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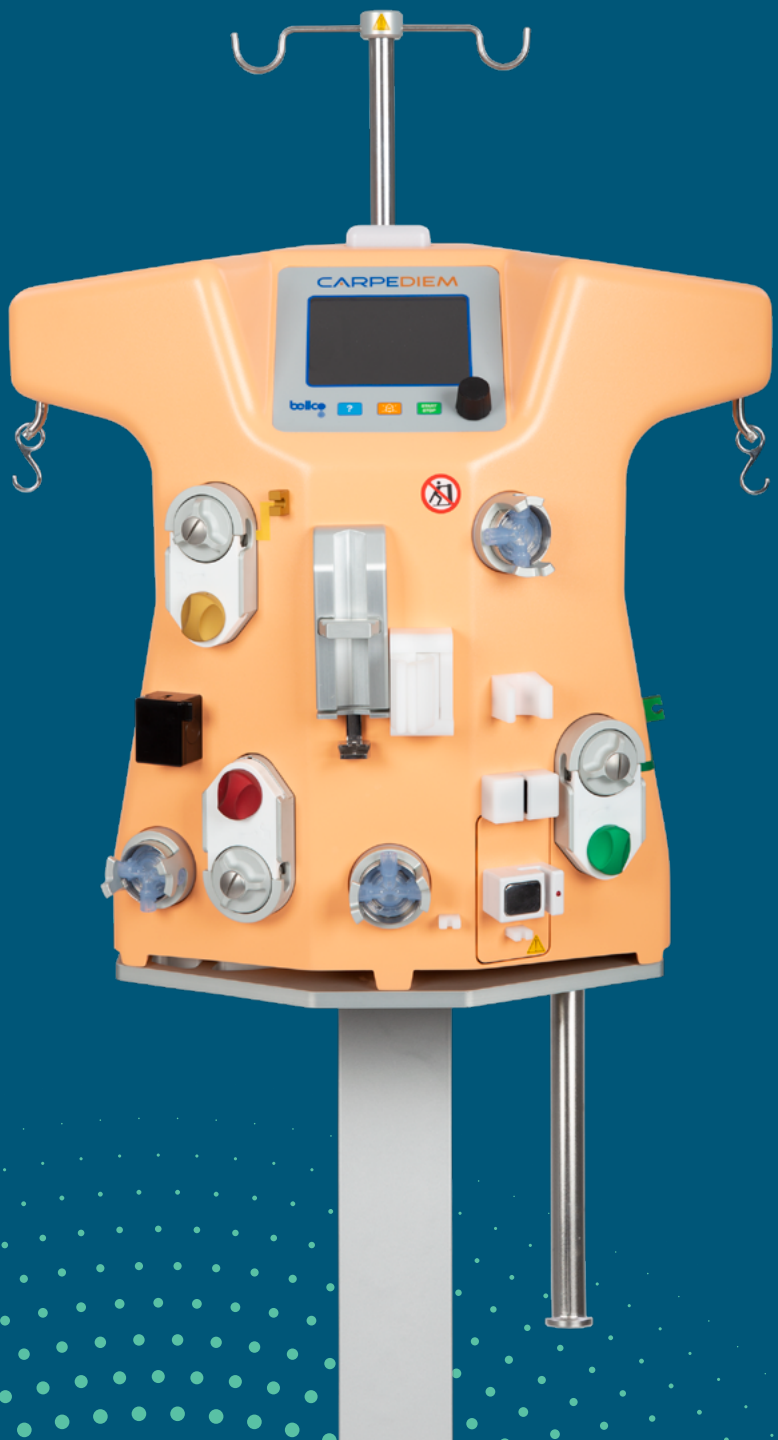
# Acute Renal Supportive Therapies in Neonates and Children: A Clinical Compendium

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# Introduction

The field of critical care nephrology has witnessed exponential growth over the past two decades, with 1) standardization of the definition and staging for acute kidney injury (AKI), 2) discovery and validation of novel urine biomarkers of tubular injury to distinguish true damage from functional changes in creatinine, 3) recognition of the association between AKI and chronic kidney disease development and 4) recognition that AKI is more often a result of a systemic illness, or its treatment, and not of primary kidney disease.

The advancements were initially achieved in critically ill adults but have been replicated in children, infants, and neonates, with some important modifications, for as the saying goes, “Children are not just small adults.” This adage is no more apropos than for the provision of renal supportive therapy, where errors in fluid balance or clearance that would be negligible for adult patients could have severe consequences for the smallest patients under our care. Yet, the demand and need for competent neonatal and pediatric renal supportive therapy programs has grown as advancements in prenatal, neonatal, congenital heart disease, and sepsis care led to increased incidence of AKI. This demand catalyzed the development of pediatric-specific RRT platforms and adaptation of other platforms in novel ways to provide renal support for small children.

The current compendium is aimed at providing a useful reference for the bedside clinician faced with the critically ill neonate, infant, or child requiring renal supportive therapy. It was not designed to promote the use of one platform over another, and the options available in any one institution or setting may be limited by factors beyond clinician control. It is also not meant to provide a comprehensive review of the pediatric critical care nephrology literature. We hope that you find the information herein to be useful, and would appreciate any feedback to improve the next edition.


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# 1

# Pediatric and Neonatal Continuous Renal Supportive Therapies, Demographics and Outcomes

**Melissa Muff-Luett, MD**

Pediatric and neonatal kidney replacement therapy (KRT) is instrumental in the treatment of acute kidney injury and fluid overload in children. KRT utilization to support children is becoming more commonplace, likely due to the increasing complexity of hospitalized pediatric patients, especially those requiring critical care. The technological advancements made in KRT device technology has allowed for improved safety and efficacy in the pediatric population. In the past 20 years, pediatric dialysis has expanded beyond just peritoneal dialysis and hemodialysis to include continuous renal replacement therapy (CRRT). The growth of CRRT is due not only to advancements in this technology, but also to changes in the pediatric population, with an increased predominance of acute kidney injury (AKI) in critically ill patients. CRRT is now the preferred modality of KRT for critically ill patients with AKI in centers with the necessary resources and expertise.

Pediatric CRRT patient volumes are relatively low (compared to adults) at any single center, which led to a lag in pediatric-specific research publications. Initial pediatric CRRT data were reported primarily from single-center studies with small patient cohorts, and showed overall low survival rates near 40%.[1-4] In 2007, the Prospective Pediatric Continuous Renal Replacement Therapy (ppCRRT) Registry, a multi-center retrospective registry, published data from a five-year period (2001 to 2005).[5] This study still represents the community's primary source for pediatric CRRT data, including patient demographics and outcomes.[5] Since 2007, numerous advancements in procedures and technologies have been developed, including modifications of machines designed for adults, new pediatric-sized dialyzers, and development of new devices specifically designed for CRRT in patients <10 kg. Whether these advancements have improved survival rates over the last 15 years has not yet been fully examined. The aim of this review is to define the population of pediatric patients receiving CRRT and examine the outcomes of these patient populations over time, to determine if advancements in the field of pediatric CRRT correlate with improved outcomes.

## Early Pediatric CRRT Data

The modalities used for pediatric KRT have evolved with time. Early pediatric dialysis literature on KRT use in acute renal failure (now termed acute kidney injury) focused primarily on peritoneal dialysis, hemodialysis and, much less commonly, continuous venovenous hemofiltration or continuous arteriovenous hemofiltration.[1,6,7] The primary diagnoses listed as causes of AKI in these cohorts differed from those that we see today. Primary diagnoses often included primary renal causes, mainly hemolytic uremic syndrome (HUS) or acute renal failure. These studies also included diagnoses involving multiple organ systems — sepsis, burns, cardiac surgery, acute respiratory distress syndrome, liver transplant, and intoxications.[8-10]

Initial overall survival rates of pediatric patients receiving CRRT in the 1990-2005 era were reported near 40%.[2,4,6,11] An early study comparing continuous hemofiltration (CVVH) with hemodialysis (HD) in children showed lower survival of patients on hemofiltration (31% survival on CVVH vs 96% on HD), However, this study was biased with a predominance of hemofiltration use in critically ill children, as the predominant diagnosis in CVVH was sepsis (45% of patients) and renal failure was the primary diagnosis (46%) in HD patients.[1] Smoyer et al likely had the largest cohort of patients treated with either continuous arteriovenous hemofiltration/hemodiafiltration and continuous venovenous hemofiltration/hemodiafiltration with a 43% survival rate, with the best survival in patients with tumor lysis and lupus at 100%, HUS 89%, but much lower survival in patients with leukemia (25%), hypoplastic left heart syndrome (20%) and bone marrow transplant (0%).[3]

| Pediatric CRRT Studies Stratified by Diagnoses | | | | | |
|---|---|---|---|---|---|
| **Manuscript** | **Hayes et al** | **Santiago et al** | **ppCRRT Symons et al** | **Riley et al** | **Westrope et al** |
| **Cohort Years** | 2000-2005 | 1996-2009 | 2001-2005 | 2004-2013 | 2005-2012 |
| **Total Number Patients** | 76 | 174 | 344 | 273 | 2,207 |
| **Sepsis** | 9(11.8%) | 34(19.5%) | 81(23%) | 15(5.5%) | 527(23.9%) |
| **Malignancy (includes TLS† and BMT‡)** | 17(22.4%) | 5(2.9%) | 96(28%) | 68(25%) | |
| **Cardiac Disease** | 7(9.2%) | 97(55.7%) | 41(12%) | 24(8.8%) | 394(17.9%) |
| **Primary Kidney Disease** | 15(19.7%) | 21(12.1%) | 32(9%) | 28(10.3%) | 381(17.3%) |
| **Liver Failure** | 5(6.6%) | | 29(8.4%) | 56(20.5%) | 141(6.4%) |
| **Ischemia/ Shock** | | | 19(5.5%) | | |
| **Metabolic Disorder** | | 5(2.9%) | 15(4.5%) | 15(5.5%) | 131(5.9%) |
| **Drug Intoxication** | | 3(1.7%) | 13(4%) | | |
| **Pulmonary Disorders** | | | 11(3%) | 15(5.5%) | 246(11.1%) |
| **Other** | 11(14.5%) | 9(5.2%) | 7(2%) | 29(10.6%) | 387(17.5%) |

†TLS= tumor lysis syndrome, ‡BMT= bone marrow transplant

| Pediatric CRRT Survival Stratified by Diagnoses | | | | | |
|---|---|---|---|---|---|
| **Manuscript** | **Hayes et al** | **Santiago et al** | **ppCRRT Symons et al** | **Riley et al** | **Westrope et al** |
| **Cohort Years** | 2000-2005 | 1996-2009 | 2001-2005 | 2004-2013 | 2005-2012 |
| **Total Number Patients** | 76 | 174 | 344 | 273 | 2,213 |
| **Overall Survival** | 55.3% | 64.4% | 58% | 48% | 73.8% |
| **Sepsis** | 66.7% | 55.9% | 59% | 33% | 64.7% |
| **Malignancy (includes TLS† and BMT‡)** | 76.5% (TLS 90.1%) (BMT 16.7%) | TLS 100% | 48% (TLS 83%) (BMT 45%) | 37% (BMT 24%) | |
| **Cardiac Disease** | 28.5% | 59.8% | 51% | 42% | 62.4% |
| **Primary Kidney Disease** | 66.7% | 95.2% | 84% | 64% | 92.9% |
| **Liver Failure** | 40% | | 31% | 41% | 52.8% |
| **Ischemia/ Shock** | | | 68% | | |
| **Metabolic Disorder** | | 60% | 73% | 80% | 69.3% |
| **Drug Intoxication** | | 67% | 100% | | |
| **Pulmonary Disorders** | | | 45% | 40% | 59.3% |
| **Other** | 63.6% | 62.7% | 71% | 69% | 62% |

†TLS= tumor lysis syndrome, ‡BMT= bone marrow transplant

Though these early CRRT cohorts did include some infants, their data was not analyzed to focus on the indications for dialysis in this population and the outcomes of infants and neonates on dialysis. In 2003, Symons successfully reported on the use of CRRT for the treatment of children less than or equal to 10 kg.[12] This study collected data on 85 patients weighing 1.5-10 kg, in five US centers from 1993 to 2001, with 16 of these patients weighing less than 3 kg. The primary diagnoses of these infants were congenital heart disease/heart failure, metabolic disorders, multi-organ dysfunction, sepsis, liver failure and malignancy, with several other diagnoses all relating to primary kidney disorders. They reported an overall survival rate of 38% and a 25% survival rate for infants <3 kg.

Indications for dialysis in the early studies often focused most on diagnoses of acute kidney failure or AKI. However, during this time, we began to see suggestions of the impact of fluid overload on survival outcomes with CVVH. A single-center study by Goldstein et al reported an overall survival rate of 42.8% in 21 pediatric ICU patients, but when stratified by fluid overload, survivors were noted to have a significantly lower percentage of fluid overload when compared to non-survivors (16.4% vs 34%).[4]

These early single-center studies on CRRT paved the way for early CRRT and in the pediatric intensive care unit, but a multi-center pediatric study was needed to show the efficacy and safety of CRRT in critically ill children.

## The Prospective Pediatric CRRT Registry Experience

Prospective Pediatric CRRT Registry was a multi-center retrospective study which included 344 pediatric CRRT patients from 13 US centers during a five-year period (2001-2005), making this study very impactful in the field of pediatric nephrology.[5] ppCRRT solidified CRRT as the new standard of care of children with AKI. ppCRRT helped define the population of pediatric patients receiving CRRT and helped guide the field with current outcome data. ppCRRT was the first study to show a new way to utilize KRT. This study showed that CRRT could be utilized to improve outcomes of critically ill children, which was a significant change from prior studies which focused on the use of KRT in non-critically ill children with primary kidney disease.

## ppCRRT Outcomes According to Diagnoses

While all children are at risk for AKI, this risk is greatest in critically ill patients. The pCRRT registry focused mainly on a critically ill population. The primary diagnoses within the ppCRRT cohort were sepsis (23%), bone marrow transplant (16%), cardiac disease (12%), intrinsic kidney disease (9%), liver disease (8%), and malignancy (8%).[5] Other indications included ischemic shock, inborn errors of metabolism, drug intoxications, tumor lysis syndrome, and pulmonary disease or transplant.

The overall survival rate in the ppCRRT registry was 58%, which was a significant improvement from previous KRT literature. The best survival rates for patients on KRT included conditions that were either reversible or do not involve multi-organ dysfunction. All patients in the ppCRRT registry with the primary diagnosis of intoxication survived, as did 83% of patients with tumor lysis syndrome, and 84% with primary kidney disease.[5] Surprisingly, sepsis patients had a 59% survival rate. Patients with liver failure had the poorest survival within the ppCRRT cohort at 31%.[5] Additionally, patients with pulmonary disease or transplant and bone marrow transplantation had a low rate of 45%.[5,13] The mortality of cardiac patients in ppCRRT was 51%.[5]

## ppCRRT Outcomes According to Patient Age and Size

Perhaps the greatest challenge in pediatric KRT is how to care for patients with extremes in age and size. Performing CRRT in neonates and infants is complicated by their small size, which makes the use of standard hemodialysis or CRRT machines that were designed for use in adults either challenging or unsafe in the smallest patients. Together with the 2003 study from Symons et al, ppCRRT began to solidify CRRT as a safe and recognizable modality of dialysis for infants and neonates.[12] The ppCRRT study was the first CRRT literature to show that infants and neonates are a significant proportion of the pediatric CRRT population. Twenty percent of patients were less than 1 year of age at CRRT initiation with 24% of patients weighing ≤10 kg.[14]

The ppCRRT cohort ranged in age from newborn to 25 years, with weights ranging from 1.3 kg to 160 kg.[5] When stratified by size and age, the ppCRRT cohort showed similar results to previous studies with a lower survival rate across all centers in children <10 kg and less than 1 year of age (43%) when compared to children >10 kg (64%).[14] No significant difference was seen in survival between infants <5 kg (44%) and 5-10 kg (42%). Infants with primary kidney disease had the best survival rate (80%) and those with liver disease had the lowest survival rate, with none surviving.[14]

Diagnostic indications for CRRT in the infant and neonatal population in ppCRRT differed slightly from those in their standard pediatric population. The primary disease categories for infants and neonates on CRRT were sepsis (30%), cardiac disease (19%), and inborn errors of metabolism (IEM) (15%), hepatic (11%), oncology (7%), pulmonary (6%), and renal (6%).[14] The highest survival rate was seen in patients with primary renal (80% survival rate) along with IEM (62%) and pulmonary (60%) diagnoses. Similar to the older patients in ppCRRT, the patients with the lowest survival rates were liver (0%). However, sepsis (36%) and cardiac disease (38%) resulted in a lower survival rate in this infant population when compared to the larger patients.

## ppCRRT Outcomes According to Indication for CRRT Initiation

Indications for pediatric CRRT initiation remain an important focus of pediatric CRRT literature starting with the ppCRRT cohort. Both AKI and CRRT pediatric literature have shown that fluid overload is associated with increased mortality and morbidity in critically ill children. ppCRRT was one of the first studies to identify fluid overload as an important indication for CRRT initiation and has since increased awareness of the risks associated with fluid overload in pediatric AKI. Forty-six percent of patients received CRRT for fluid overload and electrolyte imbalance, 29% for isolated fluid overload, 3% for prevention of fluid overload and 13% for electrolyte imbalance alone.[5] Patients who required CRRT for both fluid overload and electrolyte imbalances had the lowest rate of survival. Within this cohort, 51.5% of patients developed ≤10% fluid overload, 17.2% developed 10%-20% fluid overload, and 31.3% developed ≥20% fluid overload.[15] The authors found that the risk of mortality increased with the percentage of fluid overload even after adjusting for severity of illness.

## Pediatric CRRT after ppCRRT/Modern CRRT Cohorts

Unfortunately, despite the fact that the pCRRT data is now over 15 years old, it remains the current benchmark for CRRT indication and outcome data. Numerous studies are published every year on pediatric CRRT, but these studies often involve small patient cohorts which lack the impact of ppCRRT as a multi-center cohort.

In low- and middle-income countries, CRRT is now the primary mode of KRT with rates up to 68% for patients including neonates.[16] Since the time of ppCRRT, CRRT has become the main form of dialysis utilized in pediatric AKI. The primary causes of AKI in the ICU setting are not primary kidney diseases but rather systemic conditions, including primary respiratory, cardiac, liver failure, hematologic diseases, and malignancy.[16,17] Children with complex medical conditions often develop chronic kidney disease (CKD) as a consequence of their underlying disease, which unfortunately places them at high risk for developing AKI superimposed on CKD. Children with one or multiple co-morbidities are known to have an increased risk of AKI, possibly due pre-exisiting CKD.[16,18] With the high incidence of AKI in the pediatric ICU setting, 81% of pediatric KRT now occurs within intensive care units.[16]

## Pediatric CRRT after ppCRRT Outcomes by Diagnoses

Within the pediatric intensive care unit, the principal diagnoses for patients on CRRT often involve multisystem organ dysfunction.[5,17,19] Sepsis was the primary diagnosis in patients on CRRT in a large AKI cohort in the United Kingdom from 2005 to 2012.[17] Riley et al showed that the primary diagnoses for CRRT from their single-center study changed over time. They experienced an increase in CRRT for patients with primary kidney disease and liver failure from their 2004-2008 cohort to their more recent 2009-2013 cohort.[19] CRRT use in patients with malignancy and bone marrow transplant remained stable during their 10-year study, but they saw a decreased predominance of use in cardiac patients, attributed to a shift toward peritoneal dialysis in these patients at this center.[19] This is likely due to increased literature on the benefits of early peritoneal dialysis use in the post-operative period in the cardiac population.[20,21] Interestingly, CRRT use in their patients with sepsis declined during this study era, presumably due to improved outcomes with a center-wide focus on septic shock management. However, a 2011-2014 cohort from Turkey reported the highest incidence of sepsis in their CRRT population at 30%.[22]

Other previously common indications for CRRT have changed slightly in predominance, including hyperammonemia and tumor lysis syndrome. Increased use of CRRT for IEM has led to new, effective protocols for high effluent volume (clearance) rates, similar to what can be achieved with hemodialysis.[23,24] CRRT use in tumor lysis syndrome has decreased over time, likely due to the introduction of rasburicase for treatment of hyperuricemia.[19]

In comparing more recent pediatric CRRT cohorts to ppCRRT, the overall reported survival rates are similar, ranging from 48% to as high as 70%.[22,25-28] Patients on CRRT continue to have a higher mortality rate than other, more intermittent forms of dialysis, but this is likely due to the fact CRRT is mainly used in critically ill patients with a higher mortality at baseline from other hospitalized patients.[1,18]

Although the overall CRRT survival rate has not improved significantly over the last 15 years, survival on CRRT has improved for conditions that are either reversible or do not involve multi-organ dysfunction. Modern studies show survival rates for patients requiring CRRT for primary kidney disorders as high as 93%.[17]

In contrast, post-ppCRRT studies have not shown any improvement in morbidity and mortality for patients with multi-organ dyfunction. Data from the same era as ppCRRT showed a 40%-50% mortality rate for patient with multiple organ dysfunction syndrome (MODS).[11,26-29] Liver failure continues to carry a high risk of mortality for patients on CRRT. Recent cohorts have shown similar survival rates of 32%-54% for patients with liver failure on CRRT, which is minimally improved over the survival rate of 31% in ppCRRT.[17,19,28] There have been reports of renal recovery following

liver transplantation.[30] Bone marrow transplant (BMT) patients on CRRT have also not shown a significant improvement in survival, with early survival rates near 45% in the ppCRRT cohort, but a recent single center cohort showed only a 24% survival rate for BMT patients.[5,13,19] Cardiac patients on CRRT have also not exhibited an improvement in mortality with a 43% mortality rate reported in a large cohort of 1650 pediatric cardiac surgery patients from 1996 to 2009 as compared with 51% in ppCRRT.[16]

## Pediatric CRRT after ppCRRT Outcomes by Age and Size

Since the time of the ppCRRT registry, new equipment and devices have been developed to address limitations with initial CRRT devices mainly with respect to size. These new devices involve adaptations to minimize the extracorporeal volume of the circuit, decrease the need for a blood prime, allow for the use of smaller vascular access with lower flow rates, and increase accuracy. In a single-center study, the number of infants <10 kg who received CRRT increased by 10% from a 2004-2008 cohort to a later 2009-2013 cohort.[19] Modified aquapheresis utilizing the Aquadex FlexFlow System™ (CHF Solutions Inc., Eden Prairie, MN) was reported to be used successfully in 72 infants weighing <10 kg and 13 children 10-20 kg.[31] The first multi-center study utilizing the Carpediem™ machine (Bellco-Mozarc Medical, Mirandola, Italy) included a cohort of 26 infants with a median age of 1 day (IQR 1-11 days) and a median weight of 2.9 kg (IQR 2.2-3.6 kg).[32] Ninety-six percent of these patients survived until CRRT discontinuation and 50% survived until ICU discharge. Goldstein et al reported that a cohort of 38 infants weighing less than 10 kg treated with Carpediem™ were compared to 84 patients from the ppCRRT registry. Survival to CRRT discontinuation for infants less than 5 kg was significantly better for those in the Carpediem™ registry at 97% when compared to those in the ppCRRT registry, however, no significant difference was seen in survival to ICU discharge between the cohorts.[33]

Indications for CRRT in the infant and neonatal population differ slightly from the standard pediatric population. The primary disease categories for infants and neonates on CRRT were cardiac (38%), IEM (15%-20%), sepsis (12%-15%), primary kidney (12%-15%), and pulmonary (12%-15%).[32,33] Primary kidney causes include congenital kidney anomalies and diffuse mesangial sclerosis. In other studies, the primary indication for CRRT initiation was volume overload, AKI with electrolyte abnormalities, AKI with volume overload, end stage kidney disease (ESKD) and hyperammonemia.[31,34]

## Pediatric CRRT after ppCRRT Outcomes by Indication for CRRT Initiation

Recent studies on the outcomes of pediatric patients on CRRT have focused more on mortality associated with dialysis indications and severity of illness and less on the primary disease process or comorbidities. Patients with AKI and evidence of other multi-organ failure seem to carry the highest mortality across all primary diagnosis indications.[25] This has been replicated in several studies with increased mortality in patients with higher PRISM II and PRISM III scores.[5] Similarly, additional studies since that time have shown fluid overload to be the most commonly listed indication for CRRT.[19,22] Repeated studies have shown that when adjusted for the severity of illness, worsened fluid overload carries a higher risk of mortality.[15,25] Fluid overload is also associated with increased duration of CRRT, increased length of admission, and increased incidence of invasive ventilation.[15] Inotropic support also appear to be a risk factor for increased mortality on CRRT.[22]

| Pediatric CRRT Studies in Children ≤10 kg Stratified by Diagnoses | | | | | |
|---|---|---|---|---|---|
| **Manuscript** | **Symons et al** | **ppCRRT Askenazi et al** | **Garzotto et al** | **Goldstein et al** | **Menon at al** |
| **Cohort Years** | 1993-2001 | 2001-2005 | 2013-2016 | 2013-2018 | 2012-2018 |
| **Total Number Patients** | 85 | 84 | 26 | 34 | 72 |
| **Sepsis/ Multi-Organ Dysfunction** | 21(25.6%) | 25(30%) | 4(15%) | 4(12%) | |
| **Cardiac Disease** | 16(18.8%) | 16(19%) | 10(38%) | 13(38%) | 21(29.2%) |
| **Metabolic Disorder** | 14(16.5%) | 13(15%) | 4(15%) | 7(20%) | |
| **Liver Failure** | 9(10.6%) | 9(11%) | | | |
| **Malignancy** | 5(5.9%) | 6(7%) | | | |
| **Primary Kidney Disorder** | 8(9.4%) | 5(6%) | 3(12%) | 5(15%) | 31(43%) |
| **Pulmonary Disorders** | 3(3.5) | 5(6%) | 3(12%) | 5(15%) | |
| **Other** | 5(5.9%) | 5(6%) | 2(8%) | | 20(27.8%) |

| Pediatric CRRT Outcomes Stratified by Size | | | | | |
|---|---|---|---|---|---|
| **Manuscript** | **Symons et al** | **ppCRRT Askenazi et al** | **Garzotto et al** | **Goldstein et al** | **Menon at al** |
| **Cohort Years** | 1993-2001 | 2001-2005 | 2013-2016 | 2013-2018 | 2012-2018 |
| **Total Number Patients** | 85 | 344 | 26 | 38 | 72 |
| **Overall Survival in Infants <10 kg** | 38% | 59% | 50% | | 32% |
| **Survival Rate According to Size** | ≤3 kg (25%)<br>>3 kg (41%) | ≤5 kg (44%)<br>5-10 kg (42%)<br>≤10 kg (43%)<br>>10 kg (64%) | <3 kg (31%)<br>>3 kg (69%) | <5 kg (50%) | <10 kg (32%) |

## The Future of Pediatric CRRT

Our community is entering an exciting time in pediatric CRRT, with the recent availability of new technologies and devices. The introduction of HF-20 CRRT filter, the Carpediem™ system, and the Aquadex™ device for modified aquapheresis provide hope for us to continue to improve the care of the pediatric patients who previously may have not had any pediatric dedicated options. The Improving Carpediem™ Outcomes in Infants and Neonates through Collaboration (ICONIC) study will provide international, multi-center data for infants treated with the Carpediem™ device. Additionally, the Contemporary Infant and Neonatal Dialysis (COINED) study will provide insight as to the outcomes of infants treated with CRRT as compared with peritoneal dialysis and hemodialysis.

Additional devices and filters in the field of CRRT have brought new possibilities. The Molecular Adsorbent Recirculating System (MARS)™ device combines dialysis with clearance of protein-bound-particles by utilizing albumin-enriched dialysate with a secondary circuit that regenerates the albumin by treating the dialysate with two regenerating columns — charcoal and an anion exchange resin.[35,36] This device was first reported in 2002 and has primarily been studied in adults with acute liver failure. There is scant pediatric data with this device and the new Mini-MARS™ system. Similar to adult studies, the utility of this device for treatment of acute liver failure is remains unclear. Pediatric studies with both MARS™ and Mini-MARS™ have shown slight reductions of ammonia and bilirubin levels, but this was not seen to be superior to the combined use of plasma exchange and hemodialysis in infants and children with liver failure.[30,36,37] Another more recent addition to extracorporeal therapies is the development of the Selective Cytopheretic Device (SCD).[38] The SCD is a specialized membrane that is designed to be entered into an extracorporeal blood circuit and sequester activated leukocytes. The rationale behind this therapy is to decrease the pathogenesis and progression of many conditions which can cause systemic inflammatory conditions, like sepsis, which commonly cause AKI. Adult studies including a randomized control trial are showing promising results with an excellent safety profile, but inconclusive efficacy.[39] A single multi-center

study in pediatrics (16 patients) shows promising safety but no clear efficacy data.[38] Similarly, the Seraph®100 Microbind Affinity Blood Filter is a hemoperfusion device which is designed to adsorb bacterial and viral toxins when used in line with extracorporeal circuits. This device is was granted emergency use authorization for patients 18 years of age or older with COVID-19 infection, but its use has been successfully reported in a 17-year-old patient with promising safety and efficacy.[40] We look forward to the continued developments of these technologies with hope that they may improve survival of our CRRT patients with multi-organ dysfunction and liver failure as we have failed to improve our CRRT outcomes for these patients in the last 15 to 20 years.

In pediatric CRRT, our patient numbers will always remain low when compared to adult patient volumes. As a field, we must continue to embark on multi-center collaborative studies and registries to increase patient numbers within the field of pediatric dialysis. The field of pediatric CRRT has changed significantly in recent years; however, ppCRRT remains our most recent large, multi-center pediatric CRRT registry. A modern multi-center international pediatric CRRT cohort is urgently needed. We eagerly await the results from the Worldwide Exploration of Renal Replacement Outcomes in Kidney Diseases Collaborative (WE-ROCK), an international multi-center retrospective cohort of pediatric patients who received CRRT for AKI or fluid overload.

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# 2

# Continuous Renal Supportive Therapies Prescription in Neonates and Children

**Shina Menon, MD**

Continuous renal replacement therapy (CRRT) is commonly used for the management of acute kidney injury (AKI) and fluid overload in critically ill children, particularly those with hemodynamic instability.[1,2] Provision of pediatric CRRT has evolved from the use of machines designed for adults and older children to machines and filters designed for smaller children and neonates.[3,4] These newer devices with smaller filters, more precise control of blood flow, and more accurate ultrafiltration (UF) have led to an increase in the use of CRRT to support critically ill children. This chapter will discuss the components of a CRRT prescription, and provide important considerations for optimal use of the therapy. Numerous CRRT devices are available across the world, each with its own unique characteristics, and the choice of a particular device at any center depends on cost, availability, and local expertise. Despite the differences between devices, the main technical aspects of pediatric CRRT are similar across the board and can be generalized.

## Components of CRRT Prescription

**Vascular Access:** The quality of vascular access is key to successful delivery of CRRT. A well-functioning catheter provides adequate blood flow (Qb), and appropriate access and return pressures to prevent related complications. Based on Poiseuille's law, the flow (Q) of fluid is related to several factors including the viscosity (η) of the fluid, the pressure gradient across the tubing (P), and the length (L) and diameter(r) of the tubing.

$$Q = \frac{\pi P r^4}{8 \eta L}$$

Thus, the shortest catheter with the widest luminal diameter is likely to provide the best flow, with the least resistance. This concept was highlighted by the Prospective Pediatric Continuous Renal Replacement Therapy Registry (ppCRRT) which looked at the impact of catheter size and location on circuit survival.[5] They reported significantly longer circuit life with larger catheters, with a 48-hour circuit survival of 76% with 8-french (Fr) catheters compared to 26% with 7-Fr catheters. They also reported very low circuit survival with 5-Fr catheters, with none lasting longer than 20 hours.[5]

Since the ppCRRT experience more than a decade ago, there have been reports of successful use of smaller catheters for neonates and infants with the onset of newer pediatric-specific devices that can function with lower Qb. El Masri and colleagues described using two single-lumen hemostasis valve sheaths (3-, 4- and 5-Fr) for CRRT in neonates who were too small for an 8-Fr double-lumen catheter.[6] The 3-French sheath has a similar external and internal diameter to a 5-French single-lumen catheter (Medcomp Medical Components, Inc., Harleysville, Pennsylvania, USA), and the 4-French sheath has an external diameter just slightly smaller than a 7-French dialysis catheter. They observed a mean circuit life of 55 hours, with more than half functioning >60 hours. However, their thin walls were prone to kinking. Onwubiko et al showed that cuffed 6-Fr double-lumen catheters (PowerHohn®, Bard Peripheral Vascular, Inc., Tempe, AZ) lasted longer, required fewer revisions, and had fewer complications of occlusion, or malposition, compared to traditional hemodialysis catheters.[7] These catheters are available in a 50-cm length, but may be cut to the desired length. In their report of 26 neonates who received CRRT with the Cardio-Renal Pediatric Dialysis Emergency Machine, (Carpediem™, Bellco-Mozarc Medical, Mirandola, Italy), Garzotto, et al reported on 19 patients (73%) managed with double-lumen catheters ranging from 3- to 5-Fr.[8]

The optimal site for catheter placement depends on various clinical factors including the operator expertise and risks of the procedure, including possibility of stenosis and infection. The right internal jugular vein is preferred because of its large caliber, more direct route to the superior vena cava, and

lower recirculation rate.[9] Femoral veins are used occasionally due to their accessibility and relative ease of placement. However, they may have flow issues secondary to patient movement or increased intraabdominal pressure, and are also prone to higher recirculation, which is when dialyzed blood returning through the venous lumen re-enters the extracorporeal circuit through the arterial side, rather than returning to the systemic circulation. Subclavian veins should be avoided due to risk of stenosis, and potential challenges with a future arteriovenous graft or fistula if the patient progresses to chronic kidney disease. A temporary or non-tunneled line is often used in those likely to need therapy for less than seven days; for more prolonged therapy, a tunneled dual-lumen dialysis catheter with a subcutaneous cuff is recommended. Suggested catheter sizes are shown in Table 1.

**Table 1: Recommendations for appropriate vascular access for CRRT based on patient size**

| Weight Category | Vascular access options |
|---|---|
| **<5 kg** | • 2 single-lumen power rated catheters (3 Fr and 4 Fr or 4 Fr and 5 Fr)<br>• 4.5-6.5 Fr DLC<br>• 6 Fr double-lumen power rated catheter<br>• 7 Fr DLC |
| **5-10 kg** | • 6.5 Fr DLC<br>• 7-8 Fr DLC |
| **10-30 kg** | • 9-10 Fr DLC |
| **>30 kg** | • 12 Fr DLC<br>• A 12 or 13 Fr triple-lumen dialysis catheter may also be used (extra port for calcium and other infusions) |

DLC, Double-lumen dialysis catheter; Power rated catheters are not traditional dialysis catheters, but may be used for that purpose in neonates and infants; Not all catheter sizes are available everywhere.

## Blood Flow Rate (Qb)

A blood pump flow rate of 3-8 mL/kg (patient body weight)/minute is often suggested for CRRT; however, the achievable Qb is ultimately determined by the size of vascular access and type of CRRT machine. Older machines designed for adults often required a blood flow higher than 60-80 mL/min, which translates to 10-15 mL/kg/min for a neonate or small infant. Newer devices like Aquadex™ (Nuwellis Inc., Minneapolis, Minnesota, USA) or Carpediem™, or the smaller HF-20™ (Baxter healthcare, Deerfield, Illinois, USA) filter can work with lower blood flows in the 20-50 mL/min range.[8,10] Table 2 provides details of the commonly available CRRT machines, filters, prescription ranges, and accuracies.

As opposed to intermittent hemodialysis, a higher blood pump flow rate does not impact solute clearance in CRRT significantly, as CRRT clearance is determined (and prescribed) by effluent rate flow (see below).

**Table 2: Commonly available CRRT machines, filters, prescription ranges and reported accuracy[a]**

| Device and Filters | ECV (mL) | Filter ($m^2$) | Qb (mL/min) | UF (mL/hour) | Accuracy |
|---|---|---|---|---|---|
| **Prismaflex™/ Prismax™** | | | | | |
| **HF-20** | 60 | 0.2 | 10-100 | 0-1440 | +10% of UF setting |
| **M-60** | 97 | 0.6 | 50-180 | 0-3300 | |
| **M-100** | 155 | 0.9 | 75-400 | 0-6420 | |
| **HF-1000** | 165 | 1.1 | 75-450 | 0-6420 | |
| **Multifiltrate®** | | | | | |
| **Ultraflux® 400/600/1000** | 52-130 | 0.75-1.8 | 10-500 | 0-1800 | +10% |
| **AV Paed®** | 72 | 0.2 | 10-100 | 0-500 | |
| **NxStage™** | | | | | |
| **CAR 500/502/505** | 171-221 | | 10-600 | | +10% |
| **CAR 125 with Renaflo filters** | 83-138 | | 10-200 | | |
| **Aquadex™** | 33 | 0.12 | 10-40 | 0-500 | +10 |
| **Carpediem™** | 26<br>32<br>41 | 0.072<br>0.17<br>0.29 | 2-50 | 0-150<br>0-240<br>0-600 | 1 g/h |

Prismaflex™/Prismax™ Baxter healthcare, Deerfield, Illinois, USA; Multifiltrate® Fresenius Medical Care, Waltham, Massachusetts, USA; NxStage Medical, Inc, Lawrence, Massachusetts, USA; Aquadex™ Nuwellis Inc., Minneapolis, Minnesota, USA; Carpediem™, Bellco-Mozarc Medical, Mirandola, Italy

a. Data were abstracted from public facing sources, neither the authors nor the publisher are responsible for the accuracy of the content.

## Anticoagulation

Adequate anticoagulation of the CRRT circuit is crucial for the effective delivery of CRRT. The ideal anticoagulant is regional, limited to the circuit, easy to implement and monitor, has minimal adverse effects, and allows provision of therapy without unplanned downtimes. Systemic unfractionated heparin and regional citrate anticoagulation are used in pediatric CRRT most commonly, although there are newer reports of agents like prostacyclin, nafamostat, and bivalirudin.[11-13]

Heparin is typically infused pre-filter, with a starting dose of 20-30 units/kg, followed by an infusion rate of 10-20 units/kg/hour. The rate is titrated to maintain a post-filter partial thromboplastin time (PTT) 1.5-2 times normal range, or an activated clotting time (ACT) of 180-220 seconds. The ppCRRT registry showed that the use of heparin or citrate led to similar filter life, and they were both superior to no anticoagulation.[14] Other studies have shown better circuit life with citrate compared to heparin.[15,16] The use of heparin is associated with more severe bleeding complications and the rare complication of heparin-induced thrombocytopenia.[14,15]

Regional citrate anticoagulation is the most widely used strategy in pediatric CRRT.[11] The coagulation cascade is highly dependent on the availability of calcium ions. Citrate is infused into the arterial limb of the CRRT circuit where it chelates calcium ions, leading to regional hypocalcemia and inhibition of clotting within the circuit. To prevent systemic hypocalcemia, calcium chloride or calcium gluconate is given to the patient either through a separate central line, or at the venous lumen of the dialysis catheter where blood from the circuit is returned to the patient. Commercially available citrate solutions include anticoagulant citrate dextrose solution (ACD-A, Baxter Healthcare), with 224 mmol/L of sodium, 74.8 mmol/L of citrate and 38 mmol/L citric acid and 4% trisodium citrate solution (TCA), with 420 mmol/L of sodium and 136 mmol/L of citrate.[17] ACD-A, which is more commonly used, is infused at a rate (in mL/hour) equal to 1.5 times the blood flow rate in mL/min, and this is titrated to achieve a circuit ionized calcium (iCa) of 0.2-0.4 mmol/L.[18] Calcium chloride (8 g/1000 mL) is infused at a rate (in mL/hour) of 0.6 times the blood flow rate in mL/min. For example, if the Qb is 100 mL/min, ACD-A is infused at 150 mL/hour, and calcium chloride is infused at 60 mL/hour. The rate of calcium infusion may vary, however, depending on the type (calcium chloride vs calcium gluconate) and the concentration of the product available.

By limiting hypocalcemia to the CRRT circuit only, this system can provide regional anticoagulation, without increasing the risk of systemic bleeding. There are, however, other adverse effects that need to be watched for. A large proportion of the calcium–citrate complex is removed in the ultrafiltrate or dialysate effluent. The remaining calcium–citrate complex returns to the patient, where it is metabolized to bicarbonate by the liver, kidney, and skeletal muscle, with each citrate molecule resulting in three bicarbonate molecules.[17] The ensuing metabolic alkalosis can be managed by either increasing CRRT clearance, or by decreasing the rate of citrate infusion.[19] Citrate overload or toxicity may be seen when citrate delivery overwhelms citrate clearance. This may be characterized by difficulty maintaining systemic iCa despite increasing calcium infusion, elevated total calcium levels, elevated total calcium to the iCa ratio, and ultimately metabolic acidosis. Infants and neonates with less mature hepatic metabolisms and lower muscle mass, and patients with severe hepatic dysfunction are at higher risk of developing citrate overload. For these patients, a lower initial citrate rate is recommended.

Prostacyclin, or its synthetic equivalent epoprostenol, is a platelet aggregation inhibitor, and is emerging as a good alternative to regional citrate or heparin, especially in patients with liver failure.[13] Given its very short half-life, it tends to function as a regional anticoagulant. Epoprostenol is a

vasodilator, which can lead to systemic hypotension. However, this effect is less common with the usual dose range of 2-8 ng/kg/minute.

Nafamostat mesilate is a synthetic serine protease inhibitor placed, and a prostacyclin analog used for CRRT anticoagulation in Japan and Korea.[12] In addition to inhibiting platelet aggregation, it also binds with thrombin and blocks its clotting activity, and suppresses various activated clotting factors including factor XIIa, Xa, and plasmin. With its short half-life of 8 minutes, it also functions as a regional anticoagulant, similar to prostacyclin.

## CRRT Dose and Clearance

CRRT dose is often discussed in terms of solute clearance, which can be calculated based on either the disappearance of solute from the blood, or its appearance in the effluent fluids. For low-molecular-weight solutes with sieving coefficients close to unity, the solute clearance during continuous hemofiltration is approximately equal to the ultrafiltration (effluent) rate.[20] CRRT is prescribed with relatively lower effluent fluid flow rates compared with intermittent HD dialysis fluid rates, thus, complete equilibration can occur between blood and dialysis or replacement fluid for low molecular weight solutes, resulting in a nearly linear relationship between effluent flow and small solute clearance. In adults, the CRRT dose at initiation of therapy was standardized after the results of two large randomized controlled trials.[21,22] These studies showed that there was no significant benefit to delivering greater than 20–25 mL/kg/hour of clearance. “Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Acute Kidney Injury” recommends a delivered dose of 20-25 mL/kg/hour for AKI. Given the interruptions that occur during provision of CRRT, such as alarms, and radiology and operative procedures, it has been suggested that an initial prescription of 30-35 mL/kg/hour might deliver a dose of 20-25 mL/kg/hour.

There are no randomized controlled trials looking at the dose of CRRT and outcomes in pediatrics. In pediatrics, a dose of 2000 mL/1.73m$^2$/hour is often recommended as it corresponds to approximately 35 mL/kg/hour in an adult patient weighing 70kg and a body surface area (BSA) of 2m$^2$.[23] However, significant variation in CRRT dose prescriptions exist in the literature. A systematic review evaluating CRRT prescription in children showed that pediatric dose ranged from <1,000 to more than 4,000 mL/1.73m$^2$/hour and from 20-150 mL/kg/hr.[24] While the conversion from a weight-based dose in adults matches well with a BSA-based dose in older children, the nonlinear relationship between weight and BSA will result in a disproportionately high dose in neonates and infants. It has been presumed that younger children, with higher metabolic demand, and larger volume of distribution, may need a higher dose of CRRT. There are limited data from neonates and infants on intermittent maintenance hemodialysis for end stage kidney disease (ESKD) that suggest benefit from a higher dose than what is recommended for adults and older children.[25] However, it is not known if this concept of augmented dialysis in infants with ESKD applies to those with AKI receiving CRRT. While more intensive CRRT may results in greater improvement of the uremic milieu, it may be counterbalanced by potential complications of therapy including hypophosphatemia, increased losses of amino acids and other micronutrients.[26-28]

## CRRT Dosing for Specific Clinical Situations

**Acute Liver Failure:** In a single-center study looking at the effect of low (35 mL/kg/hour) and high (90 mL/kg/hour) CRRT dosing on ammonia clearance, Slack et al found that clearance

correlated closely with ultrafiltration rate.[29] Chevret and colleagues reported significantly improved hemodynamic stability and neurological status in children with acute liver failure awaiting liver transplantation.[30] Deep et al recommend a starting dose of 60-90 mL/kg/hour and adjusting as needed based on response.[31] Centers that use a BSA-based dosing will usually do 3000-4000 mL/1.73m$^2$/hour.[31,32]

**Hyperammonemia due to Inborn Errors of Metabolism:** Neonatal hyperammonemia, seen in inborn errors of metabolism, requires prompt intervention to reduce neurological damage. Traditionally hemodialysis has been used to rapidly reduce ammonia, particularly when levels are higher than 400 μmol/mL, followed by CRRT to prevent rebound.[33,34] Spinale et al reported successful reduction in ammonia with high-dose CRRT using a clearance of 8000 mL/1.73m$^2$/hour, four times higher than that used for AKI.[35] That dose was selected to match small solute clearance of hemodialysis in an infant with a low Qb. Using high-dose CRRT allowed them to provide therapy without interruption for modality change, and prevented rebound.[35] A recent multicenter retrospective analysis of 51 neonates with inborn errors of metabolism and hyperammonemia who were treated with renal replacement therapy showed that hemodialysis was associated with a higher risk of death compared with CRRT.[36]

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3

# Timing of Pediatric Renal Replacement Therapy for Acute Kidney Injury

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Acute kidney injury (AKI) is a common development in critically ill patients and has been shown repeatedly to be associated with increased morbidity and mortality in adults and children.[1,2] The optimal timing for initiation of renal replacement therapy (RRT) for AKI remains unknown. There is a consensus that the benefits of RRT outweigh the risks, and continuous renal replacement therapy (CRRT) is indicated in patients with hemodynamic instability or shock.[3] There is still no consensus on whether earlier RRT initiation can benefit patients with AKI. Data existing prior to the last decade were derived largely from observational studies. These are limited due to confounding by indication, considerable heterogeneity in case mix and illness severity.

It is important to recognize that the associations between AKI and poor outcomes that occur with the Kidney Disease Improving Global Outcomes (KDIGO) guidelines defined increases in serum creatinine or oliguria duration[3,4] are not coincident to life-threatening electrolyte disturbances seen with progression from chronic kidney disease to end-stage kidney disease. Currently, the only modifiable aspects of AKI, once it has developed, are mitigation of nephrotoxic medication exposure (where possible) and fluid balance management. Critically ill patients often require life-saving medications that are primarily excreted by the kidney and/or nephrotoxic, so exposure is often unavoidable.[5,6] Fluid management strategies include fluid restriction, use of loop diuretics and initiation of renal replacement therapy to manage fluid homeostasis.[7,8] Yet, most recent large randomized CRRT trials do not use fluid accumulation thresholds to differentiate “early” vs “late” or “standard” timing of CRRT initiation.[9-11] Rather, studies of critically ill adults use changes in serum creatinine and/or elapsed time from AKI development to CRRT initiation for randomization. An excellent meta-analysis of these studies through July 2020 conducted by Li et al included 11 studies comprising more than 5,000 patients.[12] The median time of RRT initiation across studies ranged from 2 to 7.6 hours in the early RRT group and 21 to 57 hours in the delayed RRT group. The pooled results showed that early initiation of RRT, however defined by the study, was not associated with a decrease in 28-day all-cause-mortality. In addition, early initiation of RRT could lead to unnecessary RRT exposure in some patients and was associated with a higher incidence of hypotension and RRT-associated infection events.

While these studies have generally not found improved outcomes with earlier CRRT initiation, they remain incredibly important to highlight that AKI is a systemic disease or syndrome that is not yet modifiable based on decreases in kidney function far below imminent life-threatening sequelae including hyperkalemia, metabolic acidosis, hypocalcemia, and/or pulmonary edema. Many organizations have published clinical practice guidelines or consensus statements regarding timing of the initiation of RRT in critical care settings (Table 1).

The major goals of RRT in ICU are to achieve and maintain fluid, electrolyte, acid-base, and uremic solute homeostasis, along with facilitating additional supportive measures when indicated, such as nutritional support, medications, and blood products transfusion. Earlier initiation of CRRT might provide better control of acid-base and electrolyte balance. Moreover, it can be more helpful in maintaining hemodynamic stability and reducing the risk of potential complications of AKI. However, early initiation of CRRT can also increase the unnecessary financial burden of patients with AKI, it can increase the risk of coagulopathy, lead to inadequate medication dosing, and even delay recovery of kidney function, which may negatively affect the prognosis of patients. The use of clinical prediction tools such as the renal angina index (RAI) or fluid overload kidney injury score to identify patients most likely to benefit from RRT early in their ICU stays is compelling.[13,14] Emerging biomarkers are increasingly being used to predict the need for RRT. For example, urine neutrophil gelatinase-associated lipocalin (uNGAL) has been shown to accurately detect AKI earlier and predict the need for RRT in children after cardiac surgery better than serum creatinine alone.[15] Integration of NGAL

with the renal angina improves predictive performance for AKI over RAI alone.[16,17] The use of the furosemide stress test (FST), which finally standardizes both diagnostic dose of furosemide (1 to 1.5 mg/kg) and urine output response (200 mL/hour for 2 hours for adults[18,19], 3-4 mL/kg/hour for 2-6 hours for children[20]), shows promise for identifying patients who will need to escalate from diuretics to RRT to maintain acceptable fluid balance homeostasis without fluid restriction.

While no definitive evidence and consensus for CRRT initiation are currently available for pediatric patients, multiple pediatric studies have identified fluid accumulation thresholds at CRRT initiation that are associated with worsening morbidity and mortality. In general, fluid accumulation is defined from ICU admission to CRRT initiation as a percentage of body weight[21]:

$$\frac{\text{(Fluid input in liters)} - \text{(Fluid output in liters)}}{\text{ICU admission weight (kg)}} \times 100$$

A recent meta-analysis of pediatric studies demonstrated the persistent association between fluid accumulation at CRRT initiation and poor outcomes.[22] The recent 26th Acute Disease Quality Initiative consensus conference, which was the first devoted to children (pADQI) differentiated between the terms fluid accumulation and fluid overload, the latter of which had been biased in the literature.[6] Concisely, fluid accumulation is a mathematical calculation (as above), whereas fluid overload connotes a degree of positive fluid accumulation that is associated with physiological changes, morbidity, and/or mortality. Observational studies which are included in the aforementioned meta-analysis suggest a 10%-20% fluid accumulation threshold meets the definition of fluid overload. A current study has just been completed to integrate AKI risk stratification, urinary biomarker thresholds, and the FST to direct RRT initiation to prevent >20% fluid accumulation.[23] Results of this study may shed light on a potential to standardize clinical care in the most complex component of critical care nephrology: the timing of CRRT initiation.

Table 1: Summary of clinical practice guidelines for starting RRT in critically ill patients with AKI

| Organization | Recommendation |
|---|---|
| **Kidney Disease: Improving Global Outcomes (KDIGO)[3]** | (i) Initiate RRT emergently when life-threatening changes in fluid, electrolyte, and acid-base balance exist (not rated).<br>(ii) Consider the broader clinical context, the presence of conditions that can be modified with RRT, and trends of laboratory tests rather than single BUN and creatinine thresholds alone when making the decision to start RRT (not rated). |
| **National Institute for Health and Care Excellence (NICE)[24]** | (i) Discuss any potential indications for RRT with a nephrologist, pediatric nephrologist, and/or critical care specialist immediately to ensure that the therapy is started as soon as needed.<br>(ii) Refer adults, children, and young people immediately for RRT if any of the following are not responding to medical management:<br>• Hyperkalemia<br>• Metabolic acidosis<br>• Complications of uremia (i.e., pericarditis, encephalopathy)<br>• Fluid overload<br>• Pulmonary edema<br>(iii) Base the decision to start RRT on the condition of adult, child, or young person as a whole and not on an isolate urea, creatinine, or potassium value. |
| **French Intensive Care Society (SRLF)[25]** | (i) RRT should be initiated without delay in life-threatening situations (hyperkalemia, metabolic acidosis, tumor lysis syndrome, refractory pulmonary edema). (Expert opinion; strong agreement)<br>(ii) The available data are insufficient to define optimal timing of initiation RRT outside life-threatening situations. (Expert opinion; strong agreement)<br>(iii) In children, fluid and sodium overload probably >10%, and very probably >20% should be considered as one of the criteria for initiation RRT. (Expert opinion; poor agreement)<br>(iv) "Early" initiation of RRT means at KDIGO stage 2 or within 24 hours after onset of acute renal failure of which reversibility seems unlikely. (Expert opinion; poor agreement)<br>(v) "Late" initiation of RRT means >48 hours after onset of acute renal failure, KDIGO stage 3, or when a life-threatening situation arises because of acute renal failure. (Expert opinion; poor agreement) |

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# 4

# Extracorporeal Membrane Oxygenation and Continuous Renal Replacement Therapy

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## Types of ECMO

There are two major forms of Extracorporeal Membrane Oxygenation (ECMO) support. The critical care, ECMO, and surgical teams discuss the etiology of the patient's disease and decide on the appropriateness of each form of support prior to cannulation.

**Veno-Arterial (VA) ECMO:** This form supports both pulmonary and cardiovascular systems. Patients with congenital heart disease, post-cardiac arrest, heart failure, or myocarditis are the usual candidates for VA-ECMO support (Figure 1a).

**Veno-Venous (VV) ECMO:** This form of support is used for primary pulmonary pathologies. It is usually used in patients with acute respiratory distress syndrome, asthma, or pneumonia. This form of support requires a functional myocardium so the oxygenated blood returned from the circuit to the right side of the heart can be pumped through the pulmonary circulation (Figure 1b).

The duration of ECMO is dependent on the etiology of the patient's illness and reason for cannulation. Patients on VV-ECMO tend to have longer ECMO runs, solitary organ (lung) dysfunction, and better outcomes. In addition to the types of ECMO noted above, there are various hybrid cannulation strategies where multiple venous or arterial cannulas are placed in order to achieve adequate oxygen delivery to organ tissue beds.[13] There is emerging data on the utility of ECMO in refractory in and out of hospital cardiac arrest (eCPR).[14] Recent literature has suggested the increase in the utilization of eCPR is associated with improved patient survival and more favorable neurological outcomes.[15]

Figure 1a: VA-ECMO

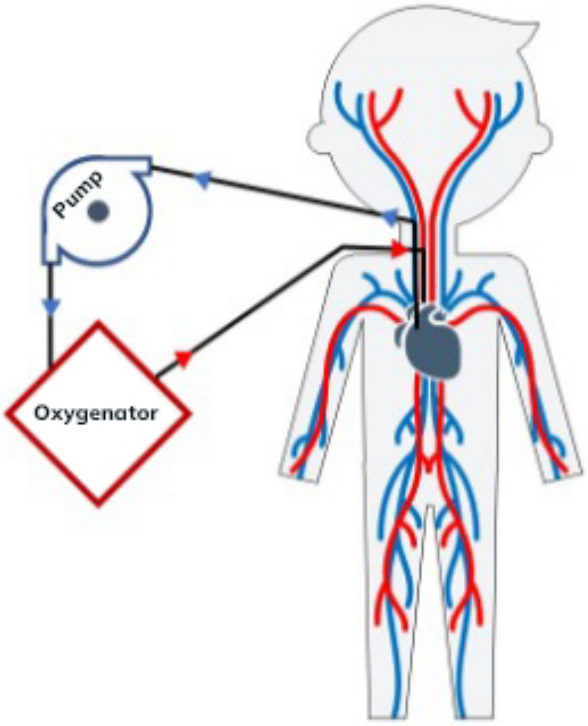
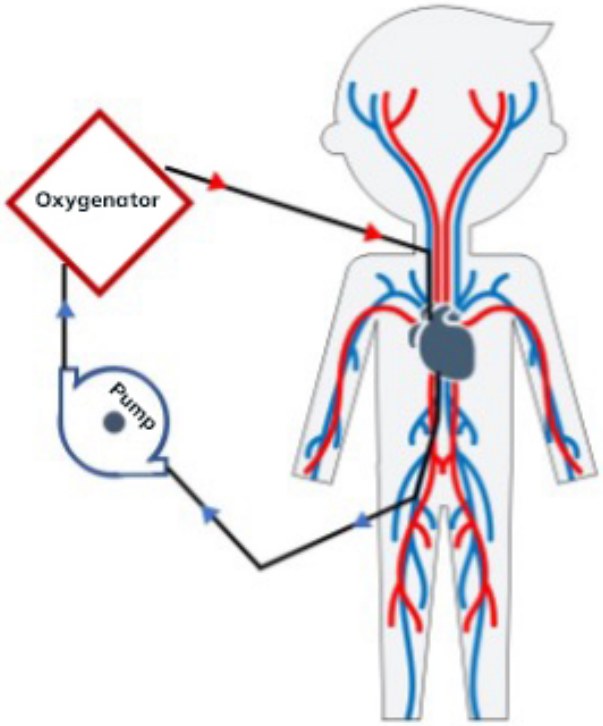


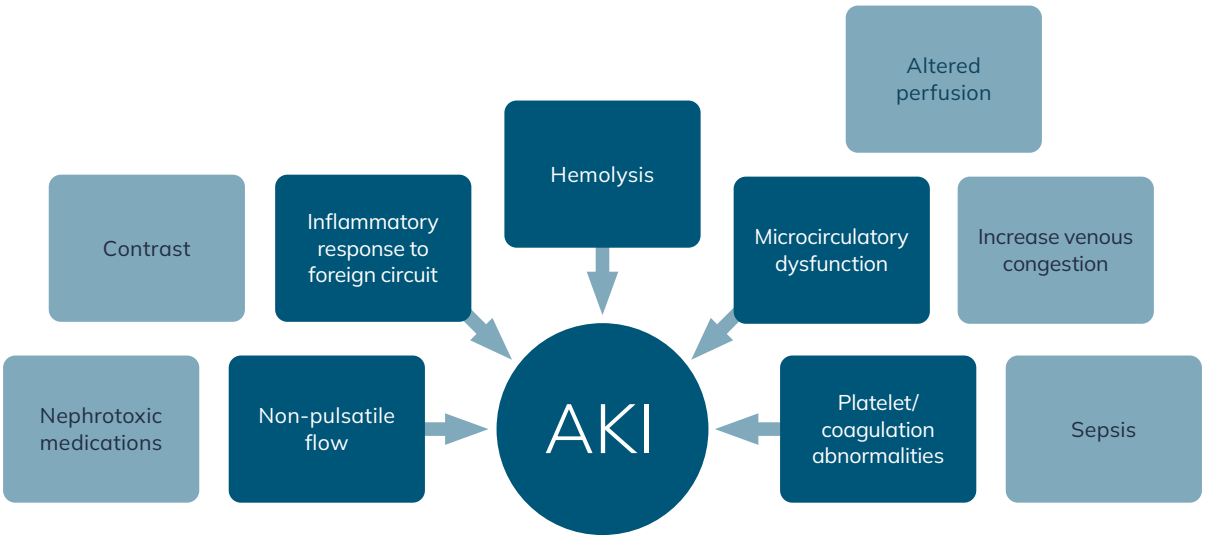

Figure 1b: VV-ECMO (dual-site cannulation strategy)



## Acute Kidney Injury and Extracorporeal Membranous Oxygenation

Acute Kidney Injury (AKI) occurs in one in four critically ill pediatric patients.[1,2] Those patients requiring extracorporeal membranous oxygenation (ECMO) are almost two times more likely to incur AKI with incidence ranging from 42%-85%[3] and the highest reported incidence within the neonatal congenital cardiac population.[4] The etiology of AKI within this population is multi-factorial (Figure 2). Around 35% of pediatric patients on ECMO require some variation of renal replacement therapy (RRT).[5]

**Figure 2: Factors influencing the development of AKI in patients on ECMO**




## Indications

The indications for continuous renal replacement therapy (CRRT) do not vary much from the core indications for dialysis within the critically ill pediatric population.

**1. Acidosis**

a. Refractory to medical management. In adults on VA-ECMO, progressive lactic acidosis is associated with in-hospital mortality and cerebral vascular accidents.[6]

**2. Electrolyte derangements**

a. Hyperkalemia and hypocalcemia can occur given the large volume of blood products required to prime the ECMO circuit, as well as to maintain optimal hemostatic parameters during the ECMO treatment.

**3. Ingestions**

a. There are many ingestions/overdoses that lead to cardiovascular collapse, and some are dialyzable. Therefore, the use of RRT in these cases can decrease the duration of extracorporeal therapy and reverse end organ dysfunction. These include but are not limited to salicylates, ethylene glycol, phenytoin, and lithium.[7] Other agents with larger volume of distribution or greater protein binding (such as calcium channel blockers, hydroxychloroquine) might require albumin-augmented dialysis in tandem with ECMO circuit.[10]

**4. Fluid overload**

a. As with other critically ill patient populations, fluid overload at the start of ECMO therapy is associated with increased risk for mortality.[5] Optimizing fluid status can improve myocardial function, pulmonary edema, and other organ venous congestion, allowing for improved organ function and therefore recovery. Although reversal of fluid overload through mechanical removal has failed to mitigate the increased risk associated with fluid accumulation in children, raising questions about optimal time of CRRT and critical threshold where fluid accumulation becomes pathological fluid overload.[11]

b. In many cases, the inflammatory cascade occurring in patients prior to and while on ECMO leads to patients who are intravascularly depleted while overloaded in total body fluid. Therefore, slow fluid removal will maintain optimal microvascular perfusion. Aggressive slow continuous ultrafiltration (SCUF), especially in younger children, can lead to metabolic acidosis due to unregulated bicarbonate loss, and has also been reported in adults.[12] Vigilance for this complication is required when only SCUF is used.

**5. Uremia/nutrition**

a. Patients on ECMO are at high risk for hypermetabolic states given their inflammatory burden, underlying illness, catecholamine release, and increased amino acid losses. The application of CRRT can allow for optimization of nutritional support earlier during ECMO therapy, minimizing the time spent in a pathological catabolic state.[8]

## Configurations of ECMO with CRRT

When initiating CRRT in tandem with ECMO, there are multiple configurations. When discussing the configuration of this tandem therapy, there are a couple of key factors to consider:

1) Body surface area (BSA)/weight of the patient

2) Pressure ranges within the CRRT machine

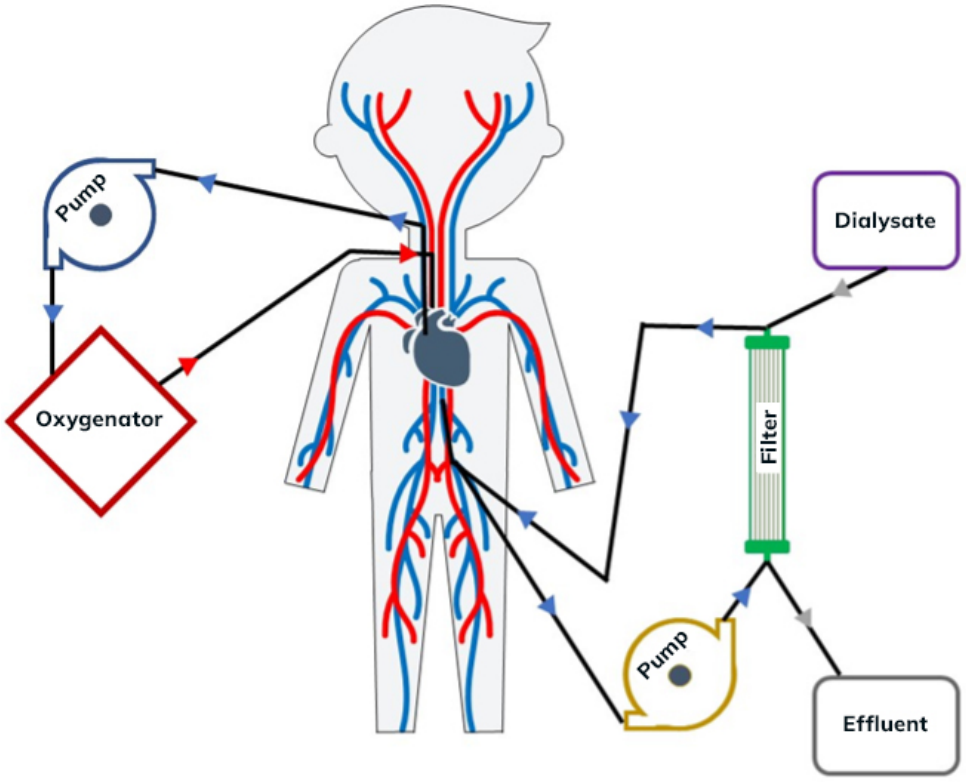
3) Pressures within the ECMO circuit

4) Recirculation

5) Prolonging extracorporeal circuit life

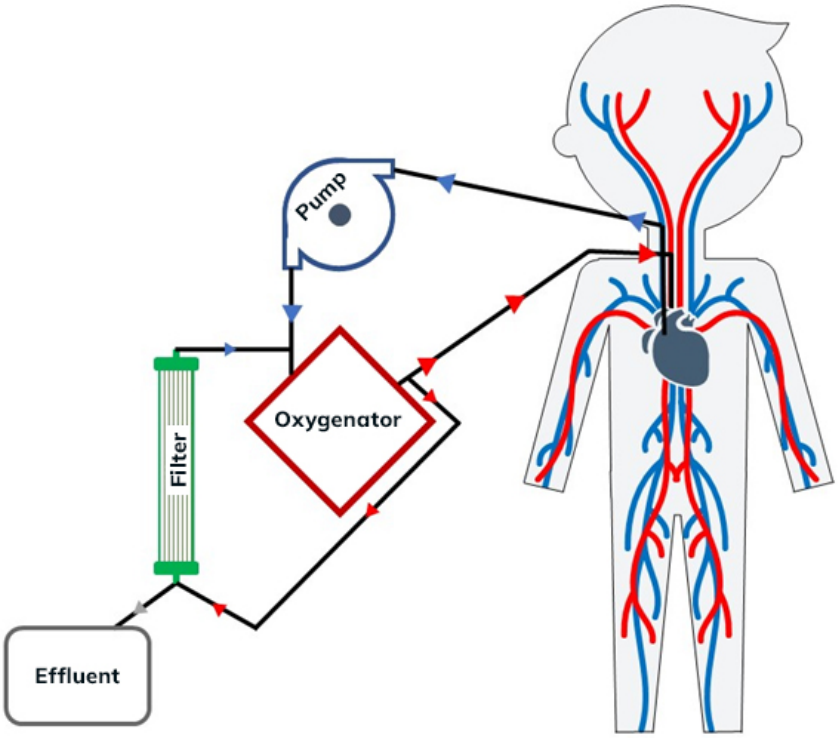
| Parallel | | |
|---|---|---|
| **Type of ECMO Circuit Configuration** | **Advantages** | **Disadvantages** |
| **Parallel Circuits**<br>With this configuration, there are three points of access. CRRT will be run in parallel through a separate double lumen hemodialysis catheter. | • Allows for each circuit to sense the appropriate pressures, decreasing alarms<br>• Provides safe CRRT in the setting of high ECMO pressures<br>• Can continue to provide CRRT during ECMO weaning and decannulation. Minimizes the risk of metabolic derangements during these high-risk procedures (weaning and decannulation).<br>• Protects either circuit from clot burden imposed by slower flows | • Two points of access, increasing the risk for infection<br>• Placement of the hemodialysis line is higher risk while patients are on systemic anticoagulation therapy |

Parallel configuration: Parallel circuits



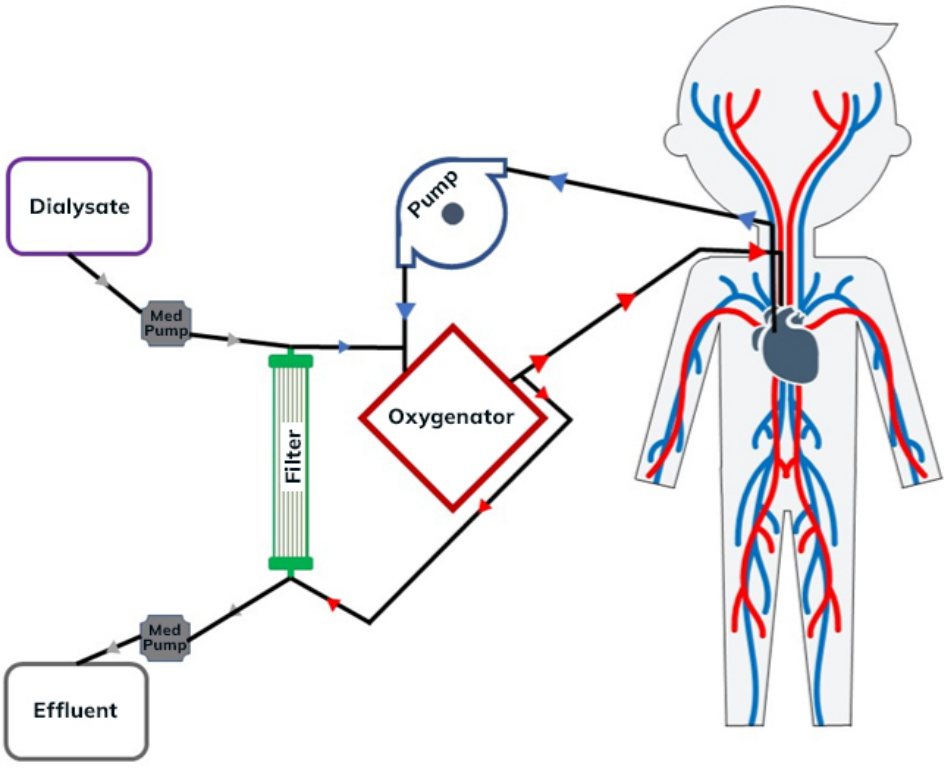
| Series | | |
|---|---|---|
| **Type of ECMO Circuit Configuration** | **Advantages** | **Disadvantages** |
| **Pure Ultrafiltration**<br>Small hemoconcentration filter is added in-line to the ECMO circuit, allowing clinical teams to provide slow continuous ultrafiltration (SCUF). Indicated for patients with fluid overload without uremia or electrolyte/ metabolic abnormalities. | • Theoretical improved precision of fluid removal when compared to diuretics<br>• Simple setup usually does not involve increased nurse or perfusionist staffing<br>• Additional anticoagulation is not indicated or required | • Given the addition of the filter, there is an additional risk of decreased ECMO circuit life and increased thrombosis<br>• Little to no metabolic control and reports of increased bicarbonate losses, which can lead to a non-gap hyperchloremic metabolic acidosis<br>• Use of volumetric pumps to drive fluid removal can lead to imprecision, especially with faster rates |

Series configuration: Pure ultrafiltration



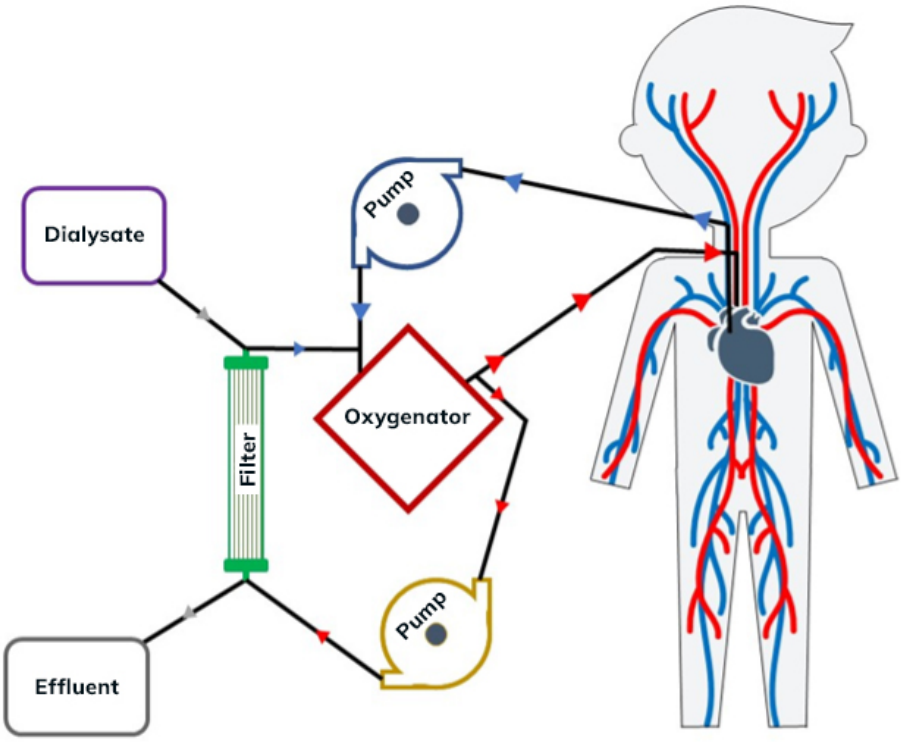
| Series | | |
|---|---|---|
| **Type of ECMO Circuit Configuration** | **Advantages** | **Disadvantages** |
| **Modified CRRT (CVVHD)**<br>A small hemoconcentration filter is placed in-line and countercurrent exchange is provided using standardized dialysate. This requires two volumetric infusion pumps: one pre-filter to infuse the dialysate and one post-filter to dictate the rate of ultrafiltration. | • Improved metabolic control when compared to SCUF/ pure ultrafiltration and diuretics<br>• Can be used in patients with fluid overload and uremia/electrolyte derangements<br>• Simple setup eliminates the need for increased nursing or perfusionist staffing<br>• Depending on the practice standards, may require procedural consent | • Most med pumps can only run at a maximum rate of 999 mL/hr, limiting the clearance and ultrafiltration rates that can be provided to patients<br>• The accuracy of fluid removal is only as precise as the error range of the med pumps<br>• This form of RRT is usually limited to patients weighing less than 10 kilograms (BSA <0.5 $m^2$) |

**Series configuration: Modified CRRT (CVVHD)**



| Series | | |
|---|---|---|
| **Type of ECMO Circuit Configuration** | **Advantages** | **Disadvantages** |
| **Tandem CRRT**<br>A CRRT circuit is connected in tandem with the ECMO circuit. | • Allows for more precise fluid and metabolic control when compared to the previously discussed therapies<br>• No separate dialysis catheter required for therapy, therefore decreasing the risk for line-associated thrombus and possible nidus for infection<br>• Not limited by patient's weight/BSA | • Depending on how the circuit interconnects, there can be an increased risk of recirculation and theoretical risk of increased circuit clot formation<br>• Complex tandem therapy likely requires additional nursing and/or perfusionist education and training |

**Series configuration: Tandem CRRT**



## Anticoagulation

To maintain ECMO circuit patency, systematic anticoagulation is initiated at the time of cannulation. The additional tandem CRRT has a theoretical increased risk of thrombosis, given the additional connections and tubing required, leading to non-laminar flow.

**Systemic:** The three most common systemic anticoagulants are 1) heparin, 2) bivalirudin, and 3) argatroban. Heparin has been the standard of care, but there is emerging evidence that bivalirudin has been associated with decreased risk of major bleeding, thrombosis, and in-hospital mortality in pediatric patients.[9] Goal levels (unfractionated heparin or activated PTT hepazyme) can be adjusted based on the patient's clinical status as well as indication for ECMO therapy. This can lead to time points in which patients have subtherapeutic anticoagulation, which can lead to premature CRRT filter clotting and failure. Functional assays of coagulation such as Rotational thromboelastometry (ROTEM) are ideal to monitor anticoagulation. Note that bivalirudin is dialyzable.

**Regional citrate anticoagulation (RCA):** This form of anticoagulation allows the prescriber to minimize the side effects of systemic anticoagulation while allowing for localized circuit anticoagulation. Literature has shown the use of RCA was associated with increased filter life, decreased risk for filter failure, and decreased risk for bleeding. RCA allows the prescribing team to continue to anticoagulate the CRRT circuit despite changes to systemic anticoagulation therapy, therefore allowing patients to continue to achieve metabolic and fluid control.

### Complications during Tandem Therapy

Premature clotting

Pressure alarms

Air embolism

Premature failure of oxygenator

Recirculation

Changes to pharmokinetics and volume of distribution

Increased technical workload

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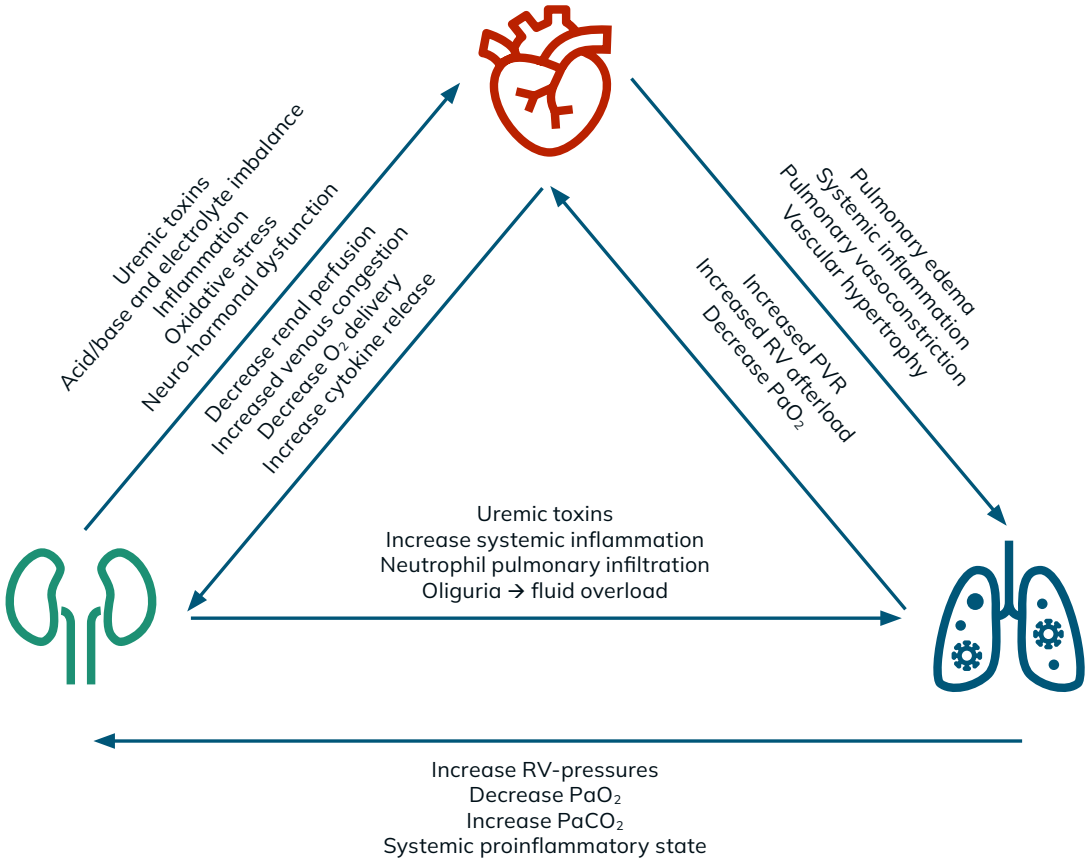
# Appendix

## Mechanical Ventilation and Continuous Renal Replacement Therapy

Mechanical ventilation (MV) is one of the most utilized therapies provided within the PICU. Anywhere from 30%–64% of all pediatric patients admitted to an ICU require invasive MV.[1] The need for respiratory support in pediatric patients requiring CRRT surpasses 90%.[2] Upon initiation of MV, many pathological changes occur within the cardio-pulmonary-renal systems, leading to increased risk for development of AKI (Figure 1). This triad of pathological organ cross-talk determines the impact of ultrafiltration on hemodynamics and lung compliance.

**Figure 1**




## Indications

The indications for CRRT in MV patients do not differ compared to the general critically ill pediatric population. The patients that require MV usually have a higher illness severity than those patients who do not require mechanical respiratory support. The underlying pathology leads to changes in cardio-renal-pulmonary interactions, which puts MV patients at higher risk for FO, AKI, metabolic and respiratory acidosis.[3]

## Measurements of Respiratory Dysfunction

**Dead space ventilation:** In the setting of lung disease, there are alveoli that do not participate in gas exchange. This can be measured by using the Bohr-Enghoff equation [Dead space = ($PaCO_2$ – $PECO_2$)/($PaCO_2$)]. As this ratio increases, there is likely to be an increase in the severity of the patient's lung disease. This ratio has been shown to be associated with mortality in adult acute respiratory distress syndrome (ARDS), but its utility to measure the impact of CRRT on acute lung injury (ALI)/ARDS has yet to be investigated.[4]

**Oxygenation Index (OI):** This is a measure of the impact of the underlying lung disease on diffusion of oxygen into the pulmonary circulation, accounting for the amount of respiratory support needed by incorporating mean airway pressure, the main determinant of oxygenation, into the equation. It has been used to predict need for escalation of respiratory support and mortality. Most importantly, this index is one of the criteria used to classify the severity of lung disease in pediatric ARDS.[5]
OI = ($FiO_2$x$Paw$)/($PaO_2$).

**Oxygen Saturation Index (OSI):** Similar to OI, this measurement can be used to objectively classify the diffusional defect within the respiratory system. Additionally, this measurement can be calculated without the need of a $PaO_2$ and therefore without an arterial blood gas.
OSI = ($FiO_2$x$Paw$)/($SpO_2$) in additional an OSI can be converted to an OI and has been shown to have a similar predictive value as OI.[8]

**$PaO_2$/$FiO_2$ ratio (P/F):** Similar to OI and OSI, this ratio can be used to objectively classify the severity of the underlying lung disease. P/F = $PaO_2$/$FiO_2$. Unlike the measurements above, P/F does not account of the pressure delivered by the ventilator and therefore previously published studies have shown that OI is a better predictor of mortality when compared to P/F ratio.[9]

**Access:** Prior to the placement of a hemodialysis catheter, there should be a multi-disciplinary team discussion on the most appropriate size, length, and location for the catheter. Ultimately the decision on the location of the hemodialysis catheter should be left to the proceduralist. A recent secondary analysis of the ATN study showed that patients who had femoral catheters were more likely to be coagulopathic (thrombocytopenia, elevated INR), younger, and had multiorgan failure. Of note, those with femoral catheters had a lower delivered dialysis dose measured using Kt/V.[10] Additionally, in-line with KDIGO recommendations, we would recommend minimizing subclavian access to prevent loss of a future arteriovenous fistula site.[6] Most importantly for those patients prescribed physical therapy while intubated, a femoral HD catheter can severely impede this therapy.

**Figure 2: The Pediatric Acute Lung Injury Consensus Conference (PALICC) definition and classification of pediatric ARDS (PARDS)[5]**

| | | | | |
|---|---|---|---|---|
| **Age** | Exclude patients with peri-natal related lung disease | | | |
| **Timing** | Within 7 days of known clinical insult | | | |
| **Origin of Edema** | Respiratory failure not fully explained by cardiac failure or fluid overload | | | |
| **Chest Imaging** | Chest imaging findings of new infiltrate(s) consistent with acute pulmonary parenchymal disease | | | |
| **Oxygenation** | **Non Invasive mechanical ventilation** | **Invasive mechanical ventilation** | | |
| | **PARDS (No severity stratification)** | **Mild** | **Moderate** | **Severe** |
| | Full face-mask bi-level ventilation or CPAP ≥5 cm $H_20^2$<br>PF ratio ≤ 300<br>SE ratio ≤ 264[1] | 4 ≤ OI < 8<br>5 ≤ OSI < 7.5[1] | 8 ≤ OI < 16<br>7.5 ≤ OSI < 12.3[1] | OI ≥ 16<br>OSI ≥ 12.3[1] |
| **Special Populations** | | | | |
| **Cyanotic Heart Disease** | Standard Criteria above for age, timing, origin of edema and chest imaging with an acute deterioration in oxygenation not explained by underlying cardiac disease.[3] | | | |
| **Chronic Lung Disease** | Standard Criteria above for age, timing, and origin of edema with chest imaging consistent with new infiltrate and acute deterioration in oxygenation from baseline which meet oxygenation criteria above.[3] | | | |
| **Left Ventricular Dysfunction** | Standard Criteria for age, timing and origin of edema with chest imaging changes consistent with new infiltrate and acute deterioration in oxygenation which meet criteria above not explained by left ventricular dysfunction. | | | |

## Balancing Starling Forces/Ultrafiltration

In the setting of lung disease requiring MV, pulmonary edema is usually caused by changes in endothelial integrity and is usually non-cardiogenic pulmonary edema. Given this, it is unlikely that this form of pulmonary edema will respond to aggressive fluid removal. Therefore, net ultrafiltration goals should minimize fluid accumulation while maintaining hemodynamics and renal prefusion, abating progressive renal damage.[7]

## Pediatric ARDS (PARDS) and Fluid Management

The pediatric acute lung injury consensus conference group have published recommendations in nine specific domains that pertain to PARDS diagnosis and treatment. When it comes to fluid management, this guideline focuses on three.[5]

1. PARDS patient should receive fluids to maintain adequate intravascular volume, end organ perfusion, and optimal oxygenation.
2. Fluid balance should be monitored and titrated to maintain sufficient intravascular volume while aiming to prevent positive fluid balance.
3. Fluid titration should be driven by a goal directed protocol that accounts for but is not limited to intake, output, and net fluid balance.

With these recommendations in mind, hourly fluid goals should be titrated as a patient's underlying lung pathology evolves with a focus on preventing/minimizing FO.

Initially, unless there is a contradiction or the patient's clinical status prevents the clinical team from doing so, patients should be prescribed diuretic therapy with the goal to prevent worsening fluid overload. Despite >1 mL/kg/hr of urine output, patients can still have relative oliguria in which the volume of fluid in (blood products, antibiotics, sedation, and/or nutrition) far exceeds the patient's ability to tolerate increased output in the form of urine. Patients who have relative oliguria will continue to stack fluid leading to worsening fluid overload and lung disease. In adults with sepsi-associated ARDS, survivors had 10% FO while non-survivors have >19% FO.[12] One could infer that when patient's reach ~10% FO [[FO = ((fluid intake (L) – fluid output (L))/ICU admission wt (kg)] x100][11], clinicians should start discussing the need for renal replacement therapy.

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# 5

# Acute Kidney Injury in Children: Selection of CRRT Versus Other Modalities

**Jaime Fernández-Sarmiento, MD**

## Summary

Acute kidney injury (AKI) is a frequent complication in children with critical illness. The patients with the highest risk are those who require mechanical ventilation, vasoactive drug support and/or have multiple-organ failure. Acute kidney injury is associated with increased risk of mortality, especially in patients who need dialysis. Renal replacement therapy (RRT) can provide lifesaving supportive therapy, and the final patient outcome may be determined in part by the timing of initiation and type of therapy used. There are many RRT options for critically ill children, including acute peritoneal dialysis, continuous renal replacement therapies, intermittent hemodialysis and hybrid therapies. The choice of modality is also determined by a variety of factors such as age, vascular access, hemodynamic condition, available institutional resources and the experience of the treatment team, among others. In this article, we review the recent recommendations on therapy choice according to these considerations, taking into account the advantages and disadvantages of each modality in critically ill children with AKI.

## Introduction

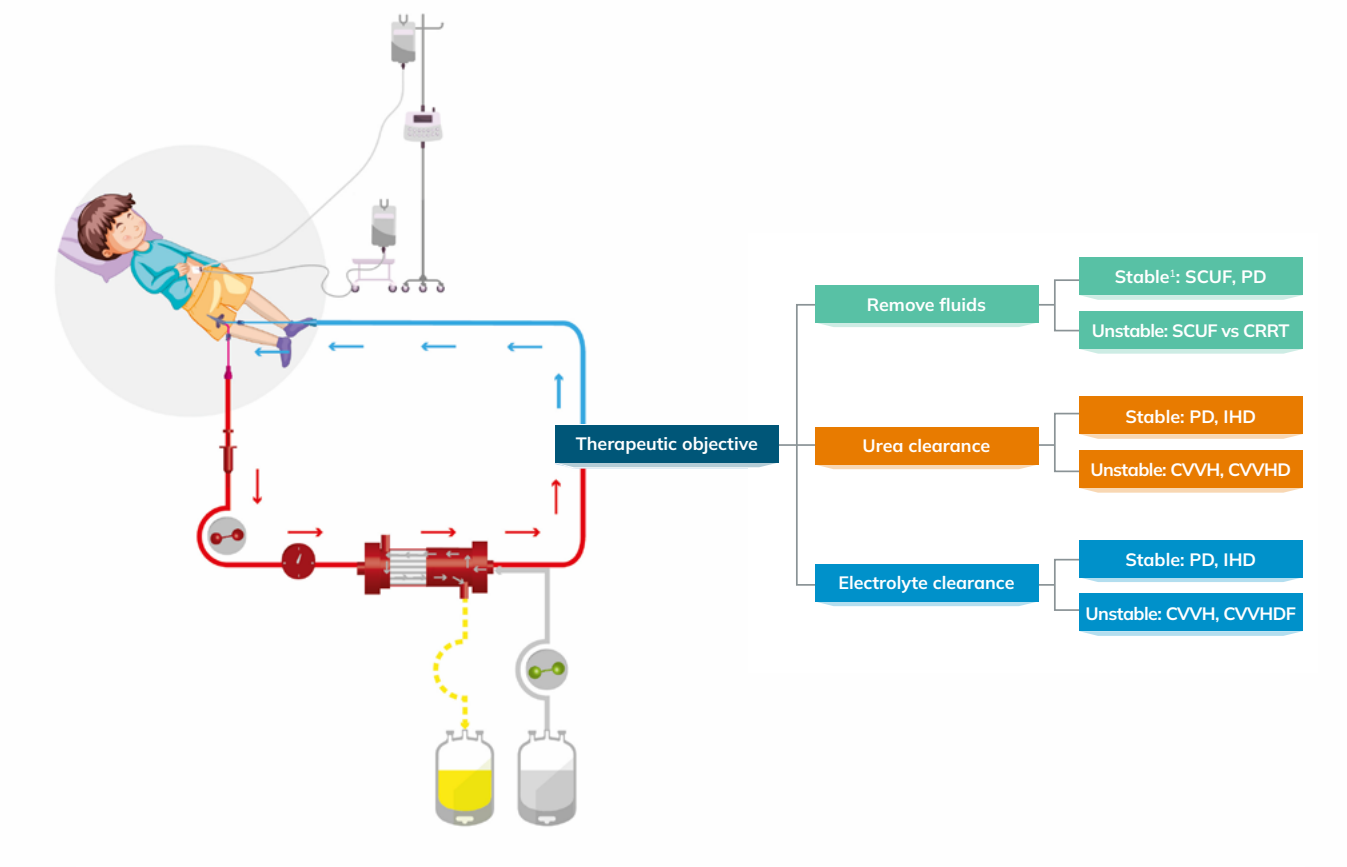
In all critically ill patients, acute kidney injury (AKI) is associated with increased morbidity and mortality.[1,2] A recent multinational prospective study of 4,638 children admitted to intensive care found AKI in 26.7% of the cases. Severe AKI was associated with a greater risk of death (11% vs 2.5%; aOR 1.77; 95% CI 1.17-2.68), with 5.8% of the patients requiring renal replacement therapy (RRT) including peritoneal dialysis, hemodialysis and continuous RRT (CRRT). Renal replacement therapy provision conferred an even greater risk of 28-day mortality in this study (aOR 3.38; 95% CI 1.74-6.54). Acute kidney injury was also associated with a greater need for mechanical ventilation (74% vs 30.2%; aOR 3.02; 95% CI 2.16-4.76), vasoactive support (63.9% vs 12.8%; aOR 4.67; 95% CI 3.18-6.87) and extracorporeal membrane oxygenation (ECMO) in the group of patients who died. Acute kidney injury mortality may be higher in newborns (31.3%), patients needing dialysis (27.1%), depending on the percent cumulative fluid balance[3], and those needing CRRT (30%-50%). The incidence of chronic kidney disease after having AKI may vary by center, but may range from 30% to 50% of the cases. Of these, 10 to 15% may need chronic dialysis after overcoming the acute phase and being discharged from the hospital.[4-7]

In this review, I discuss the RRT modality of choice according to each patient's clinical condition, the factors to consider in choosing the different modalities, their advantages and disadvantages, as well as the most frequently described complications in critically ill children.

## Selection of CRRT

Over the last few years, we have advanced substantially in the technological development of the different RRT modalities used in critically ill patients. Particularly in children, unlike adults, we have special challenges to consider when choosing a type of therapy, such as patient size and weight, availability of an adequate vascular access, dialysis machines with pediatric-specific software, the extracorporeal priming blood volume, heparin kinetics in children, and finally, the presence of childhood illnesses such as inborn errors of metabolism (Figure 1).

**Figure 1: Indications for and selection of RRT in the PICU**




PD: peritoneal dialysis, SCUF: slow continuous ultrafiltration, IHD: intermittent hemodialysis, CVVH: continuous veno-venous hemofiltration, CVVHD: continuous veno-venous hemodialysis, CVVHDF: continuous veno-venous hemodiafiltration.
1. Stable refers to hemodynamic condition.

The size of t*he patient* is a fundamental aspect to consider when choosing RRT modality. In newborns and children who weigh less than 10 kg, CRRT requires a lot of experience and expertise, supplies, and special conditions of an inter- and multidisciplinary group.[7,8] High-flow vascular access to accommodate needed blood pump flow rates in small children presents a challenge for the teams. Given the catheter size, there are frequent complications due to venous flow obstruction in the lower limbs, which is why larger bore vessels are often used, such as the jugular vein. For these reasons, as well as the availability of supplies and resources to ensure good vascular access, peritoneal dialysis (PD) is frequently used in critically ill children. Peritoneal dialysis is the treatment of choice in newborns weighing less than 2 kg and in patients with a high risk of AKI following surgical correction of congenital heart defects.[8-11] In general, it is safe and effective after cardiopulmonary bypass and there is growing evidence of its prophylactic use to prevent volume overload and electrolyte imbalance after surgery.[12]

The *priming volume and availability of specific equipment* for CRRT for children is another challenge in selecting treatment modality. With the use of extracorporeal therapies CRRT and intermittent hemodialysis (IHD), the volume of extracorporeal blood may be greater than 10-15% of the child's total blood volume. This could affect unstable patients or those with significant hemodynamic support. For these cases, packed red blood cells are often used to prime the circuit.[13,14] Blood priming a dialysis circuit increases the risk of reactions such as hypotension, hyperkalemia, hypocalcemia

and/or coagulopathy on circuit initiation. Some of these reactions may be related to bradykinin release when packed red blood cells come into contact with filter or circuit components, as well as the age of the red blood cells and amount of citrate used as a preservative.[14,15] Another risk of using circuit priming with red blood cells is related to the transmission of infectious diseases or immune system sensitization to antigens which can delay a kidney transplant in potential candidates due to reduction in available organs. Recently, filters and circuits with equipment specifically designed for patients under 10 kg have been incorporated to decrease these risks.[16] They generally use a low-circuit priming volume (less than 30 mL), miniaturized roller pumps, and accurate ultrafiltration control via calibrated scales with a precision of 1 gram per hour.

*Vascular access* for dialysis is another great challenge in the smallest children requiring CRRT, as has been mentioned. Usually, 6.5 or 7.0 French double-lumen catheters are recommended for those under 6 kg.[17] These sizes are not always available at all centers. They may be made of polyurethane (generally lasting less than three weeks), or silicone (usually tunneled to last longer than three weeks). The latter composition decreases the risk of infection and is very useful when patients are discharged from the hospital and need to continue dialytic therapy. Besides the material from which they are made, the catheter length must be taken into account. If we consider *Poiseuille's law* (the resistance to flow through a tube is inversely proportional to the radius to the fourth power), a catheter as wide and short as possible will achieve better flow and fewer complications for the dialysis goals.[18] Despite these considerations, the factors associated with the greatest risk of catheter obstruction or dysfunction in critically ill children tend to be the presence of comorbidities, the need for mechanical ventilation or vasopressors, and not reaching adequate targets in system anticoagulation.[19] A recent single-center pediatric experience found that vascular access with a caliber larger than 8 Fr (HR 0.37 95% CI: 0.19-0.72); p = 0.004) and a regional citrate anticoagulation strategy (HR 0.14 95% CI:0.03-0.60); p = 0.008) were associated with a lower risk of catheter and circuit coagulation and dysfunction.[20]

The *type of anticoagulation* available at each center is another factor to consider when selecting the therapy modality of choice. In centers without adequate monitoring of anticoagulants or immediately available drugs to revert their effect, peritoneal dialysis (PD) is often used. This is especially common in lower- and middle-income countries. Regional anticoagulation with citrate in CRRT has proven to be effective and safe in children of all ages, reducing the risk (RR=0.204 95% CI 0.144-0.265) of circuit and filter coagulation.[21] These findings have also been seen in countries with limited resources.[22] However, this type of anticoagulation is not always available, and some centers prefer to use systemic anticoagulation with unfractionated heparin due to its easy accessibility and low cost.[23] At the same time, one of the major limitations of heparin is that it does not just produce circuit and filter anticoagulation, but systemic anticoagulation in the patient as well. This could cause undesirable effects in critically ill children. A recent systematic review found that thrombocytopenia was more frequently associated with the use of heparin and the need for red blood cell transfusions in critically ill children undergoing CRRT.[21] Heparin-related worsening of thrombocytopenia in critically ill children can be an undesirable complication, especially in children with sepsis. These patients tend to have endothelial activation, glycocalyx degradation, a systemic inflammatory response, and multiple organ dysfunction which favors hematological complications in children with AKI who require CRRT.[24,25]

# Renal Replacement Therapy Modalities Commonly Used in the PICU

## Continuous Renal Replacement Therapy (CRRT)

Continuous renal replacement therapy is increasingly being used in the PICU (Table 1). This has occurred due to technological advances and the greater availability of supplies and resources for all ages. The modification of the extracellular fluid (ECF) and removal of solutes occurs gradually and continuously during CRRT and, therefore, unstable children (who often do not tolerate abrupt volume or solute concentration changes) tend to benefit from this type of intervention (Figure 2). The Prospective Pediatric Continuous Renal Replacement Therapy (ppCRRT) Registry is one of the most robust studies published to date on CRRT. It included children from 13 centers in the United States, from newborns up to 25-year-olds, with weights ranging from 1.3 kg to 160 kg.[26,27] More than half of the patients were on diuretics and 70% received vasopressor support. Based on these data, it is reasonable to consider that CRRT is commonly used in children with fluid overload (FO) and diseases with multiple organ involvement. In fact, these patients had a lower survival (51%) when they had associated fluid overload and fluid and electrolyte imbalances.[27] A recently published meta-analysis and systematic review found a significant association between FO and mortality in critically ill children (Figure 3).[28] There was a wide variability in the methods of fluid balance assessment in the studies, in the way fluids were quantified, and in the appropriate timing for FO assessment after PICU admission. The investigators found four possible definitions of FO associated with worse outcomes: (1) early FO, with a cumulative FO percentage exceeding 5% in the first 24 hours; (2) a peak FO percentage exceeding 10% during PICU admission; (3) a cumulative FO percentage exceeding 10% at CRRT initiation; and (4) a cumulative FO percentage exceeding 20% at CRRT initiation. A recently published expert consensus suggests the use of the term “percent cumulative fluid balance” to describe patients with a significant percentage of FO and separate the pathological state from specific calculations.[29]

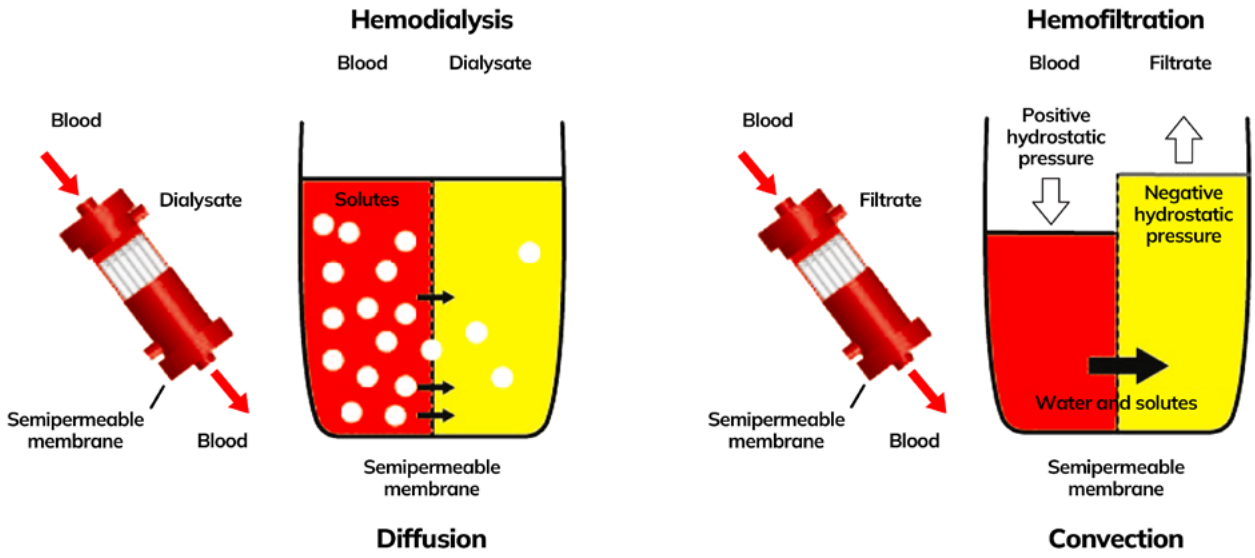
To adequately understand the processes related to renal replacement therapies, a few related concepts must be understood. Continuous renal replacement therapy is defined as extracorporeal clearing of substances using semipermeable membranes which substitute for the kidney function, applied over 24 hours or more. Intermittent therapies are those used for less time.[30] The clearing of substances is based on the fundamental physical principles of **ultrafiltration, convection, diffusion or adsorption** (Figure 2). Ult*rafiltration* is solvent (the liquid part of plasma) transport through a semipermeable membrane by a pressure gradient between the blood compartment and the dialysate/ultrafiltrate compartment. It is affected by the filter’s physical properties and the pressure gradient. It is a technique which can be used on its own, as in slow continuous ultrafiltration (SCUF), or as part of hemofiltration (CVVHF) or hemodiafiltration (CVVHDF).[30,31] These different modalities, their clearance mechanisms, and potential advantages and disadvantages are discussed in greater detail in another chapter of this compendium.

**Table 1: Comparison of various RRT modalities in critically ill children**

| Characteristic | IHD | CRRT | PIRRT | Peritoneal dialysis |
|---|---|---|---|---|
| Machine | Standard IHD machine | Standard machine CRRT | May be performed with a standard machine | Manual or cycling machine |
| Mode of clearance | Primarily diffusion | Diffusion, convection, or both | Diffusion, convection, or both | Diffusion and convection |
| Qb (mL/min) | 5-10 mL/kg/min | 3-5 mL/kg/min | 3-5 mL/kg/min | N/A |
| Qd | 500-800 | 25-30 mL/kg/h | 100-300 mL/min | N/A |
| Standard duration | 3-4 h | Continuous | 6-12 h | Anywhere from every hour to continuous, depending on the patient's condition |
| Frequency of procedure | 3 days/week | Continuous | 3-7 days/week | As above |
| Timing of procedure | Usually daytime | Continuous | Day or night | As above |
| Anticoagulation | Heparin/saline | Heparin/citrate/ saline | Heparin/saline | May be added to the PD without the risk of systemic anticoagulation |
| Vascular access | Areteriovenous fistula/high-flow central line | High-flow central line | High-flow central line | N/A |
| Intensity of nursing | Low | High | Low to moderate | Low to moderate |
| Patients' location | PICU, ward, step-down unit | PICU | PICU or step-down unit | PICU or hospitalization |
| Cost | + | +++ | ++ | + |

Qb: pump flow, Qd: dialysate or replacement flow, IHD: intermittent hemodialysis, PIRRT: prolonged intermittent renal replacement therapy or SLED, PD: peritoneal dialysis, PICU: Pediatric Intensive Care Unit, N/A: not applicable. Modified reference 41.

Figure 2: Basic physical principles in RRT



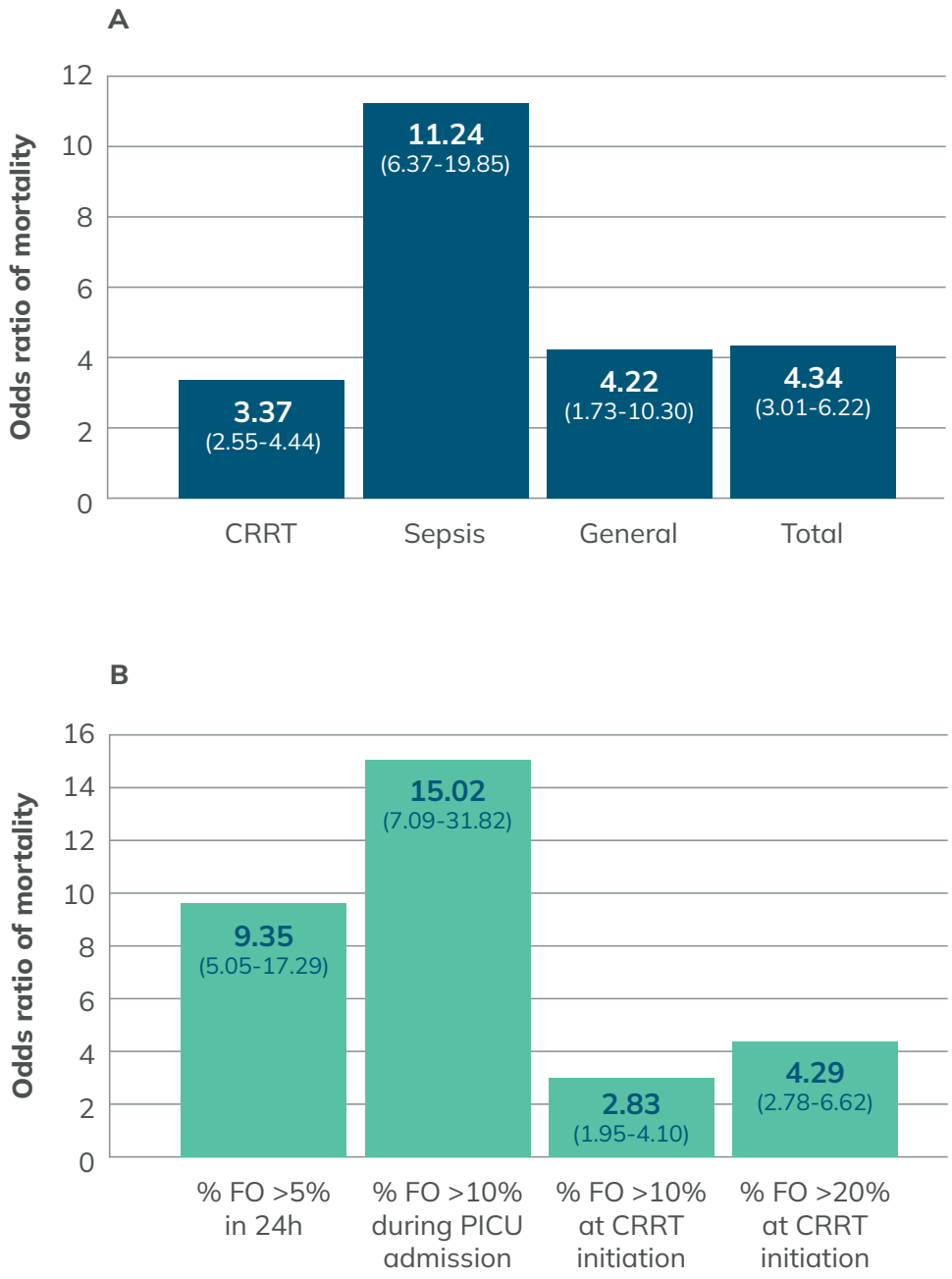

### Advantages

Critically ill children often require vasoactive support due to hemodynamic instability and have multiple organ failure. As previously mentioned, FO that does not respond to diuretics is also common in these cases for many reasons, but mainly due to the excessive use of crystalloid boluses for fluid resuscitation. A recent study found that critically ill children with sepsis have more endothelial activation, glycocalyx degradation and increased vascular permeability when unbalanced solutions are used for fluid resuscitation, which is associated with metabolic acidosis and AKI.[24] The major advantage of CRRT is the gradual removal of fluids and solutes which allows a slow and progressive recovery. This is why CRRT is considered the modality of choice in patients with hemodynamic instability or the need for high vasopressor support. Compared with PD, CRRT provides more efficient clearance and more precise fluid balance control. A more predictable solute removal and fluid management allows critically ill children to receive the needed enteral or parenteral nutritional support, and to receive blood products more safely and with fewer associated complications.[32,33]

### Disadvantages

While there have been significant technological advances over the last 10 years in the availability of CRRT machines that are safer and more user-friendly, they are still not available for use at all centers. An inter- and multi-disciplinary team is needed for successful therapy. Joint intensive care management between nephrologists, intensivists, surgeons, and interventionist radiologists is essential for achieving the goals. Perhaps the biggest challenge for the teams is to maintain a permeable system and avoid filter and circuit coagulation. Another CRRT disadvantage, especially in countries with limited resources, is the availability of supplies, adequate anticoagulation monitoring, and the high cost of therapy.[34] In this regard, another limiting factor for CRRT use is the availability of adequate vascular access. Often, this is not easily achieved or there are contraindications due to coagulopathy, prior vessel thrombosis, or simply unavailability of an appropriate catheter for the patient's size.[34]

**Figure 3: Fluid overload and mortality in the PICU**




A. Odds ratio and mortality in patients with CRRT, sepsis, critical general illness and total (all critically ill patients including the above). B. Odds ratio and mortality according to percentage of FO and PICU stay or start of CRRT. CRRT: continuous renal replacement therapy, FO: fluid overload, PICU: pediatric intensive care unit. (Modified from reference 28).

## Hemodialysis

Intermittent hemodialysis (IHD) modalities are also used in the PICU for AKI management, though less often than CRRT. Their frequency of use may range from 10%-36%, but it depends on each center's experience and availability of resources.[20,22,27] It is preferred under certain conditions which require rapid and efficient removal of solutes or fluids. It is often used in patients with intoxications, tumor lysis syndrome, hyperkalemia, and profound acidemia, or in children with life-threatening inborn errors of metabolism. In patients with hyperammonemia, specifically, rapid and efficient reduction of the ammonia levels with dialysis has been associated with better neurological outcomes.[36,37] In children with cardiogenic pulmonary edema and hemodynamic stability, IHD is considered to be an alternative for removing excess fluids.

### Advantages

The components of a hemodialysis prescription are similar to those used in patients with CRRT. They include a filter (which should be high efficiency for therapies outside of the PICU or lasting less than four hours), a circuit, a pump with adequate blood flow (Qb), dialysate solutions, and anticoagulation. If the extracorporeal circuit exceeds 10% of the blood volume, it should be primed with packed red blood cells or 20% albumin. A hollow-fiber design within the dialyzer is most commonly used today and contains thousands of hollow fibers in a parallel structure, similar to the human capillary network. Small solute clearance is dependent on the clearance characteristics of the dialyzer, as determined by its surface area.[38] Small solute clearance, typically measured by urea clearance, is dependent on the clearance characteristics of the dialyzer which, in turn, are determined by the surface area of the dialyzer and the Qb. To optimize diffusion, dialysate flow should be countercurrent to the blood flow and, to maximize the bidirectional transport of small solutes between the blood and dialysis fluid, the Qd should be set at a rate at least 1.5–2 times the Qb. The main advantage for some centers is that there is more experience in children on chronic therapy — and sometimes the teams — feel more confident using IHD. If the patients are hemodynamically stable and not on mechanical ventilation, they may be transferred to the dialysis unit and continue with a chronic treatment plan once they are discharged from the PICU. Perhaps this is why it has been associated with lower mortality (9.8% vs 32%) when compared with CRRT.[35]

### Disadvantages

The *sine qua non* condition for using HID is hemodynamic stability. This important factor represents the greatest limitation on its use in the PICU. Critically ill children often require fluid resuscitation and vasopressor support and are very hemodynamically labile. In addition, there is a need for a high-flow vascular access to ensure an adequate route for therapy. In children under 10 kg, vascular access and hemodynamic instability often make PD or CRRT necessary. Another potential disadvantage is muscle cramping which may be related to hypovolemia, hypotension or electrolyte changes during IHD. Treatment may include increasing the dialysate sodium concentration or administering hypertonic saline solution in the event of hyponatremia. In addition, dialysis disequilibrium syndrome (DDS) has been reported in children, which may present with symptoms similar to those of hypovolemia (i.e., nausea, vomiting, blurred vision, seizures, altered consciousness, or coma).[39]

This may occur more often in patients with very high levels of blood urea nitrogen, sodium, glucose, pre-existent metabolic disease, and a high rate of ultrafiltration with more than 30% reduction in the level of urea in less than 24 hours. The cause of DDS is not entirely clear and may be related to the brisk lowering of serum osmolality that occurs during HID, with the subsequent development of acute cerebral edema. During the initial phase of HD, the rapid lowering of blood urea creates an osmotic gradient since there is a lag in the influx of urea from brain cells to the intravascular space across the blood–brain barrier. The subsequent fall in intravascular osmolality leads to a compensatory rapid efflux of water from the intravascular compartment into the brain, resulting in cerebral edema. These compensatory fluid shifting dynamics have been well studied and observed in patients undergoing rapid hypernatremia correction, requiring very close observation and management of the patients as they receive treatment. The differential diagnosis includes but is not limited to the following: subdural hematoma, malignant hypertension, posterior reversible encephalopathy syndrome (PRES), acute cerebrovascular events, hard water syndrome, and electrolyte disturbances such as hyponatremia. It can be avoided by slowing the rate of reduction of nitrogenous compounds and the blood pump flow and considering the use of mannitol in patients with very high BUN rates associated with risk factors.[39]

## Peritoneal Dialysis (PD)

Traditionally, the modality of choice in the PICU was PD. Its safety, effectiveness, and availability made this the most common therapy in critically ill children with AKI. However, with the availability of new technologies, more intuitive CRRT machines and vascular accesses for smaller children, its use has decreased. In a recent multicenter study, PD accounted for 18% of all the renal replacement therapies in 7,106 critically ill children with AKI.[35] It was associated with lower mortality (12.8%) compared with CRRT, and was considered to be the strategy of choice in premature patients with AKI, or as prophylaxis in risk groups undergoing congenital heart defect correction. A systematic review and meta-analysis found that early initiation of PD after cardiac surgery was associated with a reduction in postoperative mortality (OR, 0.43: 95% CI, 0.23-0.80), as well as a shortened duration of mechanical ventilation and intensive care length of stay.[40]

### Advantages

Peritoneal dialysis is the least complex and safest technique, is universally available and, as with HID, can be performed outside of the PICU. The big advantage is that it can be three to five times less expensive than HID or CRRT, making it one of the preferred RRT options, especially in low-income countries.[41-44] There is a continuous removal of solutes and fluids which allows large volumes of ultrafiltrate (UF) to be extracted, making it useful in patients with hemodynamic instability as well. However, fluid extraction is not easily predictable and depends on various factors which tend to be affected in critically ill children, for example, adequate perfusion of the spleen bed. The fluid used as a dialysate often contains dextrose, which may be an additional caloric supplement, especially in small children who, due to fluid restrictions, may have hypoglycemia. In addition, PD does not require a high flow vascular access, which from a technical and resource availability standpoint makes it easier to carry out.[7-10]

**Disadvantages**

The main disadvantage of PD in the PICU is its gradual solute clearance and unpredictable ultrafiltration volume, potentially leading to an excessively slow fluid removal which is unacceptable for life-threatening hyperkalemia or pulmonary edema. In patients with sepsis and FO who require high vasopressor support, splenic perfusion may be compromised and further limit adequate solute or fluid clearance. In addition, these patients may be hyperglycemic, and this would be aggravated by the use of solutions with higher dextrose concentrations (2.5% or 4.25%). Peritoneal dialysis requires an intact abdominal cavity and is contraindicated in patients who have had recent abdominal surgery, abdominal cellulitis, inguinal hernia, diaphragmatic hernia, or peritonitis. A theoretical limitation which has not been proven in clinical studies is the increased intra-abdominal pressure which limits diaphragmatic excursion and makes protective mechanical ventilation more difficult.[41] In addition, manual PD increases the workload and overburdens the nursing staff who must carry out exchanges as often as every 60 minutes, depending on the patient's clinical condition.

## Conclusion

Acute kidney injury occurs in one of every four children in intensive care. Often, RRT is necessary to reach metabolic equilibrium and control the FO. The type of therapy for each patient depends on various factors which are important determinants of the observed outcomes. In particular, the participation of an inter- and multi-disciplinary group, in specialized centers, allows the various RRT alternatives to be carried out safely and effectively, with adequate support offered to the families and critically ill children with AKI.

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# 6

# Renal Recovery and Chronic Kidney Disease Following Acute Kidney Injury

**Scott M. Sutherland, MD**

## Introduction

Over the past several decades, our epidemiologic understanding of acute kidney injury (AKI) has grown substantially. The development and application of standardized, consensus diagnostic criteria has reduced the heterogeneity of studies, highlighting the consequences of AKI events.[1] The short-term ramifications of AKI have been well established; children who experience AKI while hospitalized experience lower survival, longer lengths of stay, and higher costs.[2,3] Additionally, once discharged, AKI survivors are more likely to need ambulatory medical care and rehospitalization and have higher overall health care utilization.[2-6]

AKI survivors experience problematic mid- and long-term kidney-specific outcomes as well. While some AKI events are transient, many patients with AKI fail to recover their baseline renal function and data suggests that AKI survivors are more likely to develop hypertension, proteinuria, chronic kidney disease (CKD), and end-stage renal disease (ESRD).[7-11] While these findings are well established in the adult literature, over the past several years, these risks have become more commonly described in children as well.[12-14] In particular, the data support a dose-dependent effect with greater risk seen in those who have more severe AKI, including episodes requiring renal replacement therapy.[8,15,16] The goal of this manuscript is to summarize what is known about renal recovery and CKD in children who experience AKI.

## Renal Recovery

The temporal concept of AKI is relatively new and has been best described by the Acute Disease Quality Initiative (ADQI) group (Table 1).[17] This concept categorizes AKI events based upon temporal aspects of the disease. Transient episodes of AKI resolve within 48 hours, whereas patients with persistent AKI continue to meet either the creatinine or the urine output criteria for more than 48 hours. Recovery from AKI is defined as resolution of the creatinine and/or urine output abnormalities within seven days (Table 2); patients who fail to recover from AKI during the first 90 days after diagnosis are considered to have acute kidney disease (AKD). Patients with AKD at 90 days should be categorized as having CKD.

Although AKI was historically thought to be a self-limited disease, resolution of AKI is far from universal. Basu et al. examined 136 children with AKI who were treated with peritoneal dialysis (PD).[18] While 84% of these children recovered enough kidney function to become dialysis independent, 73% had an estimated glomerular filtration rate less than 90mL/min/1.73m$^2$. Similarly, Bai and colleagues evaluated AKI in a critically ill pediatric population.[19] Although they did not delineate between persistent AKI and AKD, they reported that non-recovery was seen in 49% of cases. When performing a sub-analysis of the AWARE dataset which included more than 1,200 children with AKI, Ruth and colleagues found a nearly identical non-recovery rate of approximately 50%.[20] Hessey et al. found a dose-dependent effect of AKI on recovery in a cohort of more than 2,000 children; those with Stage 3 AKI had the highest risk of non-recovery at hospital discharge (adjusted OR 3.51, 95$^{th}$ CI 1.33-9.19).[16]

This phenomenon has also been described in specific AKI populations. For example, LoBasso et al. examined AKI in more than 3,600 children who underwent cardiopulmonary bypass.[21] Of those who developed AKI, recovery prior to discharge was seen in 87% of patients; 7% experienced persistent AKI and another 6% experienced AKD. Non-recovery can be seen even in non-critically ill children. Guan and colleagues examined AKI in pediatric patients hospitalized with nephrotic syndrome.[22] In

this cohort, 88.2% of cases experienced full recovery within three months, suggesting that 11.8% of these patients experienced AKD. Similarly, Al Khalifah et al. examined AKI in children with diabetic ketoacidosis and reported that non-recovery prior to discharge was seen in 17% of those who experienced AKI.[23]

**Table 1: Temporal aspects of AKI events[17]**

| | |
|---|---|
| **Transient AI** | Resolution of AKI (normalization of creatinine and/or urine output criteria) within 48 hours of identification |
| **Persistent AKI** | Continuation of AKI (ongoing elevation in creatinine or decrement in urine output) for more than 48 hours |
| **Non-Recovery** | Presence of AKI (based on creatinine and/or urine output criteria) 7 days after initial identification |
| **Acute Kidney Disease** | Persistence of AKI (ongoing elevation in creatinine or decrement in urine output) for >7 but <90 days |
| **Chronic Kidney Disease** | AKD that persists for >90 days |

**Table 2: Chronic renal sequelae**

| | |
|---|---|
| **Renal Recovery** | Resolution of AKI defining abnormalities (creatinine and/or urine output) within 7 days of initial identification |
| **Proteinuria** | Protein/creatinine ratio on first morning urine >0.2mg/mg, OR albumin/creatinine ratio on first morning urine >30mg/g |
| **Elevated Blood Pressure** | Children <13: systolic/diastolic BP ≥90th and <95$^{th}$ centile<br>Children ≥13: systolic BP 120-129 mmHg and diastolic BP <80mmHg |
| **Hypertension** | Children <13: systolic/diastolic BP ≥95$^{th}$ centile<br>Children ≥13: BP ≥130/80 |
| **CKD** | eGFR <60mL/min/1.73m$^2$ for at least three months, OR<br>eGFR <90mL/min/1.73m$^2$ with evidence of kidney damage or dysfunction |

Non-recovery is relevant as it carries clinical implications. Hollander and colleagues examined AKI in children receiving cardiac transplantation.[24] While children who experienced AKI and fully recovered were not at increased risk for CKD, the authors found that non-recovery was associated with the subsequent development of CKD. Similarly, LoBasso and colleagues found that mortality was higher in those with persistent AKI and AKD than in those who experienced transient AKI after cardiopulmonary bypass. Finally, Ruth et al. found that AKI which developed early in the ICU stay and persisted was associated with major adverse kidney events 28 days after admission. In summary, not all children recover from AKI, non-recovery is more common in those with more severe AKI, and a lack of functional renal recovery is likely to be associated with long-term ramifications.

## Proteinuria

Proteinuria is common in children with kidney disease and can be an indicator of renal damage (*Table 2*). In children with kidney abnormalities, a diagnosis of CKD can be made based upon the presence of proteinuria alone and it may precede an overt decline in GFR.[25,26] Thus, it is not surprising that it may be a common sequelae of AKI and portend the development of reduced excretory function.[27-29] Indeed, a large systematic review of eight studies found that the pooled incidence of proteinuria in AKI survivors was 13.2%.[29] Proteinuria may be more and less common in specific cohorts. For example, Askenazi and colleagues found that amongst a heterogeneous cohort of children with AKI the prevalence of proteinuria was 31% several years after the event.[30] However, in a group of children who developed AKI while in the ICU, Mammen et al. found that only 10% of AKI survivors developed proteinuria over the next 1-3 years.[31]

While many studies have identified high rates of proteinuria, the vast majority do not include a non-AKI comparator group.[32] Fortunately, some of the more contemporary studies are including such groups. For example, Menon and colleague examined 100 children who developed AKI following exposure to nephrotoxic medications.[33] Six months later, an astounding 68.5% of these AKI survivors had proteinuria; when compared with matched controls who did not develop AKI, proteinuria was significantly more common in those with AKI. However, not all such studies have found an association between AKI and proteinuria. Two prospective studies in children undergoing cardiac surgery failed to find an association between AKI and the subsequent development of proteinuria; however, both did demonstrate that the incidence of proteinuria in this population is quite high.[34,35] It is important to note that the pediatric cardiac surgery population may be a challenging cohort in which to study the relationship between AKI and chronic renal sequelae. The studies performed to date suggest that the incidence of kidney disease is generally high in those who have undergone cardiac surgery; it may be that the non-AKI related risk for CKD in this population is high enough to mask the effect of AKI. Additionally, the cardiac surgery AKI phenotype is unique, and the critical care community is coming to realize that not all AKI phenotypes carry the same outcome risks. The fact that children who experience AKI following cardiac surgery have elevated biomarkers of kidney injury compared to those who do not develop AKI may suggest that it is the former phenomenon rather than the latter.[36,37] Regardless, proteinuria remains an understudied renal outcome in patients who experience AKI and should be investigated as its presence has been associated with the development of CKD both in general nephrology cohorts as well as following episodes of AKI.[38]

## Hypertension

Many studies have demonstrated that the subsequent development of hypertension is common in children who experience AKI (Table 2).[14,29] A systematic review by Greenberg and colleagues found a pooled incidence of hypertension of 6.6%.[29] More specifically, in the study by Menon et al., just over one third of children who developed AKI after exposure to nephrotoxins were found to have hypertension six months later; this was significantly higher than matched controls who did not experience AKI (37.7% vs. 19.3%, p=0.01).[33] Similar findings were seen in a study by Hoffmeister and colleagues which examined hypertension in pediatric stem cell transplant recipients.[39] In this cohort, hypertension was quite common (15% overall prevalence) and those who experienced AKI were at increased risk (HR=2.5, 95$^{th}$ CI 1.7-3.7). Hessey and colleagues evaluated more than 1,900 children who experienced AKI while receiving critical care.[40] Children who experienced AKI were over two

times more likely to develop hypertension five years after discharge (adjusted HR 2.19, 95th CI 1.47-3.26). Interestingly, Hessey and colleagues conducted a similar study that diagnosed hypertension based upon ambulatory blood pressure monitoring (ABPM); using this technique, they found that while 13% of children who survived an episode of AKI while hospitalized in the PICU developed hypertension, the risk of hypertension was not associated with AKI.[41] As with the data pertaining to proteinuria, the association between hypertension and AKI is less strong in children who develop AKI following cardiac surgery. In the ASSESS-AKI study, AKI was associated with HTN one year after surgery but not at subsequent time points.[35] In the TRIBE-AKI study, while hypertension was common (17% or 10 times the general pediatric prevalence), it was not associated with prior episodes of AKI.[34] However, it is quite possible that this is related to sample size and some of the aforementioned aspects of cardiac surgery associated AKI. Indeed, when Robinson and colleague evaluated 1,688 children with AKI severe enough to require dialysis, these children did indeed have an increased risk of hypertension when matched to children who did not have AKI (adjusted HR 3.4, 95th CI 2.6-4.3). In summary, hypertension is common in children who survive episodes of AKI. While the findings are not universal, there does seem to be an increased risk of hypertension with more severe events as well as certain AKI phenotypes and patient populations.

## Chronic Kidney Disease

With regard to the renal sequelae of AKI, CKD is probably the most relevant and the one for which it is easiest to draw causal ties (Table 2). Data from animal models suggest that a number of factors may contribute to the development of CKD following AKI including inflammation, endothelial injury, maladaptive repair, and fibrosis.[14,42-46] Studies examining the relationship between AKI and the subsequent development of CKD in children have been challenging to interpret due to the application of heterogeneous definitions of both AKI and CKD, small samples sizes, and the lack of comparator groups without AKI.[29] Thus, while many studies demonstrate that the incidence of CKD is high in children who experience AKI, not all of them are able to identify an increased risk specific to AKI. However, more contemporary studies using standard definitions applied to larger datasets do seem to support this risk. Overall, a systematic review suggested that the incidence of CKD following AKI (defined as an eGFR <90mL/min/1.73m$^2$) was 28%.[29] Studies using a more traditional definition of CKD (eGFR <60mL/min/1.73m$^2$) identify a lower prevalence.[24,38] For example, in a cohort of 119 children who experienced AKI in the PICU, Jan and colleagues found that one year after the episode, 9% of children experienced at least Stage 3 CKD (eGFR <60mL/min/1.73m$^2$).[38] This is an impressive finding given that the authors specifically excluded children who had experienced AKI previously or had pre-existing CKD. Benisty and colleagues found a dose-dependent effect of AKI on the presence of albuminuria, pre-hypertension, and/or a reduced eGFR (eGFR <90mL/min/1.73m$^2$) in a cohort of 277 critically ill children.[9] Those with AKI and severe AKI (KDIGO stage 2/3) had a 2.2- and 6.6-fold increased risk for this composite outcome six years after the AKI event. Robinson and colleagues evaluated 1,688 dialysis-requiring AKI survivors.[15] In this cohort, de-novo CKD developed in 13.1% of AKI survivors and 2.6% of children developed renal failure (required dialysis or received a kidney transplant). The risk for both de novo CKD (adjusted HR 8.7, 95th CI 6.7-11.3) and kidney failure (adjusted HR 17.9, 95th CI 8.6-37.1) were higher in those who experienced AKI. Similarly, Hessey and colleagues studied 2,235 children who developed AKI while in the PICU and found that those with Stage 2/3 AKI had an increased risk for CKD (OR 2.5, 95th CI 1.1-5.7). Thus, while earlier data was mixed, more contemporary data in larger cohorts supports the association between AKI and the subsequent development of CKD.

## Conclusion

The association between AKI and chronic renal sequelae is highly relevant yet underrecognized. Although clinical practice guidelines suggest standard follow-up for patients who experience severe AKI, in practice, this does not occur with regularity. For example, in a cohort of neonatal patients with AKI, Roy and colleagues found that only 4% of neonates who experienced AKI had nephrology follow-up.[47] Patients with more severe episodes of AKI and those who require dialysis are more likely to receive follow-up, however, longitudinal care following AKI is not prioritized appropriately.[16] This is, in part, due to a lack of robust data supporting the association between AKI and chronic renal dysfunction. Fortunately, the critical care nephrology community has begun to highlight this relationship and newer data supports a connection. The best data available in children with AKI demonstrate that renal recovery does not occur in all patients. Those with more severe AKI and those who require dialysis are likely to experience persistent AKI and AKD. Non-recovery is an important provisional metric as it can be identified during the index hospitalization and is associated with greater risk for chronic renal sequelae. Additionally, it is likely that at least a subset of children with AKI are at increased risk for proteinuria, hypertension, and CKD. Future studies may better describe this relationship, however, at present it seems that these risks are greatest in those with severe disease including those who require renal replacement therapy.

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# Author Bios

## Ayse Akcan-Arikan, MD

**Extracorporeal Membrane Oxygenation and Continuous Renal Replacement Therapy**

Dr. Akcan Arikan is a dual-trained pediatric intensivist and nephrologist and an Associate Professor of Pediatrics with tenure at Baylor College of Medicine. She is the Associate Chief (Research) of the Division of Critical Care Medicine. Dr Arikan is a clinician-scientist whose research focus is on the recognition and management of acute kidney injury in the critically ill, pharmacokinetics in extracorporeal therapies, management of multiple organ failure, as well as sepsis resuscitation and outcomes. She is supported by the National Institutes of Health (NIH) for her work in new noninvasive methods for real-time monitoring of organ dysfunction and pharmacokinetics in critically ill children. She is an Executive Committee member of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) supported Collaborative Pediatric Critical Care Research Network (CPCCRN) and serves as a core site principal investigator. She is an executive committee member for the Prospective Pediatric Acute Kidney Injury Research Group (ppAKI-RG) and Worldwide Exploration of Renal Replacement Therapy Outcomes (We-ROCK) research collaboratives as well as the site principal investigator of multiple pediatric renal support device studies and urinary biomarkers. Dr Arikan serves as the Medical Director of the Critical Care Nephrology and Inpatient Dialysis and the Medical Director of the Extracorporeal Liver Support programs at Texas Children's Hospital. The critical care nephrology program houses the inaugural postdoctoral advanced training in pediatric critical care nephrology in North America as well as a unique quality assurance and improvement program in acute renal extracorporeal therapies based on active surveillance of patient safety, both under Dr Arikan's leadership.

## Jaime Fernández-Sarmiento, MD

**Acute Kidney Injury in Children: Selection of CRRT vs Other Modalities**

Dr. Jaime Fernández-Sarmiento is a Pediatric Intensivist with a PhD in Health Sciences, specializing in microcirculation and endothelium. He is an Associate Professor at the Faculty of Medicine, University of La Sabana, and Director of the Pediatric ICU at Fundación Cardio Infantil. Dr. Fernández-Sarmiento also serves as Vice President of the Latin American Society of Pediatric Intensive Care (SLACIP) in Bogotá, Colombia. His research activities have focused on the study of children with sepsis and its complications, including AKI and TSRC. Particularly, he focuses on the damage of the microcirculation and the endothelium in sepsis in children and the therapeutic interventions that can improve endothelial activity. He is co-leader of the first Latin American Consensus on Pediatric Sepsis and a member of SepsisColab Latin America.

## Stuart L. Goldstein, MD

**Timing of Pediatric Renal Replacement Therapy for Acute Kidney Injury**

Stuart L Goldstein, MD, is the Clark D West Endowed Chair, Professor of Pediatrics and Director, Center for Acute Care Nephrology at Cincinnati Children's Hospital Medical Center. He received his medical degree from Columbia University, completed his pediatric residency at Baylor College of Medicine in Houston, Texas, and completed both clinical and research fellowships in pediatric nephrology at the Children's Hospital in Boston, Massachusetts. Dr. Goldstein is Founder and Principal Investigator for the Prospective Pediatric AKI Research Group, which conducted the largest multinational prospective AKI study in children, AWARE, results of which have been published in the New England Journal of Medicine. He has evaluated novel urinary AKI biomarkers in the pediatric critical care setting. He was one of two pediatric work group members for the KDIGO International AKI Guideline Work Group. He has led a national, multi-center effort to reduce nephrotoxic AKI in children.

In addition, Dr. Goldstein has written more than 300 journal articles, served as an editor for two pediatric nephrology textbooks, and contributed book chapters to numerous texts ,including Critical Care Nephrology, Evidence-Based Nephrology, Handbook of Dialysis Therapy, Management of Acute Kidney Problems, Pediatric Critical Care, Pediatric Nephrology, and Pediatric Nephrology in the ICU.

## Shina Menon, MD

**Continuous Renal Supportive Therapies Prescription in Neonates and Children**

Dr Shina Menon is an Associate Professor of Pediatrics, University of Washington, and faculty, Division of Nephrology, at Seattle Children's Hospital. She is the Medical Director of Acute Renal Therapies, and the Associate Medical Director of Apheresis Services at Seattle Children's Hospital. She completed Medical school and pediatric residency at Maulana Azad Medical College, New Delhi, India, followed by work as a clinical research fellow in Pediatric Nephrology at AIIMS, India. Subsequently, she completed Pediatric residency and Pediatric Nephrology fellowship at Children's Hospital of Michigan in Detroit, followed by a fourth-year Acute Care Nephrology fellowship at Cincinnati Children's Hospital.

Her research is focused on Acute Kidney Injury, long term outcomes after AKI and extracorporeal therapies including CRRT and TPE.

## Melissa Muff-Luett, MD

**Pediatric and Neonatal Continuous Renal Supportive Therapies, Demographics and Outcomes**

Dr. Melissa Muff-Luett has dedicated her time and efforts to growing and advancing the pediatric nephrology division and pediatric dialysis services at Children's Hospital & Medical Center-Omaha and the University of Nebraska Medical Center, with the goal of providing the highest standard of dialysis care for the children of Nebraska and Western Iowa. As the Medical Director of Pediatric Dialysis, she spearheaded the development of a dedicated pediatric dialysis program at Children's Hospital, including the addition of home dialysis therapies, Carpediem™, and plasmapheresis services. Dr. Muff-Luett's primary clinical interest is in the care of infants on dialysis. Her desire to improve the outcome of this vulnerable population and overcome the challenges associated with dialyzing the smallest pediatric patients has driven her to pursue research in neonatal dialysis. She is the PI of a study through the Pediatric Nephrology Research Consortium entitled "Contemporary Infant and Neonatal Dialysis study" (COINED). This is a multi-center retrospective study to examine neonatal dialysis practice patterns including modalities, patient demographics, dialysis indications, and complications. Additionally, she is an active participant in multi-center dialysis collaboratives including SCOPE, WE-ROCK, and ICONIC, with the desire to advance dialysis care for children requiring dialysis.

## Konggrapun Srisuwan, MD

**Timing of Pediatric Renal Replacement Therapy for Acute Kidney Injury**

Dr. Konggrapun Srisuwan completed his Certificate of Clinical Fellowship in Pediatric Nephrology at the Hospital for Sick Children, University of Toronto, Canada. He is currently Assistant Director of the Department of Pediatrics, and Head of the Pediatric Nephrology Division at Phramogkutklao Hospital and College of Medicine in Bangkok, Thailand, which is a center of excellence for AKI and CKD care in children, and successfully completed 100 pediatric kidney transplants in August 2023. Dr. Srisuwan has contributed more than 80 chapters to Thai nephrology articles and international textbooks, and was a principle investigator of APD Kids Project (a multi-center study of automated PD in Thai children).

## Scott M. Sutherland, MD

**Renal Recovery and Chronic Kidney Disease Following Acute Kidney Injury**

Dr. Scott Sutherland is a practicing pediatric nephrologist whose clinical and research interests focus on acute kidney injury, intensive care nephrology, and continuous renal replacement therapy. His research activities aim to analyze and improve our approach to the identification of AKI events and more effectively describe AKI epidemiology in children. Additionally, he focuses on the long-term sequale of AKI, including chronic kidney disease (CKD), hypertension, and proteinuria.

## Sameer Thadani, MD

**Extracorporeal Membrane Oxygenation and Continuous Renal Replacement Therapy**

Dr. Sameer Thadani graduated from Eastern Virginia Medical School where he obtained his Doctor of Medicine degree after graduating from the University of California Davis with a Bachelor of Science in Genetics. Dr. Thadani completed his pediatric residency training at Cincinnati Children's Hospital Medical Center where he first developed his interest in the intersection of critical care and nephrology. He then went to Texas Children's Hospital/Baylor College of Medicine to complete a fellowship in Pediatric Critical Care Medicine where he was also a chief fellow, followed by a second fellowship in Pediatric Nephrology. Dr. Thadani hopes that with his clinical training he can help bridge the complex yet harmonious aspects of critical care and nephrology to care for critically ill children.

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