by the first 2–3 days of treatment) achievement of a negative fluid balance in critically ill patients with severe AKI was independently associated with improved survival [56].

CONCLUSION

Sepsis is a global epidemic condition frequently associated with the development of multiple organ

failure, AKI and high morbidity and mortality. A consistent number of patients with SI-AKI need RRT. Although the application of new RRT biotechnologies has opened to new potential therapeutic strategies, these modified modalities and materials have yet to show cost effectiveness and benefits in terms of mortality. The choice of early RRT start requires the careful evaluation of patients' overall clinical status and the possibility to further delay the treatment. There is insufficient evidence to suggest one technique and one membrane over the others in extracorporeal SI-AKI treatment. Cumulative fluid balance should always be carefully monitored as fluid overload is clearly associated with worse outcomes and it might be an effective trigger of proactive RRT inception.

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Conflicts of interest

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