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# Hyperammonemia, the Last Indication of High-Volume Hemodiafiltration in Adult and Children: A Structured Review

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**Keywords**
Ammonia · High-volume hemofiltration · Continuous renal replacement therapy · Blood purification dose

**Abstract**
Ammonia is a neurotoxic molecule that causes cerebral edema and encephalopathy. Ammonia is either produced in excess or poorly purified during severe hepatic insufficiency, poisoning, infection, and inborn errors of metabolism. During continuous renal replacement therapy, ammonia clearance is determined by the dialysate flow rate and the dialyzer surface area. Extra-renal blood purification for ammonia clearance has been studied in neonates with urea cycle disorders. Prognostic factors affecting patient outcome are thought to be the duration of coma, the patient's clinical status prior to dialysis, and the ammonia removal rate. In this review, we discuss the various dialytic modalities used for ammonia clearance as well as the thresholds for initiating dialysis and the better strategy ensures rapid patient protection from cerebral edema and herniation induced by hyperammonemia.


## Introduction

Ammonia is a molecule with a short half-life that results from normal protein metabolism. It is neurotoxic and causes cerebral edema and irreversible neurological lesions at excess levels, leading to encephalopathy and death [1]. Hyperammonemia occurs in severe acute hepatic insufficiency, chronic liver disease (cirrhosis), poisonings, infection with bacteria capable of cleaving urea (through urease), and inborn errors of metabolism [2]. In adults, high ammonia concentrations are most often found in patients with acute hepatic failure, while in pediatrics it is mainly caused by inborn errors of metabolism. These high ammonia concentrations are associated with intracranial hypertension and hepatic encephalopathy. Bernal et al. [3] showed that an ammonia level >100 μmol/L predicted the occurrence of severe hepatic encephalopathy with 70% accuracy. They also observed that 55% of patients with ammonia levels >200 μmol/L had intracranial hypertension [3]. In hyperammonemia associated with urea cycle disorders, treatment with hemodialysis can reverse encephalopathy and prevent brain edema and death [4]. Under phys-

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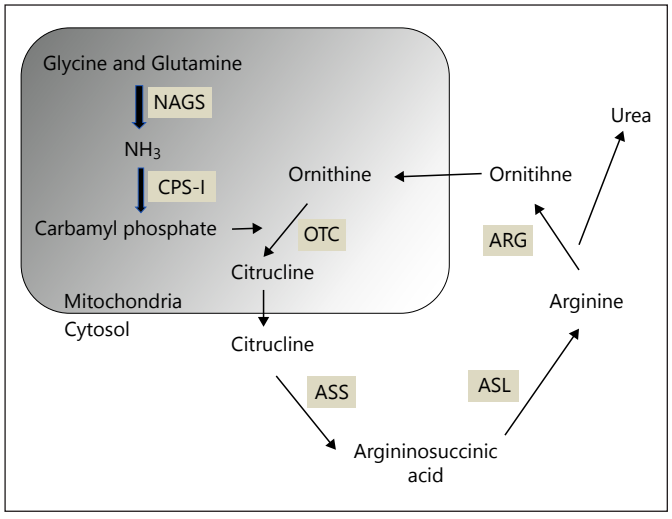


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**Fig. 1.** Simplified diagram of the urea cycle showing the metabolization of ammonia into urea. NAGS, N-acetylglutamate synthase; CPS-1, carbamoyl phosphate synthetase I; OTC, ornithine transcarbamylase; ASS, arginosuccinate synthetase; ASL, arginosuccinate lysase; ARG, arginase, mitochondrial ornithine transporter 1 (ORNT 1), and mitochondrial aspartate/glutamate carrier (CITRIN).

iologic conditions, ammonia is metabolized primarily by the liver to urea via the urea cycle (Fig. 1). The liver receives 20% of the cardiac output but extracts 90% of the body's ammonia [5]. We will discuss the principles of treatments as well as the pediatric and adult modalities of extracorporeal ammonia treatment.

## Principle of Extracorporeal Treatment

Cordoba et al. [4] showed in an experimental single-compartmental model that the extraction of ammonia is directly related to the machine blood flow rate (BFR). Above a certain BFR, ammonia clearance is modulated by the effluent flow rate. For effluent flow rates of 300 and 500 mL/min, the ammonia clearance reaches plateau values of 200 and 300 mL/min of BFR, respectively (Fig. 2a) [4]. By contrast, they did not observe a plateau for 800 mL/min of effluent flow rate within the range of BFR used (between 100 and 500 mL/min) [4]. Concerning the dialyzer surface area, the same authors showed that ammonia clearance was related to the BFR used. Between 100 and 200 mL/min, there was no influence of the dialyzer surface area; however, above 300 mL/min, there was an increase in ammonia clearance related to an increase of the dialyzer surface area (Fig. 2b) [4].

## Modality in the Pediatric Population

Modalities and thresholds of renal replacement therapy for hyperammonemia have been well-established in pediatric patients. Extra-renal blood purification has been studied in neonates with urea cycle disorders (Table 1). For reasons that include low patient weight, difficult vascular access, flow rates, and hemofilter size, peritoneal dialysis was considered to be the easiest and the most effective [6–9]. Wong et al. [10] compared ammonia clearance clearance of ammoniac ($C_{NH3}$) in a patient treated with peritoneal dialysis followed by continuous arteriovenous hemodialysis via 5 French umbilical arterial and venous catheters. In peritoneal dialysis, the $C_{NH3}$ was 0.47 mL/min (2.15 mL/min/$m^2$). In continuous arteriovenous hemodialysis, the $C_{NH3}$ was 7.45 mL/min at 300 mL/h dialysate and 10.55 mL/min at 600 mL/h dialysate. There was no further increase in the $C_{NH3}$ at 900 mL/h [10]. Rutledge et al. [7] reported a $C_{NH3}$ of 84 mL/min/$m^2$ with femoral arteriovenous hemofiltration. The BFR was 20 mL/min (3–5 mL/kg), and the effluent flow rate was 500 mL/h [7]. Following that publication, Ring et al. [11] reported 24-h continuous veno-venous hemofiltration (CVVH) performed with a 7 French double-lumen catheter placed in the right internal jugular vein in a 5-day old child with ornithine transcarbamylase deficiency. They obtained a $C_{NH3}$ of 19.4 mL/min/$m^2$. Several case series have shown that CVVH is possible in newborns. The size of the catheters ranges from 3 to 6.5 French, and the treatment is effective with a median time of 3.3–19.4 h required to decrease the ammonia level by 50%. Suspected prognostic factors include the duration of coma, the clinical state of the patient just before renal replacement therapy (high pediatric risk of mortality or multiorgan failure), as well as the ammonia removal rate (Fig. 2a) [12–18]. Continuous veno-venous hemodiafiltration (CVVHDF) should be started in neonates and children when the ammonia level exceeds 500 μmol/L or does not decrease despite 4 h of well-conducted medical treatment with a protein-restricted diet and ammonia chelators (4 h being the estimated time for placement of the dialysis catheter and preparation of the dialysis machine) [12].

Several studies have reported an association between survival and the rate at which serum ammonia decreases [13, 15, 19, 20]. Solute clearance is proportional to the effluent flow rate [21]. The higher the rate, the faster the solute is eliminated. The ideal dialytic modality and prescription for ammonia clearance are not well-described. Lai et al. [21] described successful ammonia extraction based on an effluent flow rate between 30 and 75 mL/kg

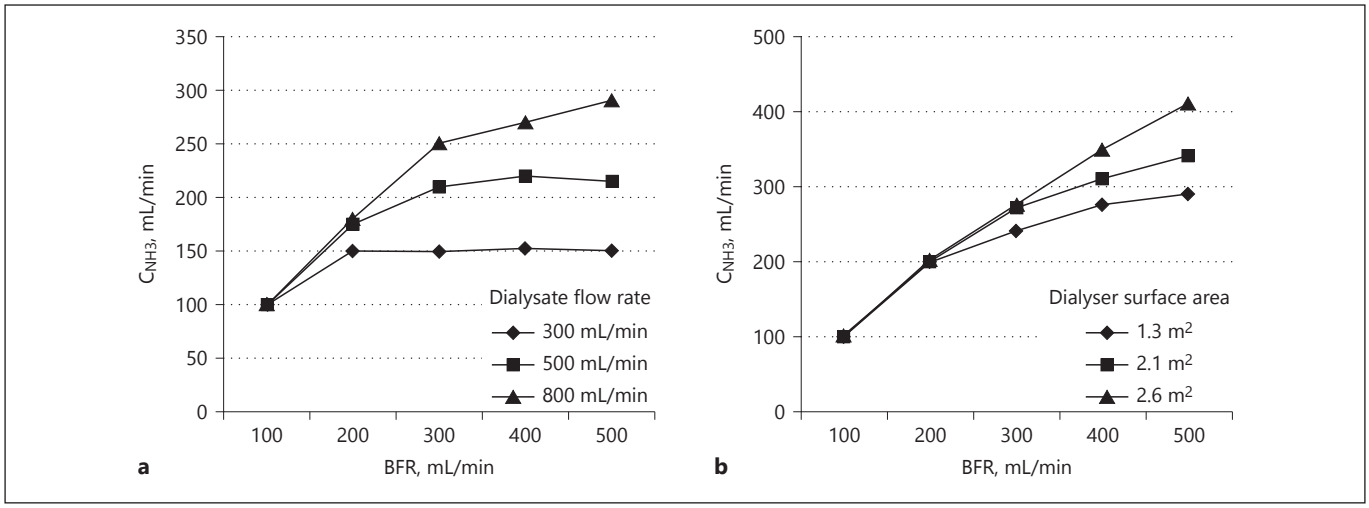


**Fig. 2. a** Clearance ammonia ($C_{NH3}$) depends on BFR and dialysate flow rate. **b** $C_{NH3}$ according to 3 levels of dialyser surface area. Adapted from [4].

**Table 1.** Comparison of published series on ammonia purification by CRRT in inborn errors of metabolism

| | Patients | Age at dialysis start | Weight, kg | Dialysis modality | Catheter size (french) | Median 50%, h | Clearance | Death | Prognostic factor |
|---|---|---|---|---|---|---|---|---|---|
| Schaefer et al [13], 1999 | 7 | 7j | ND | CVVHD | 5F | 7.1±4.1 | ND | 3 | Ammonia removal rate |
| Picca et al [14], 2001 | 10 | 5J | 2.9 | CAVHD (4)<br>CVVHD (4)<br>IHD (2) | 6.5F | CAVHD: 3.375<br>CVVHD: 4.29<br>IHD: 8.25 | CAVHD: 2.68<br>CVVHD: 9.07<br>IHD: 11.95 | 4 | Duration of coma before dialysis<br>ammonium level before dialysis |
| Rajpoot et al [15], 2004 | 4 | 3.5J | 2.9 | IHD | 7F | <4 | ND | 0 | Duration of coma before dialysis<br>ammonium level before dialysis<br>ammonia removal rate |
| Westrope et al [16], 2010 | 14 | 4J | 2.7 | CVVH | 5F | 7.4 | ND | 4 | PRISM<br>Use vasoactive drug Lactate<br>Pre-CVVH MOF |
| Arbeiter et al [17], 2010 | 17 | 4J | 2.760 | CVVHD | 6.5F | 4.5±2.4 | 18.9±7.7 | 3 | None |
| Picca et al [18], 2015 | 22 | 4.5 | 3.024 | CAVHD (5)<br>CVVHD (14)<br>IHD (3) | ND | 8.8±10.6 | ND | 9 | None |
| Cavagnaro Santa Maria et al [19], 2018 | 6 | 10 | 2.798 | CVVH: 2<br>CVVHDF: 2 | 3–4F | ND | ND | 2 | None |

CVVH, continuous veno-venous hemofiltration; CVVHDF, continuous veno-venous hemodiafiltration; PRISM, pediatric risk of mortality; CAVHD, continuous arteriovenous hemodiafiltration.

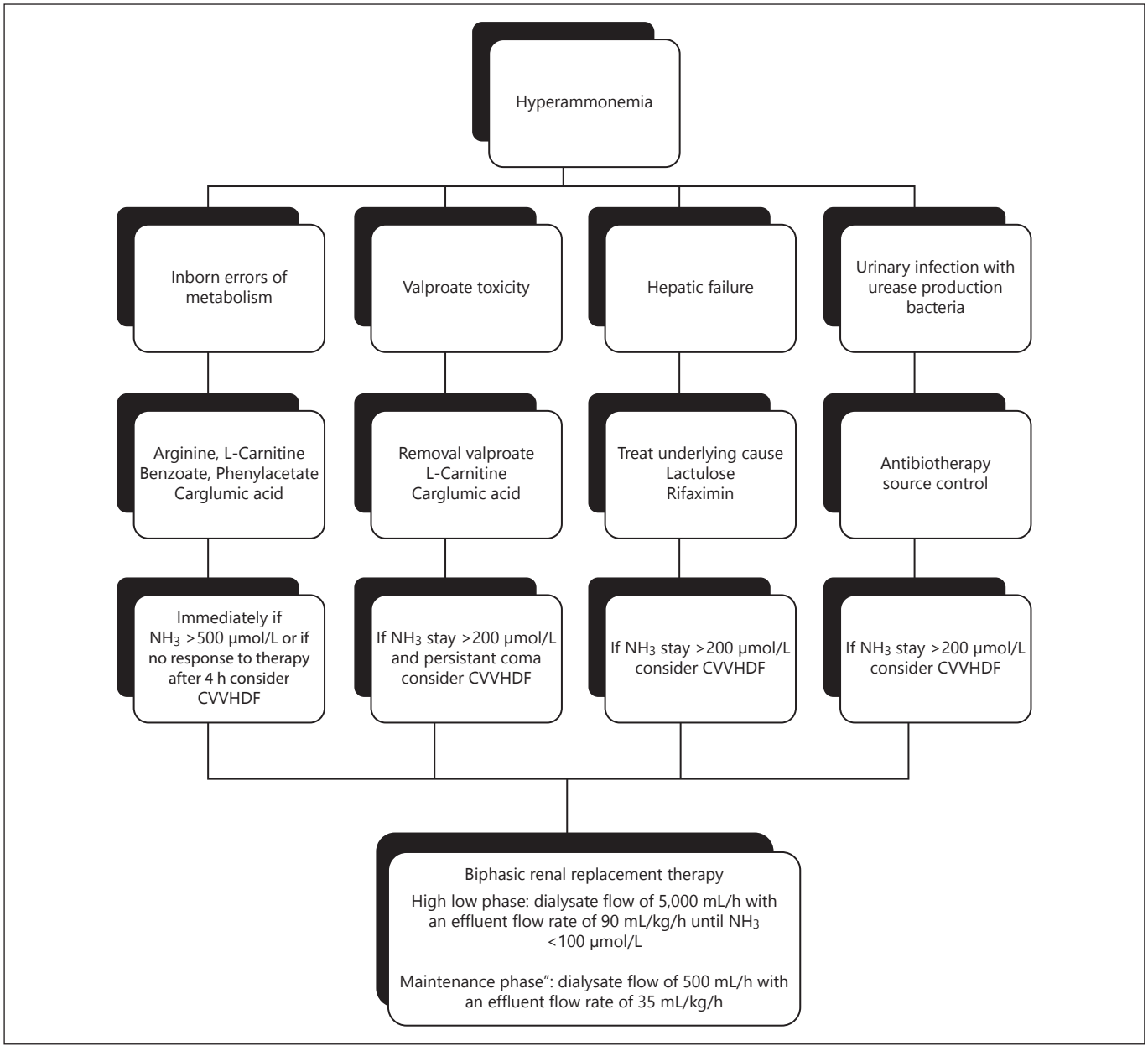


**Fig. 3.** Proposal for general management of hyperammonemia in adults and children. $NH_3$, ammonia; CVVHDF, continuous veno-venous hemodiafiltration.

in 2 patients. Chan et al. [22] described 1 patient on CVVHDF with a $C_{NH3}$ of 20 mL/min/m$^2$ with an effluent flow rate ranging from 100 to 150 mL/kg. Additionally, Spinale et al. [23] observed a fall of ammonia to <100 µmol/L after 3 h of CVVH with effluent flow rate at 8,000 mL/h/1.73 m$^2$. In a retrospective study of patients averaging 56 months of age, McBryde et al. [24] found improved ammonia extraction when patients were dialyzed by intermittent hemodialysis with a dialysate flow rate at 500 mL/min, compared to CVVHDF with a dialysate flow rate at 2,000 mL/h/1.73 m$^2$. Intermittent hemodialysis reduced the ammonia level to <200 µg/mL 15-times faster than CVVHDF [24]. However, half of the intermittent hemodialysis patients had to return to CVVH because of a rebound effect. This observation led another team to propose a successful biphasic strategy based on a continuous renal replacement therapy technique. They used a dialysate flow rate of 5,000 mL/h (40,000 mL/h/1.73 m$^2$) in

order to rapidly decrease the ammonia level and subsequently reduced the dialysate flow rate to 500 mL/h (approximately 4,000 mL/h/1.73 $m^2$) [25].

### Modality in the Adult Population

The same observations regarding dialytic modality and prescription have been made in adults, where hyperammonemia was more related to liver failure. Slack et al. [26] showed that ammonia clearance unmistakably correlated with the effluent flow rate (rho = 0.86 and $p < 0.0001$). Similarly, ammonia clearance doubled when the effluent flow rate went from 35 to 90 mL/kg/h. In a 2017 multicenter study of 340 patients diagnosed with acute liver failure, hyperammonemia was associated with high-grade HE and a worse 21-day transplantation-free survival. CRRT, prescribed for indications other than hyperammonemia, was associated with a reduction in the serum ammonia level and improvement in 21-day transplantation-free survival [27].

Currently, hyperammonemia is not a recognized continuous renal replacement therapy indication in adults. When the ammonia level exceeds 200 μmol/L, the risk of cerebral edema and herniation increases. The use of biphasic renal replacement therapy, based on a period of high flow followed by a period of classic CVVH, deserves further study in adults outside of the conventional indications for dialysis. Beside complications of cerebral edema, central pontine myelinolysis may occur as a complication of partial ornithine carbamoyl transferase deficiency [28]. This effect might be due to fact correction of hyperammoniemia [28].

### Conclusion

To our opinion, CVVHDF should be used in a biphasic manner, initially as a "high flow phase" with a dialysate flow of 5,000 mL/h with an effluent flow rate of 90 mL/kg/h, followed by a "maintenance phase" with dialysate flow of 500 mL/h and an effluent flow rate of 35 mL/kg/h (Fig. 3). This strategy will ensure that patients are rapidly protected from cerebral edema and herniation induced by hyperammonemia.


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### Ethics Statement

Not applicable.

### Disclosure Statement

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S.R., X.B.-P., and P.M.H.: designed the paper. All authors participated in drafting and reviewing. All authors read and approved the final version of the manuscript.

### Availability of Data and Materials

Not applicable.

### Consent for Publication

Not applicable.

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