# Continuous Renal Replacement Therapy for Non-Renal Indications: Experience in Children

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## Abstract

**Background:** The role of continuous renal replacement therapy in patients with acute renal failure is well recognized. CRRT has also become an important modality of treatment in various acute situations without renal failure.

**Objectives:** To describe our experience with CRRT in acutely ill infants and children without renal failure.

**Methods:** We analyzed all infants and children who underwent CRRT during the years 1998–2000 in the pediatric intensive care unit and we focus our report on those who were treated for non-renal indications.

**Results:** Fourteen children underwent 16 sessions of CRRT. The indications for CRRT were non-renal in 7 patients (age range 8 days to 16 years, median = 6.5). Three children were comatose from maple syrup urine disease, three were in intractable circulatory failure secondary to septic shock or systemic inflammatory response, and one had sepsis with persistent lactic acidosis and hypernatremia. Three children underwent continuous hemodiafiltration and four had continuous hemofiltration. The mean length of the procedure was 35 $\pm$ 24 hours. All patients responded to treatment within a short period (2–4 hours). No significant complications were observed. Two patients experienced mild hypothermia (34°C), one had transient hypotension and one had an occlusion of the cannula requiring replacement.

**Conclusion:** Our findings suggest that CRRT is a safe and simple procedure with a potential major therapeutic value for treating acute non-renal diseases in the intensive care setting.

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The currently available renal replacement therapy techniques include intermittent hemodialysis, peritoneal dialysis, and several forms of continuous renal replacement therapy methods. The major change in renal replacement therapy for acutely ill patients that took place over the last decade has been the move from IHD to CRRT modes of therapy. In children, CRRT was first reported 15 years ago with the principal indication being acute renal failure [1]. Over the last 10 years, new non-renal indications for CRRT, such as septic shock, systemic inflammatory response syndrome [2], metabolic diseases [3], tumor lysis syndrome [4] and others, were introduced.

The main concerns with administering CRRT to infants are the establishment of vascular access, hemodynamic instability, hypothermia and hemodilution, all of which may occur more often than in older patients during the procedure. In the last decade, smaller single-dual lumen catheters and smaller hemofilters have been introduced, allowing application of this method to treat infants and small children. We report our experience with CRRT in children without renal failure in the intensive care setting.

CRRT = continuous renal replacement therapy
IHD = intermittent hemodialysis

## Patients and Methods

We analyzed all children who underwent CRRT in the pediatric intensive care unit during the years 1998–2000. Only those in whom the indication for CRRT was not renal were included in the study cohort. Demographic data, diagnosis, mode and length of therapy, complications associated with the procedure, effectiveness of treatment, and outcome were recorded for each patient. Response to therapy was defined as a significant improvement in clinical status that occurred within the first 2–6 hours from the start of CRRT. Complications were defined as: a drop in blood pressure that required intervention, hypothermia < 35°C, bleeding, vessel thrombosis, and occlusion of the cannula.

### Hemodiafiltration technique

Continuous venovenous hemofiltration or hemodiafiltration was performed using a single-dual lumen cannula inserted in the internal jugular, subclavian or femoral vein using the Seldinger technique. Normal saline solution (NaCl 0.9%) or packed red cells (in young infants) was used to prime the extracorporeal blood circuit. A Hospal AN69HF membrane was used (Hospal industrie-69330 Meyzlu, France). Anticoagulation was achieved with a loading dose of heparin 50 IU/kg followed by a continuous infusion of 10–20 IU/kg/hour into the circuit. Heparinization was controlled by partial thromboplastin time measurements in the circuit and was maintained at a level two times that of baseline. The ultrafiltrate was totally replaced with Hemosol BO solution (Manufactured for Hospal by Ivex Pharmaceutics Ltd.) (zero balance CRRT). The dialysate solution was the same as that used for ultrafiltrate replacement.

All patients were mechanically ventilated and sedated with morphine and/or midazolam. Blood pressure was monitored with a radial or femoral arterial line. The levels of arterial blood gases, electrolytes, renal function, glucose, total protein, lactate and branched chain amino acids in children with maple syrup urine disease were monitored before, during and at the end of treatment.

## Results

Sixteen CRRT sessions were performed in 14 infants and children during the study period. Two sessions, one week apart, were performed in each of two cases. The indication for CRRT was non-renal in 7 cases (43%; age range 8 days to 16 years). Four patients had a CVVHF and three patients underwent CVVHDF [Table 1].

**Table 1.** Demographic characteristics and treatment data of the study cohort

| Patient | Age | Gender | Disease | Indication for CRRT | Mode | Duration (hr) | Complications | Outcome |
|---|---|---|---|---|---|---|---|---|
| 1 | 6.5 yr | F | SIRS | Intractable circulatory failure | CVVHF | 36 | Line occlusion | Survived |
| 2 | 10 yr | M | Septic shock | Intractable circulatory failure | CVVHF | 72 | – | Survived |
| 3 | 13 yr | M | Septic shock | Intractable circulatory failure | CVVHF | 54 | – | Survived |
| 4 | 16 days | M | MSUD | MSUD | CVVHDF | 4.5 | Hypothermia | Survived |
| 5 | 8 days | F | MSUD | MSUD | CVVHDF | 10.5 | Hypothermia | Survived |
| 6 | 12 days | F | MSUD | MSUD | CVVHF | 24 | – | Survived |
| 7 | 16 yr | F | Sepsis | Persistent acidosis with hypernatremia and diabetes insipidus | CVVHDF | 44 | – | Died |

CVVHF = continuous venovenous hemofiltration, CVVHDF = continuous venovenous hemodiafiltration, SIRS = systemic inflammatory response syndrome.

The seven patients with non-renal indications for CRRT consisted of two groups. Three were infants in coma with acute metabolic crisis due to MSUD and four were children with sepsis or SIRS. Three of them were put on CVVHF due to intractable circulatory failure and one because of persistent metabolic acidosis with hypernatremia.

All seven patients responded to treatment within 2–6 hours. The treatments were terminated within 35 ± 24 hours when the patients' clinical status significantly improved and a steady state was achieved.

### Patients with MSUD

CRRT was started when patients were in coma and blood leucine levels were extremely high (3,261 ± 656 μmol/ml). A dramatic neurologic improvement was observed after 2–4 hours of treatment that was associated with a reduction in leucine levels. The treatment was terminated within 4.5–24 hours when blood leucine levels reached 1,295 ± 151 μmol/ml (> 50% reduction) [Figure 1]. In two patients who underwent CVVHDF the procedure was terminated within 4.5–10 hours, while in the patient who had a CVVHF the procedure lasted 24 hours. All three infants were extubated 2–4 days after the procedure and were discharged from hospital 10–15 days later. On follow-up more than a year after the crisis their developmental examination was normal.

### Patients with septic shock and SIRS

Three patients with intractable hypotension and low perfusion state due to sepsis or SIRS unresponsive to fluid and inotropic support responded to CVVHF with improved perfusion, decreased fluid requirement, and reduction in inotropic support. During the 6 hours before treatment these patients required substantial fluid support, resulting in a positive balance of 79, 41 and 26 ml/kg. Following 6 hours of treatment (zero balance CVVHF) these patients improved hemodynamically and required significantly less fluid intake, resulting in a fluid balance of 36, 22 and –18 ml/kg respectively.

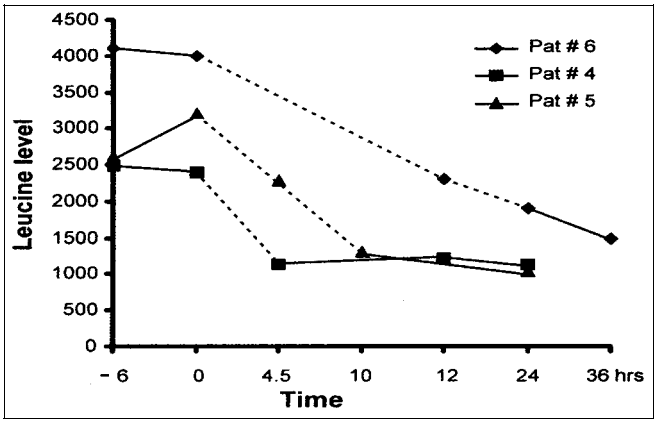


**Figure 1.** Leucine plasma levels in mmol/L 6 hours before treatment, at the beginning of treatment (time 0), end of treatment, and 12 hours later. The dotted line represents the CRRT treatment period, and the solid line the pre- and post-treatment period.

### Patient with persistent lactic acidosis and hypernatremia

One patient (no. 7) with diabetes insipidus, sepsis, persistent lactic acidosis (lactate 11.9 mmol/L, normal 0.5–2.2 mmol/L) with base deficit of -10 mmol/L, and hypernatremia (163 mmol/L) due to bicarbonate supplements, improved within 4 hours of treatment. Her lactate level dropped to 4.4 mmol/L (base deficit 5) and sodium dropped to 154 mmol/L. She continued to improve and her acidosis resolved within 8 hours. Treatment was terminated after 36 hours with normal sodium, lactate and pH.

Two patients developed mild hypothermia (34°C) that required external heating, one patient had transient hypotension that required fluid administration, and one patient required replacement of the cannula due to occlusion. No bleeding or vessel thrombosis was detected throughout the treatment. One patient required a second session of treatment due to renal failure that developed 7 days later. Six of the seven patients survived 30 days after treatment [Table 1].

## Discussion

The main advantages of CRRT are a better control of fluid and electrolytes removal during the procedure, more versatility in combined diffusive and convective solute transport, and simplicity in performing the procedure without specially designated staff.

CVVHF = continuous venovenous hemofiltration
CVVHDF = continuous venovenous hemodiafiltration
MSUD = maple syrup urine disease
SIRS = systemic inflammatory response syndrome

Today, the CVVHF or the combination with hemodialysis, CVVHDF, is the preferred modes of CRRT in critically ill pediatric patients [5]. The present report describes the contribution of CVVHF/CVVHDF to the treatment of acutely ill infants and children without renal failure. Three were newborns with acute metabolic crisis due to MSUD. The main objective of treatment in such crisis, in addition to hemodynamic and respiratory stabilization, is the prompt removal of leucine that may cause irreversible brain damage unless promptly removed. The treatment in all three cases was short, 4.5 and 10 hours for the CVVHDF and 24 hours in the case of CVVHF. Treatment was terminated when the leucine level decreased by more than 50% and there was an amelioration of encephalopathy. Only two cases of MSUD treated with CVVHDF have been previously reported [3,6]. In these cases the procedure lasted for 12–24 hours compared to 4.5–10 hours in our children. These patients were comparable to our patients for their pre- and post-procedure leucine levels. We believe that the higher blood flow (80–120 ml/hour) used in our patients compared to 20 ml/hour used in the previous studies improved the efficacy and enabled us to complete the procedure more rapidly. Jouvet et al. [3] compared three modes of treatment: CVVHDF, CVVHF and continuous venovenous hemodialysis in three infants with MSUD, where each patient was treated by a different modality. They found that CVVHDF was superior to the other two in terms of leucine clearance. This is similar to our observation that leucine levels decreased more rapidly with CVVHDF than CVVHF. This is due to the major contribution of both the convective and the diffusive effects used in CVVHDF compared with the diffusive process applied in CVVHD or the convective process in CVVHF [7]. It is interesting to note that Jouvet et al. [3] recommended CVVHD as the procedure of choice because of problems with regulation and maintenance of flow rates during CVVHDF due to the absence of a flow equalizer device, even though the latter method proved more efficient. We used an automatic self-controlled machine that overcame these problems and thus we were able to employ the two modes of treatment (hemofiltration and dialysis) simultaneously.

Three patients in the early phase of sepsis were put on CVVHF when conventional therapeutic strategies with inotropes and fluids failed to restore blood perfusion. A dramatic hemodynamic improvement was observed within 2–6 hours; perfusion improved dramatically, fluid requirement decreased significantly, and the inotropic support could be decreased. A similar observation was reported by Honore and colleagues [8] in a recently published study in adults. They demonstrated that early institution of CVVHF in patients with intractable cardiocirculatory failure due to sepsis resulted in rapid hemodynamic improvement and reduction in mortality by 30%. No such study has yet been performed in children.

Sepsis and SIRS are the most promoted and attractive non-renal indications for hemofiltration. The systemic inflammatory response seen in sepsis is due to an over-reaction of the immune system, with uncontrolled production and release of pro- and anti-inflammatory mediators to the circulation [9]. Since many of these mediators are medium size (<30,000 Da) molecules, the underlying hypothesis is that hemofiltration during sepsis is capable of removing them from the circulation. Both experimental and clinical trials have confirmed that mediators are removed or absorbed on the membrane during hemofiltration [10,11]. Clinical observations of hemofiltration in animal models and in adult patients with sepsis have shown a positive effect on hemodynamics [8,12], lung mechanics [13], cardiac contractility [14], and oxygenation [15]. Although, to date, the trend is in favor of a positive effect on survival, CRRT impact upon outcome has been demonstrated only in small series of adult patients but not in randomized control studies [8,16,17].

One patient with sepsis, persistent lactic acidosis and diabetes insipidus was treated with continuous infusion of bicarbonate until a severe hypernatremia appeared, whereupon CVVHFD was instituted. Regardless of the debate whether correcting metabolic acidosis during septic shock is beneficial, reports from adults showed that hemofiltration contributes to the elimination of lactate and correction of acidosis by extracorporeal removal of lactate [18]. In addition, as presented in our case, hemodiafiltration minimized fluid overload and hypernatremia, both of which were due to bicarbonate administration.

The main concerns with the administration of CRRT to children are associated with the establishment of vascular access. The smallest infants are particularly challenging due to the technical difficulties in cannulating small blood vessels. We successfully cannulated three newborns with a 6.5 F catheter that was inserted into the right internal jugular vein. We believe that this factor was crucial for the achievement of adequate flow rates, bearing in mind that clotting and low solute clearance are more likely to occur when blood flow is unsatisfactory.

No significant complications occurred throughout the treatment and none necessitated the cessation of treatment.

Besides the above clinical examples of non-renal indications for CRRT in acutely ill children, the past decade has witnessed increasing interest in this modality of treatment in other non-renal indications, mainly in adult patients. Short-term CVVHF performed at the end of cardiopulmonary bypass, especially in children, has been shown to reduce weight gain and blood loss, improve cardiac performance, and reduce pulmonary vascular resistance [19,20]. During crush injury or other causes of rhabdomyolysis, CVVHF enables a more efficient clearance of myoglobin than dialysis and has been reported to obviate renal failure [21,22]. CVVHF has been used with success in tumor lysis syndrome during induction of chemotherpy in very high risk patients with Burkitt's lymphoma or T cell acute lymphoblastic leukemia with high white blood cell count (>100,000 cells $mm^3$), high lactate dehydrogenase levels and low urine output. The prospective use of CVVHF in such cases may potentially decrease the morbidity and mortality associated with renal failure [4]. Furthermore, CVVHF allows rapid removal of certain substances that are not protein bound, and the correction of acid base balance and electrolytes abnormalities that are associated with certain intoxications, such as in children with lithium intoxication [23], vancomycin overdose [24], ethylene glycol antifreeze poisoning [25] and theophylline poisoning.

CVVHD = continuous venovenous dialysis.

In conclusion, the application of CRRT to children is simple, safe and may contribute to the management of various illnesses without renal failure. We believe that further trials, especially in children, are needed to define the appropriate indications for CRRT, whether it affects survival, and the preferred timing, length and modality of treatment for each clinical situation.

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