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SUMMARY

Extracorporeal membrane oxygenation (ECMO) is a lifesaving procedure used in neonates, children, and adults with severe, reversible, cardiopulmonary failure. On the basis of single-center studies, the incidence of AKI occurs in 70%–85% of ECMO patients. Those with AKI and those who require renal replacement therapy (RRT) are at high risk for mortality, independent of potentially confounding variables. Fluid overload is common in ECMO patients, and is one of the main indications for RRT. RRT to maintain fluid balance and metabolic control is common in some but not all centers. RRT on ECMO can be performed via an in-line hemofilter or by incorporating a standard continuous renal replacement machine into the ECMO circuit. Both of these methods require specific technical considerations to provide safe and effective RRT. This review summarizes available epidemiologic data and how they apply to our understanding of AKI pathophysiology during ECMO, identifies indications for RRT while on ECMO, reviews technical elements for RRT application in the setting of ECMO, and finally identifies specific research-focused questions that need to be addressed to improve outcomes in this at-risk population.

Introduction

Extracorporeal membrane oxygenation (ECMO) is a lifesaving procedure used in neonates, children, and adults with severe, reversible, cardiopulmonary failure. These patients are at high risk of developing AKI and fluid overload (FO). Renal replacement therapy (RRT) is

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commonly used to maintain fluid balance and metabolic control; however, the optimal timing, methodology, and prescriptions to support ECMO patients with renal dysfunction have not been extensively studied. This review summarizes AKI pathophysiology in ECMO patients, appraises epidemiology data, discusses indications for RRT, explains technical aspects of concomitant RRT and ECMO, and proposes future research to improve outcomes in this vulnerable population.

Epidemiology of AKI and RRT Use in ECMO

Until recently, one of the main problems with AKI epidemiology studies was the lack of consensus definitions. The RIFLE (1,2) (risk, injury, failure, loss, and end stage) and Acute Kidney Injury Network (3) classification definitions have stratified patients by AKI severity using absolute or percentage changes in serum creatinine. Single-center studies using the RIFLE definition in ECMO patients show the incidence of AKI as follows: 71% of neonates with congenital diaphragmatic hernia (4), 71% of children with a cardiac indication for ECMO (5), 78% of adults with respiratory failure (6), and 81% of adults post-cardiotomy (7). The incidence of AKI using contemporary categorical definitions in other neonatal and pediatric patients on ECMO has not been conducted, but a multicenter retrospective analysis is underway (8).

These single-center studies also suggest an association between AKI and poor outcomes. Adults with AKI had a 78% mortality compared with 20% in non-AKI patients (6). Congenital diaphragmatic hernia infants on ECMO who developed severe AKI were more likely to die, had increased time on mechanical ventilation, and increased ECMO duration than those without AKI (4). These small, single-center studies show the strong association between AKI and mortality. However, sample size limits the ability to determine if AKI is an independent risk factor for mortality in these studies.

In a single-center study of 121 children and adults, those with AKI (serum creatinine .1.5 mg/dl or dialysis) had higher independent odds of death after controlling for confounders, with an adult odds ratio of 12.1 (95% confidence interval, 2.5–59) and a pediatric odds ratio of 24.0 (95% confidence interval, 4.2–137)] (9). Although there seems to be a significant association between AKI and mortality in these groups, the small sample size provides for an imprecise estimate of the true odds of mortality in those with AKI. Larger cohorts are needed to better understand the true effect size.

Recent evaluation of the Extracorporeal Life Support Organization (ELSO) registry sheds light on the independent association between renal dysfunction and mortality. The ELSO registry captures data from 170 centers around the world and is divided into cardiac and non-cardiac indications. To determine the effect of AKI and RRT on mortality, Askenazi et al. (10) evaluated 7941 non-cardiac neonates (aged 30 days, at initiation) and 1962 non-cardiac children (aged 19 years) from the ELSO registry between 1998 and 2008. For this analysis, AKI was defined as an International Classification of Diseases (Ninth Revision) code for ARF or serum creatinine $1.5 mg/dl, and RRT was determined by Current Procedural Terminology codes. The incidence of AKI and/or RRT in neonates and children was 25% and 46%; respectively. Patients with AKI and those who received RRT had higher mortality

than similar patients without AKI or RRT independent of potential confounders (demographics, ECMO characteristics, comorbidities, and physiologic parameters). Despite the po-tential limitations inherent to registry studies and the imprecise methods to define AKI in this population, these data suggest that therapies to prevent/ameliorate AKI and optimization of RRT could improve outcomes.

Pathophysiology of AKI in ECMO

Before patients are placed on ECMO, aggressive life-sustaining interventions have been implemented, yet the patient continues to have severe cardiopulmonary insufficiency. Indications for ECMO include reversible patient conditions with a high predicted mortality rate $80%. Before ECMO initiation, these critically ill patients are at high risk of AKI due to their condition (sepsis, ischemia, respiratory failure, cardiac failure, vasopressor requirements) and prevalent use of nephrotoxic medications.

In veno-arterial ECMO, cardiac output is a mixture of native cardiac (pulsatile) and ECMO pump flow (non-pulsatile). Although mechanical flow may be non-pulsatile, institution of venoarterial ECMO usually increases BP and flow to the vital organs including the kidneys. Veno-venous ECMO maintains native pulsatile cardiac output, and changes in renal perfusion are less than in veno-arterial ECMO. During initiation of ECMO, patient oxygenation improves, oxygen consumption is reduced, and hemodynamics improve in most patients. However, ECMO initiation with subsequent adjustments in vasopressors/ionotropes can cause rapid hemodynamic fluctuations that alter renal blood flow leading to ischemia/reperfusion-associated AKI (11).

Other factors associated with ECMO initiation predispose patients to incident or exacerbation of AKI. Blood exposure to artificial surfaces causes systemic inflammation (12, 13), a hypercoagulable state (11,14,15), and hemolysis/hemoglobinuria, which may be exacerbated by air/fluid interface and the generation of excessive negative pressure (16–20).

Indications for RRT on ECMO

As for other critically ill patients, classic RRT indications in patients on ECMO include uremia, acidosis, electrolyte abnormalities, and FO. Center-specific staff availability, local expertise, and experience with RRT on ECMO currently drive decisions to initiate RRT. We conducted a survey of participating ELSO centers that revealed tremendous inter-center variation for initiating RRT. The most common reported RRT indications were FO (43%), FO prevention (16%), AKI (35%), and electrolyte disturbances (4%) (21). These data suggest that treatment/prevention of fluid accumulation plays a major role in decision making for RRT initiation.

Cumulative FO should be calculated and assessed daily in ECMO patients to determine if RRT could benefit the overall care. The following simple formula to measure cumulative FO has been evaluated in multiple studies: [Cumulative Fluid Intake since Intensive Care Unit (ICU) Admission (in liters) – Cumulative Fluid Output since ICU Admission (in liters)/ICU Admission Weight (in kilograms)] 3 100 (22–27). Using changes in daily weight to express fluid balance provides a similar estimate of FO (28).

Cumulative FO is independently associated with mortality, worse oxygenation, longer length of stay, and mechanical ventilation in critically ill patients receiving continuous RRT, as well as in those who do not receive RRT (25,29–35) (Table 1). Early studies investigating the development of FO using radio-labeled isotopes showed an elevation in both the total body water and extracellular fluid space in ECMO patients (36). Cumulative FO and failure to return to dry weight are associated with higher mortality (28,37) and prolonged ECMO duration (38). Moreover, improvement in FO or improving fluid balance is associated with improved lung function and time to weaning of ECMO (36,39). Neonates and children who receive concomitant RRT on ECMO compared with ECMO alone have decreased cumulative FO (37,40,41). On the basis of these studies, the international ELSO guidelines recommend to “return the extracellular fluid volume to normal (dry weight) and maintain it there” (42). These studies suggest that early RRT to prevent FO may improve out-comes and warrants further investigation.

The overall treatment goals, and whether RRT would help to achieve these goals, should factor into the decision to initiate RRT. Initiation of RRT may allow for the administration of adequate nutrition, medications, and blood products, while avoiding further fluid accumulation. Likewise, if high diuretic doses are being used to maintain urine output, the risk of long-term ototoxicity and lack of data that diuretics improve outcomes in critically ill patients (43,44) should be balanced with the potential benefits of managing fluids with RRT.

Finally, when deciding to initiate RRT and evaluating overall patient prognosis, one should be aware that the likelihood of long-term ESRD in ECMO survivors requiring RRT is extremely low. Two large ECMO center studies have independently reported their experience with concomitant RRT and ECMO over a combined 20-year period and showed no incidence of ESRD in the absence of primary renal disease (45,46).

Technical Aspects of RRT While on ECMO

In unstable patients with multiple organ failure, ECMO can improve hemodynamic stability by increasing cardiac output via an ECMO pump (in veno-arterial ECMO) or by increasing native cardiac output by improved myocardial oxygenation (47). The extracorporeal circuit can serve as a platform for additional organ support therapies, including RRT. Currently, the US Food and Drug Administration has not approved any RRT device for use in conjunction with ECMO and such use is off label. Several RRT techniques are available to support ECMO patients with AKI and/or FO. Because there are no comparison studies of these techniques, practice is based on expert opinion and local experience. We therefore do not recommend a particular method to provide RRT.

RRT options during ECMO include peritoneal dialysis, intermittent hemodialysis, and continuous RRT (CRRT). Each has its own advantages and disadvantages (48–50). Patient factors, treatment goals, and center experience play a role in the RRT selected. RRT on ECMO is usually provided as a continuous modality because of hemodynamic instability. Continuous peritoneal dialysis may achieve the desired fluid management goals but provide less efficient management of electrolyte imbalance and clearance. CRRT is the most

common modality because it offers the ability of making rapid changes to targeted fluid balance and provides excellent solute clearance.

The two most common methods to provide CRRT are via the use of an in-line hemofilter or via a traditional CRRT device connected to the extracorporeal circuit. A recent international survey of 65 ECMO centers showed that 50.8% of centers exclusively use CRRT, 21.5% exclusively use an in-line hemofilter, and 23% use no RRT during ECMO (21).

RRT Using an In-Line Hemofilter

One method to provide CRRT is by incorporating an inline hemofilter into the ECMO circuit. The hemofilter is typically placed after the pump (to provide forward blood flow through the hemofilter) and before the oxygenator (to maintain the oxygenator's use as a clot and air trap in case of complications) (Figure 1). After passing through the hemofilter, the blood is returned to the prepump limb of the circuit. In this configuration, the shunt creates a disparity between the pump measured flow and the flow being delivered to the patient. An ultrasonic flow probe on the arterial return line is needed to determine the actual flow delivered to the patient. The hemofilter blood flow rate can be derived by subtracting the flow delivered to the patient from the total ECMO blood flow rate. The hemofilter blood flow rate can be adjusted via the use of a stopcock or other flow-restricting device; however, the potential for hemolysis and thrombus formation due to turbulent flow limit this practice.

Some centers use this technique to provide only slow continuous ultrafiltration. Other centers provide continuous convective clearance with replacement fluids delivered to the patient directly or through the ECMO circuit. Diffusive clearance can be achieved running countercurrent fluid using standard infusion pumps. Because these hemofilters are designed for use with high pressure systems, the fiber characteristics make diffusive clearance less effective than conventional membranes. In addition, the amount of ultra-filtration made is limited by the infusion pumps that maximize at approximately 1 L/h.

The hemofilter has the potential to generate large amounts of ultrafiltrate that can be regulated using a standard intravenous infusion device connected to the effluent port of the hemofilter. There are several methods to determine the amount of fluid being removed. The most precise method is to measure the actual volume of ultrafiltration removed using weight or a volumetric measuring device (such as a collection kit used when documenting urine output with a Foley catheter). The other method is to assume that the ultrafiltrate removed is equal to the rate programmed into the infusion device. This assumption may be inaccurate as these infusion devices (commonly referred to as "pumps") are not really pumps but are flow restrictors. Individual infusion devices (tested under low pressures) report volume delivery accuracy of 62%–10%. Studies show higher inaccuracies when these devices infuse medication via central venous catheters in patients with elevated central venous pressure (51,52). The little data available on the accuracy of these intravenous devices to regulate ultrafiltration in an ECMO circuit suggest error rates as high as 12.5% (53). In laboratory experiments using pressure settings typical of ECMO, the differences between the prescribed and the actual ultrafiltration rate were as high as 34 ml/h (.800 ml/d) (54). Therefore, when using in-line hemofilters, it is imperative to precisely measure or closely monitor ultrafiltration volumes.

RRT Using a CRRT Machine

Alternatively, a commercially available CRRT machine can be connected in-line to the ECMO circuit (Figure 2). The CRRT machine is typically connected to the venous limb of the roller-head ECMO circuit before the pump. The blood is then returned from the CRRT machine to the ECMO circuit near the venous CRRT connection and before the ECMO pump (40,55). If a centrifugal ECMO pump is used, the CRRT machine should not be placed before the ECMO pump because there is a very risk of air entrainment. Instead, the CRRT machine should be placed after the pump.

Dialysis or replacement fluid (prefilter or postfilter) is used to efficiently clear solutes, and ultrafiltrate can be generated to remove the desired fluid.

Additional anticoagulation is not routinely used for the CRRT circuit, because heparinization of the ECMO circuit anticoagulates the entire circuit. Unusual situations in which bleeding on ECMO is excessive, activated clotting time goals are very low, or heparin has been temporarily discontinued require consideration of regional citrate anti-coagulation of the CRRT circuit. Use of the heater on the CRRT device is typically not needed, but may be used.

The access pressure alarms inherent to commercially available CRRT have set limits based on the individual CRRT device. The default access pressure alarms are typically negative. However, when these machines are operated in series with ECMO, the positive pressure at the entry point of the CRRT machine will create pressures close to zero or positive. These pressures can lie outside the default pressures of the machine and thus the alarm settings may have to changed when using RRT on ECMO. Some machines (including the Gambro Prismaflex and the Braun Diapact) give the clinician the ability to adjust alarm settings. Other machines (including the NxStage System One, the Fresenius 2008K, and the older Gambro Prisma) do not have these capabilities. If the machines are not able to change the default access pressure, flow restrictors placed on the outside of the tubing have been used to keep the pressures within the pressure alarm limits. These clamps are not recommended because they portend added risk of hemolysis and thrombosis.

There are advantages and disadvantages to using an inline hemofilter or a CRRT machine for RRT. In both of these techniques, the use of commercially prepared renal replacement fluid and limiting the use of ultrafiltration without replacement or dialysis fluids can reduce development of electrolyte abnormalities. With either type of circuit, return blood from the renal replacement machine should be connected before the oxygenator so that any air or clot will be trapped into the oxygenator and not sent to the patient. Careful attention to detail and development of protocols for RRT are critical to providing the best care and outcomes.

Future Research Needs

As outlined above, ECMO patients have a high incidence of AKI and RRT provision with associated poor outcomes. There is great opportunity to answer numerous questions to better understand the epidemiology of AKI. We must better understand how fluid provision and timing of RRT can affect patient outcomes. Evaluation of new AKI biomarkers and the

application of a “renal angina” concept (56) to determine how a combination of clinical risk factors in conjunction with laboratory evidence may better identify those with AKI are greatly needed. A better understanding of the pathophysiology of AKI as related to ECMO initiation is needed to design preventative studies. Prospective evaluations of different techniques of RRT could help develop specific protocols describing optimal circuit integration parameters. A novel RRT device made specifically to interact with the ECMO circuit in a safe, accurate, effective, and simple manner could greatly improve RRT in these complex patients. The prescription of RRT (i.e., what fluids, what dose, and what method [dialysis versus replacement]) needs to be systematically explored. Answers to these and other important questions are likely to lead to improved outcomes in this vulnerable population.

The Kidney Interventions During Extracorporeal Membrane Oxygenation (KIDMO) group is an international, multidisciplinary collaboration composed of pediatric intensivists, cardiologists, ECMO experts, and nephrologists. Thus far, this group has coordinated a survey to better understand current clinical RRT practices and have altered the ELSO registry data collection forms to better document AKI and RRT. Starting in 2012, the ELSO registry is collecting more detailed serum creatinine and fluid intake/output data before, during, and after ECMO. This will allow for better data to understand the true incidence of AKI/FO and its effect on outcomes. In addition, a multicenter retrospective analysis of neonates and children on ECMO is underway to explore how AKI and FO affect clinical outcomes. Ultimately, prospective multicenter evaluations and intervention trials will be needed to prevent AKI, ameliorate the effects of AKI, and optimize RRT in ECMO patients.

AKI, FO, and RRT are common and are associated with poor outcomes in critically ill patients on ECMO. Cumulative FO should be used to help make decisions about RRT initiation. RRT on ECMO can be safely performed, but issues unique to ECMO must be carefully addressed. Centers providing ECMO should have a multidisciplinary team (involving nurses, ECMO specialists, nephrologists, surgeons, and intensivists) to devise center-specific protocols for RRT on ECMO.

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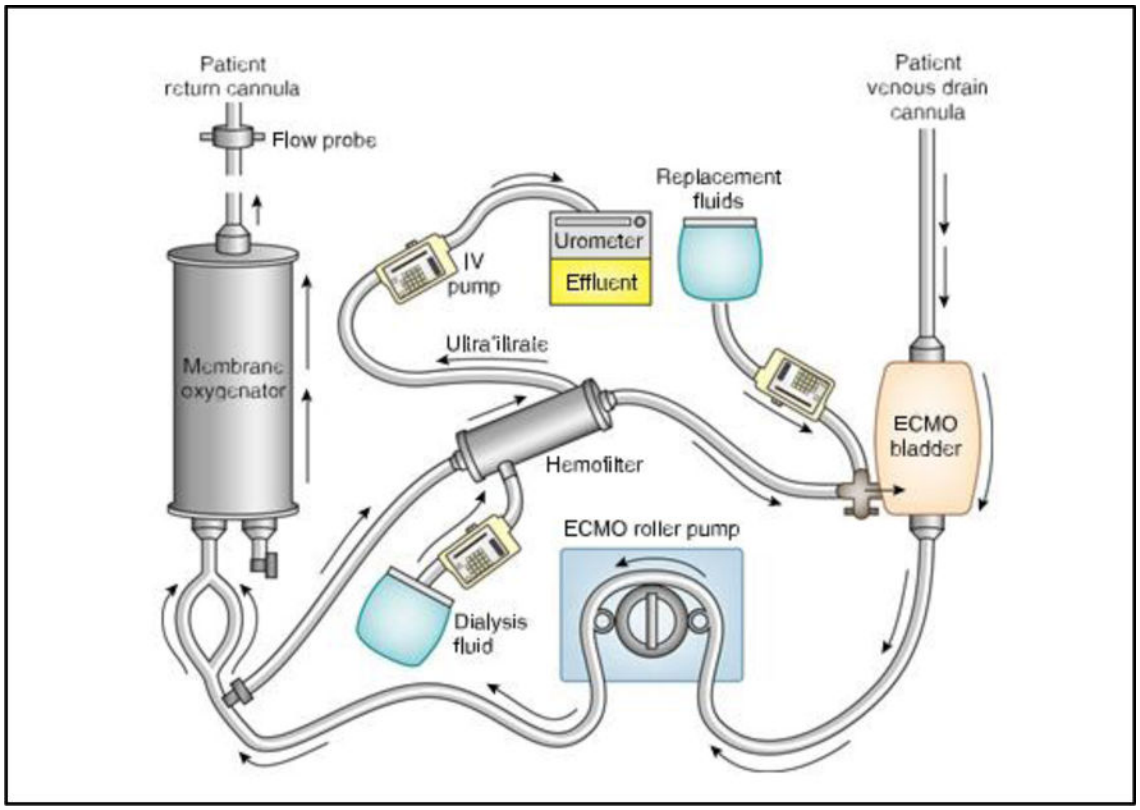

Figure 1.

Renal replacement therapy using an in-line hemofilter during extracorporeal membrane oxygenation (ECMO). As blood comes from the patient via the venous drain cannula, it goes through the ECMO bladder to the ECMO pump, to the membrane oxygenator, and back to the patient via a return cannula. Blood is shunted from the circuit to the in-line hemofilter and returned to the ECMO pump. Fluid (ultrafiltrate) can be controlled using an intravenous (IV) pump. Replacement or dialysis fluid can be used for solute clearance and/or to achieve metabolic control.

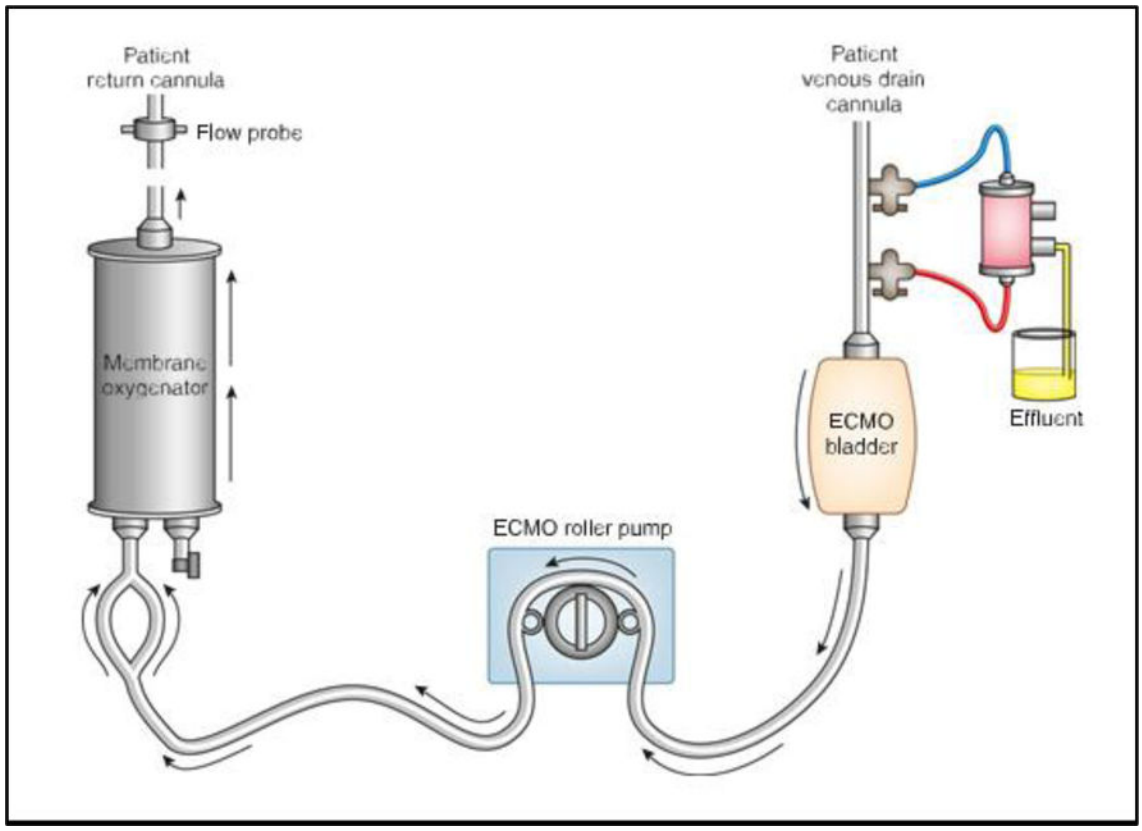

Figure 2.

Renal replacement therapy (RRT) using RRT machine during extracorporeal membrane oxygenation (ECMO). If the ECMO circuit uses a roller pump, a proportion of the circuit blood comes from the patient via the venous drain cannula and enters the RRT machine where replacement, dialysis, and ultrafiltration occurs. Blood from the RRT machine then goes back to the ECMO bladder to the ECMO pump, the membrane oxygenator, and back to the patient via a return cannula. If a centrifugal pump is used, the RRT machine must be connected after the ECMO bladder to prevent air entrapment.

TABLE 1

Representative studies demonstrating negative effect of fluid overload in patients receiving ECMO, CRRT, and those who receive both ECMO and CRRT

STUDY	N	Study Population details	Study Design	Method of FO Measurements	Main Outcomes	Main Findings
Heung *et al.*, 2011 (35)	170	AKI attributed to ATN requiring RST, aged $18 yr, hospitalized	Retrospective, single center	FO% from baseline to RST initiation[a]	Renal recovery at 1 yr	Higher degree of fluid overload at RST initiation predicts worse renal recovery at 1 yr
Selewski *et al.*, 2011 (28)	113, 50 patients on ECMO	CRRT, 2006–2010, PICU, NICU, cardiac ICU	Retrospective, single center	FO% from ICU admission to CRRT initiation[b,c]	ICU mortality	Provides evidence for a weight-based definition of FO Higher FO% associated with increased mortality, independent of illness severity score and other clinical factors in patients on ECMO and general pediatric critical care
Sutherland *et al.*, 2010 (25)	297	CRRT (all modalities), aged, 18 yr, all ICUs 2001–2005	Retrospective, using prospectively collected multicenter registry data	FO% from ICU admission to CRRT initiation[c]	PICU mortality	HiHigher FO% (continuous) and FO% .20% associated with increased mortality, independent of illness severity and other clinical factors
Elbahlawan *et al.*, 2010 (57)	30	CRRT with acute lung injury and ventilation in hematopoietic stem cell transplant, aged #19 yr, ICU, 1994–2006	Retrospective, single center	FO% at 24 h before and 48 h after CRRT initiation[c]	PaO_2/FiO_2 ratio, ICU mortality	Both FO and PaO_2/FiO_2 ratio (oxygenation) improved from 24 h before to 48 h after CRRT initiation PaO_2/FiO_2 ratio and %FO were inversely associated
Fulop *et al.*, 2010 (31)	81	CRRT (all modalities) with nephrology consultation, aged $18 yr, medical, cardiac, surgical ICUs, 2003–2004	Retrospective, using prospectively collected single-center registry data	%Volume-related weight gain from baseline to RST initiation[d]	30-d mortality	.10% weight gain associated with mortality, independent of other clinical factors
Hayes *et al.*, 2009 (30)	76	CRRT (all modalities), aged, 18.9 yr, 2000–2005, PICU	Retrospective, single center	FO% from ICU admission to CRRT initiation[c]	Hospital mortality	FO% .20% associated with increased mortality, independent of illness severity and other clinical factors. FO% .20% also independently associated with prolonged hospitalization, duration of mechanical ventilation, and time to renal recovery
Bouchard *et al.*, 2009 (58)	353	AKI/RST with nephrology consultation, aged $ 18 yr, ICU, 1999–2001[e]	Retrospective analysis of a prospective multicenter cohort study	FO% at AKI diagnosis, RST initiation, and RST cessation[f]	30-d and hospital mortality	FO% at RST initiation was associated with mortality after adjustment for illness severity score RST patients with greater days of FO% .10% had increased mortality FO at RST cessation was associated with mortality, adjusted for illness severity score

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STUDY	N	Study Population details	Study Design	Method of FO Measurements	Main Outcomes	Main Findings
Blijdorp *et al.*, 2009 (38)	61	Pre-emptive CVVH during ECMO, aged, 28 d, NICU	Retrospective case-comparison study	Average daily fluid balance while on ECMO	Time on ECMO, time from decannulation to extubation	Adding CVVH pre-emptively improves outcomes by decreasing time on ECMO because of improved fluid management
Hoover *et al.*, 2008 (40)	52	All patients receiving ECMO, aged 1 mo-18 yr, PICU, 1992–2006	Retrospective case-matched study (patients receiving CVVH plus ECMO versus ECMO alone)	Fluid balance while on ECMO[g]	ECMO survival, fluid balance, caloric intake	Use of CVVH with ECMO wasassociated with improved fluid balance, improved caloric intake and decreased diuretic exposure
Gillespie *et al.*, 2004 (27)	88	CVVH for AKI or volume overload, aged #20 yr, 1993–2002	Retrospective, single center	FO% from ICU admission to CVVH initiation[c]	Mortality, from last known survival status	FO% .10% was associated with increased mortality independent of illness severity and other clinical factors
Foland *et al.*, 2004 (59)	113	CVVH, aged, 18 yr, 1997–2003, PICU, NICU, cardiac ICU	Retrospective, single-center registry	FO% from up to 7 days before CVVH initiation[h]	PICU mortality	Higher FO% associated with increased mortality, independent of illness severity score and other clinical factors
Goldstein *et al.*, 2001 (22)	21	CWH or CVVHD, aged #18 yr, PICU, 1996–1998	Retrospective, single center	FO% from ICU admission to CVVH initiation[c]	PICU mortality	FO% at CVVH or CVVHD initiation was associated with increased mortality, independent of illness severity score

ECMO, extracorporeal membrane oxygenation; CRRT, continuous renal replacement therapy; FO, fluid overload; ATN, acute tubular necrosis; RST, renal supportive therapy; PICU, pediatric intensive care unit; NICU, neonatal intensive care unit; ICU, intensive care unit; CVVH, continuous venovenous hemofiltration; CVVHD; continuous venovenous hemodialysis.

[a][(Weight at RST Initiation – Baseline Weight)/Baseline Weight] 3 100%, with baseline weight based on prehospitalization data or hospital admission weight.

[b][(Weight at CRRT Initiation – ICU Admission Weight)/ICU Admission Weight] 3 100.

[c][(Total Fluid Intake – Total Fluid Output in liters, from ICU admission to CRRT)/ICU Admission Weight in kilograms] 3 100.

[d][(Weight at CRRT Initiation – First Available Hospital Weight)/Initial Weight) 3 100.

[e]This study included adults who did and did not receive renal supportive therapy in the ICU. We report only on those who received RST.

[f][(Total Fluid Intake – Total Fluid Output in liters, from 3 d before nephrology consultation to RST or other relevant time point)/Hospital Admission Weight in kilograms) 3 100.

[g][(Total Fluid Intake – Total Fluid Output in liters, from ICU during ECMO)/Weight in kilograms per day on ECMO].

[h][(Total Fluid Intake – Total Fluid Output in liters, from 7 days before CVVH)/estimated dry weight in kilograms] 3 100.