# Continuous Renal Replacement Therapy for Hyperammonemia Beyond Infancy

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Carbamoyl phosphate synthetase 1 (CPS1; MIM *608307; E.C. 6.3.4.16) is the first rate-limiting enzyme of the urea cycle, an essential metabolic pathway for ammonia detoxification. CPS1 deficiency (CPS1-D) is characterized by severe hyperammonemia during disease exacerbations. During a metabolic crisis, children with CPS1-D are admitted with vomiting, altered mental status, and high serum levels of ammonia. Rapid normalization of ammonia level ameliorates neurological outcome [1,2]. The first-line treatment for hyperammonemia in these patients is ammonia scavengers in combination with citrulline or arginine and high-calorie supplementation while controlling protein intake [1]. However, the effect of this treatment regimen in ammonia levels above 300 mcg\dl may not be fast enough to prevent neurologic injury [1,3]. The most effective proven method to reduce ammonia serum level is hemodialysis [1]. Unfortunately, hemodialysis for pediatric patients is not available in our hospital, whereas continuous renal replacement therapy (CRRT) is routinely used in our pediatric intensive care unit (PICU) by continuous veno-venous hemofiltration (CVVH), continuous veno-venous hemodialysis (CVVHD), and continuous veno-venous hemodiafiltration (CVVHDF). CRRT is an effective method to treat hyperammonemia in neonates born with problems with metabolism and in adults with hyperammonemia caused by various etiologies [3,4]. Treatment of children with this mode is somewhat different and there are few published reports. We present our experience treating a 7-year-old child with recurring episodes of hyperammonemia due to CPS1-D using CRRT.

## PATIENT DESCRIPTION

We retrospectively reviewed three admissions of a 7-year-old girl with CPS1-D to our PICU due to hyperammonemia. We evaluated the treatment, which included a combination of pharmacotherapy and CVVHDF, and the patient's outcome. Information was extracted from our electronic medical record (Metavision, iMDSoft, USA). The parents consented to publication of the case. The need for institutional review board approval was exempt by the local ethics committee.

A 7-year-old female weighing 16.6 kg, with known CPS1-D, was admitted to the hospital due to clinical deterioration. Within a period of 6 months, she was admitted three more times to our PICU. Her three admissions had the same pattern. She was admitted to the pediatric ward due to intercurrent viral infection (influenza B, influenza A, and a coronavirus [not COVID-19], respectively). Admission blood tests revealed high ammonia serum levels (normal value < 90 mcg/dl) but less than 200 mcg/dl. Initial management included cessation of protein intake accompanied by intravenous glucose and intravenous fat emulsion (Intralipid 20%) infusion. Intravenous administration of arginine and ammonia scavengers in the form of sodium phenylbutyrate and sodium benzoate were initiated. One to three days post-admission her ammonia levels began to rise to over 300 mcg/dl, and she became encephalopathic. She was transferred to the PICU due to failure of conservative treatment under maximal support and CRRT was initiated [Figure 1]. Prismaflex™ machine (Gambro Renal Product, Lakewood, CO, USA) in CVVHDF mode was used during all admissions to achieve maximal ammonia removal. MultiBic potassium free 5-liter bags solution (Fresenius Medical Care Deutschland GmbH, Germany), with addition of 4 mEq/L of potassium and 1 nmol/L of phosphate to both the replacement and dialysate bags was administered. The systemic anticoagulation goal of partial thromboplastin time between 60 and 90 seconds was achieved using a sodium heparin solution with an initial bolus of 50 units/kg followed by continuous infusion of 12.5–25 units/kg/h with dose titration as needed. Once hyperammonemia resolved, the patient continued intravenous treatment combined with total parenteral nutrition and intralipids. As the patient's ammonia level remained stable and her neurological status improved, she switched to oral medications and a low protein diet.

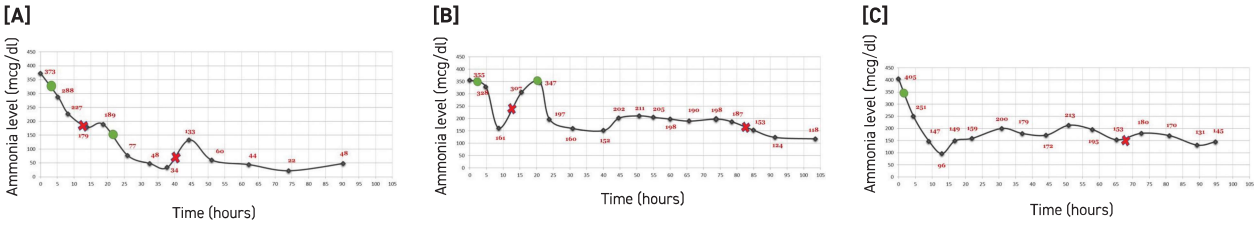
## COMMENT

We described our experience treating a child in hyperammonemia crisis using

**Figure 1.** Ammonia levels during PICU admissions

Figures 1A, 1B, and 1C describe the ammonia serum levels during the three hospital admissions, respectively. The X axis describes the PICU admission time in hours. The Y axis describes serum ammonia levels in mcg/dl. The green circle O represents CVVHDF starting time. Red X represents CVVHDF termination time. During admission A, two sets were used (two rounds of CVVHDF due to set clotting). On the first round, ammonia dropped from 373 mcg/dl to 179 mcg/dl within approximately 9 hours. On the second round, with a higher dialysate rate, ammonia level dropped from 189 mcg/dl to 77 mcg/dl within 5 hours. During admission B, we used two sets (two rounds of CVVHDF due to set clotting). During the first round, ammonia dropped from 355 mcg/dl to 161 mcg/dl within approximately 8.5 hours. On the second round, with a higher dialysate rate, ammonia level dropped from 347 mcg/dl to 197 mcg/dl within 3 hours and stayed stable (~200 mcg/dl) throughout the treatment. Admission C started with a higher dialysate rate. Ammonia level dropped from 405 mcg/dl to 147 mcg/dl within 4 hours and stayed below 200 mcg/dl throughout the treatment.

CVVHDF = continuous veno-venous hemodiafiltration, PICU = pediatric intensive care unit




CRRT. Historically, hemodialysis was the method of choice to reduce ammonia levels during metabolic crises [2-4]. Ammonia is highly amenable to diffusive clearance due to its low molecular weight (17 kilo Dalton), and low serum protein binding. The use of 500 ml/min of dialysate maximizes the diffusion gradient between the blood and the dialysate flow. However, this modality is not without considerable drawbacks. It requires stable hemodynamics and larger catheter caliber to facilitate higher blood flows. Between dialysis sessions there is a risk of electrolyte shift and rebound hyperammonemia that may worsen the patient's brain edema. CRRT in the mode of CVVHDF offers advantages such as better controls of electrolyte levels with less fluctuations, greater thermic control, and decreased risk of rebound effect [2,4,5]. Disadvantages of CRRT, as the name applies, are the need for continuous treatment up to a few days, which requires some degree of mild sedation, especially in younger patients, continuous monitoring of electrolyte balance, and titration of coagulation. Operating CRRT is more expensive than hemodialysis and requires more resources from PICU staff.

It is unclear whether brain toxicity due to hyperammonemia is due to absolute level of ammonia or hyperammonemia exposure time [2]. Ammonia levels over 300 mcg/dl are considered a metabolic emergency, especially if accompanied with a change in mental status, and require urgent intervention such as dialysis [1,3,5]. Picca et al. [2] found that in the neonatal population, the length of time until the start of purification method correlated with prognosis and that either CRRT or hemodialysis decreased ammonia levels efficiently with no difference in prognosis or outcome. During the three admissions, CRRT was started within 2–5 hours from peak ammonia levels [Figure 1]. This period included the decision to initiate CRRT, dialysis catheter insertion, and machine setup. Although this time frame can be shorter, it is still faster than managing patient transport.

The optimal dialysate flow on CRRT in cases of hyperammonemia is undetermined [5]. Our initial CRRT flows were 20/cc/kg/h (using our AKI protocol) of both replacement and dialysis, tripling the dialysate flow to 60 ml/kg/h (in addition to 20 cc/kg/h of replacement) with a total 80 ml/kg/h effluent dose increased ammonia clearance.

On CVVHDF, smaller molecules are cleared via dialysis and larger molecules are cleared via convection. Ammonia is a small molecule that easily transfers the semipermeable filter and equilibrates with the dialysate solution. Increasing the dialysate flow improves ammonia clearance [1,3].

During the second round of CVVHDF at admissions A and B and during the CVVHDF in admission C, on high dialysate flow, ammonia level decreased from 350–400 mcg/dl in less than 4 hours compared to 8–9 hours on previous, lower dialysate flows regimen. This observation supports published data in infants [4,5]. Increasing the dialysate flow rate does not influence the filtration fraction (FF) since dialysate fluid does not cross the filter membrane. We used rather high blood flow rates to maximize the dialysis effect [1]. Secondary to high blood flow rates, the FF values were low as 7–11%.

Another important advantage of avoiding transport to a hemodialysis center, which may sometimes be overlooked, is that the patient is treated by a metabolic disease specialist who has known her and

her family since birth. There is a great benefit to the patient and her family by keeping continuity of care and treatment by the same team. Based on the rapid normalization of serum ammonia in a relatively short time compared to hemodialysis, in conjunction with the favorable neurological outcome of our patient, it seems that in our setting, this mode of treatment is better.

Our study is limited by its retrospective design. However, because of the lack of published information regarding treatment of children in hyperammonemia crisis, we think that our experience treating this complicated patient may help other clinicians in similar situations.

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Capsule

## RNA surveillance turns oncogenic

Precise RNA regulation is a quality control mechanism that is important for normal development and to prevent disease. Aberrant RNAs require identification and destruction to avoid translation of defective proteins. **Insco** and co-authors reported that cyclin-dependent kinase 13 (CDK13), which activates an RNA surveillance mechanism to degrade abnormal RNAs, also has a tumor-suppressor function. When CDK13 was mutated in an animal melanoma model, accumulation and translation of aberrant RNAs resulted in more aggressive malignancy. Analysis of other cancer types revealed similar CDK13 mutations and showed that additional RNA surveillance genes were recurrently mutated in human tumors. These findings suggest that RNA surveillance may have a previously unrecognized tumor-suppressive role.

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Capsule

## Salt substitution and salt-supply restriction for lowering blood pressure in elder care facilities: a cluster-randomized trial

There is a paucity of high-quality evidence on the effectiveness and safety of salt reduction strategies, particularly for older people, who have the most to benefit but are at higher risk of adverse effects. **Yuan** et al. conducted a clinical trial in which 48 residential elder care facilities in China (1612 participants including 1230 men and 382 women, 55 years of age or older) were cluster-randomized using a 2 × 2 factorial design to provision of salt substitutes (62.5% NaCl and 25% KCl) versus usual salt and to a progressively restricted versus usual supply of salt or salt substitutes for 2 years. Salt substitutes, when compared with usual salt, lowered systolic blood pressure (-7.1 mmHg, 95% confidence interval [95%CI] -10.5 to -3.8), thus meeting the primary outcome of the trial. Restricted supply compared with usual supply of salt or salt substitutes had no effect on systolic blood pressure. Salt substitutes also lowered diastolic blood pressure (-1.9 mmHg, 95%CI -3.6 to -0.2) and resulted in fewer cardiovascular events (hazard ratio [HR] 0.60, 95%CI 0.38–0.96) but had no effect on total mortality (HR 0.84, 95%CI 0.63–1.13). From a safety standpoint, salt substitutes increased mean serum potassium and led to more frequent biochemical hyperkalemia but were not associated with adverse clinical outcomes. In contrast, salt restriction had no effect on any study outcome. The results of this trial indicate that use of salt substitutes, but not efforts to restrict salt supply, may achieve blood pressure lowering and deliver health benefits to residents of elder care facilities in China.

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