Appendix/Supplementary Material

Adult and Pediatric Literature Pertaining to Hyperammonemia, 1994-Present

Citation	Mode of RRT	Study Purpose	Study Population	Research method	Results/Conclusions
Adult					
Cordoba et al 1996[1]	Intermittent HD	To analyze the determinants of am monia clearance with the use of a single-pass dialyzer and to estimate ammonia clearance at different blood flow rates, dialysate flow rates, and with different dialyzer surfaces		Case Series	The authors found that an ammonia clearance of 225 ml/min was obtained at a Qb of 350 ml/min. Ammonia could be extracted by the hemodialyzer more than 80% by setting the both parameters at maximal flow rates. Clearance of ammonia was dependent on blood flow, the dialysate flow rate, and dialyzer membrane surface area

Levesque et al 1999[2]	Intermittent HD	To present the case of 2 patients with urinary diversions who developed hyperammonemia and were treated with hemodialysis	2 patients with urinary diversions complicated by obstruction or infection who were treated with intermittent HD	Case series	Authors found mean in vivo clearance was 261 ml/min at a blood flow rate of 350 ml/min, dialysate flow rate of 500 ml/min, and a 1.9 m^2 surface area dialyzer. One patient did not regain consciousness despite reduced ammonia levels, which was thought to be secondary to a delay in resolution of cerebral edema or rebound phenomenon
Machado et al 2013[3]	CVVHDF	To describe the case of a patient with late onset OTC deficiency who presented with infected necrotic pancreatitis and hyperammonemia and was successfully treated with CVVHD	1 patient with late onset OTC deficiency who was treated with CVVHDF	Case report	The patient was treated with CVVHDF on day 6 of hospitalization with a decline in his ammonia level from 254 µmol/L to <50 µmol/L by day 46, with improvement in mental status
Anwar et al 2014[4]	Intermittent HD, overnight slow efficiency HD	To present the cases of 3 lung post-orthotopic lung transplant patients with hyperammonemia who were treated with a multidisciplinary approach of intermittent HD, overnight slow low-	3 post orthotopic lung transplant patients who were treated with a	Case report	2 of the 3 patients survived with the institution of the multidisciplinary approach. The authors suggested that early initiation of dialysis, high dialysis dose, increased frequency, and intermittent HD (over other modalities), increased survival in three patients

		efficiency HD, and early weaning of steroids	multidisciplinary approach that included HD		
Slack et al 2014[5]	CVVHF	To determine whether CVVHF could lead to decline in arterial ammonia levels in adults with liver failure and arterial ammonia levels >100 µmol/L	24 patients with liver failure (10 with acute liver failure, 10 with chronic liver disease, and 4 following liver resection), all of whom were treated with CVVHF	Prospective study at a single institution from 2009-2010	The authors found that clinically significant ammonia clearance could be achieved in adult patients with CVVHF. They noted that higher rates of ultrafiltration led to greater reduction in ammonia concentrations, and rates were closely correlated with total ammonia clearance
Pediatric					
Sadowski et al 1994[6]	Intermittent HD	To determine whether infants fewer than 5 kg could be successfully treated with intermittent HD	33 infants weighing fewer than 5 kg, all of whom received intermittent	Retrospective review of single institution between 1980 and	Infants weighing < 5 kg could be treated successfully with intermittent HD. Survivors did not differ from those who died with respect to birthweight, weight when HD was initiated, or the number of HD treatments administered

			HD for hyperammonemia, acute renal failure, or primary renal/renovascular disease	1991	
Falk et al 1994[7]	CVVH, CVVHD, PD	To determine whether CVVH could be used for the acute clearance of toxic metabolites like ammonia in IEM, and whether it was superior to PD	4 infants, 3 with maple syrup urine disease and one with CPS deficiency. 2 pts received PD prior to CVVH and CVVHD	Case series	CVVH was successfully employed following failure of PD in 2 patients. Higher filtration rates achieved metabolic control more quickly. The addition of HD to PD and CVVH in a patient whose ammonia production exceeded clearance, led to rapid lowering of ammonia levels
Summar et al 1996[8]	ECMO driven HD	To present the case of 2 infants with urea cycle disorders with low birth weights and hemodynamic instability who underwent ECMO-driven HD	2 neonates with suspected IEM who were treated with ECMO-driven HD	Case report	By using a high-flow ECMO circuit to support hemodialysis, the investigators were able to induce rapid removal of ammonia (average clearance, 170 ml/min for both patients) while maintaining hemodynamic stability with the additional benefit of increased oxygenation

Vats et al 1998[9]	Intermittent HD	To describe the case of an infant with hyperammonemia who was treated with HD using femoral veins	1 infant with carbamoyl phosphate synthetase-1 (CPS) deficiency	Case report	High blood flow levels led to reduction in ammonia levels but there was unanticipated recirculation in the IVC and between dialysis aspirating and return catheters. Authors highlighted importance of having a defined protocol for vascular access line placement
Wong et al 1998[10]	CAVHD, PD	To present the case of a neonate with a UCD and compare the clearance rate of ammonia for CAVHD versus PD	1 neonate with a UCD	Case report	A neonate with a UCD was initially treated with PD and exchange transfusion; CAVHD was then instituted with a rapid drop in ammonia levels and superior clearance. Authors concluded that HD is the best method for ammonia removal when medical treatment fails
Schaefer et al 1999[11]	PD, CVVHD	To compare CVVHD with PD, and the effects of dialysis modality on long term outcomes	12 patients with IEM, 5 of whom received PD, 7 who were treated with CVVHD	Retrospecti ve review of single institution from 1988 to 1997	CVVHD resulted in quicker reduction of ammonia levels by 50%, and total dialysis time was shorter. Those patients who had more rapid toxin removal survived with no/moderate developmental impairment whereas those with slower detoxification died in neonatal period or the developed severe mental retardation later. Initial blood ammonia concentrations were not predictive of outcome
Chen et al 2000[12]	CAVH, CAHD, CAVHD, PD, exchange transfusion	To compare the clearance of CAVH, CAVHD, CAVHDF, PD, and exchange transfusion in 3 neonates with OTC deficiency	3 neonates with OTC deficiency who were treated with a combination of CAVH, CAVHD, PD,	Case series	Authors reported the successful use of CAVH, CAVHD, and CAVHDF in acute management of hyperammonemia in OTC deficiency and found that CAVHD provided the highest clearance compared to other modalities

			and exchange transfusion		
Picca et al 2001[13]	CAVHD, CVVHD, and intermittent HD	To study prognostic indicators in hyperammonemic patients and to determine ammonia clearance, neurologic outcome, and coma duration with each modality	10 patients with hyperammonemic coma, 4 of whom were treated with CAVHD, 4 with CVVHD, and 2 with HD	Prospective study from a single institution	Neither modality of dialysis nor rapidity of dialysis influenced outcome. Prognosis was limited by duration of coma before the start of dialysis, not total coma duration. HD provided highest ammonium extraction but clearance was lower than with CVVHD since blood flow was hampered by severe hypotension. Authors preferentially recommended use of CVVHD
Hiroma et al 2002[14]	CVVHDF	To present the case of four neonates with hyperammonemia due to suspected IEM who were treated with CVVHDF	4 neonates with suspected IEM treated with CVVHDF	Case series	CVVHDF resulted in prompt removal of ammonia within 30 hours using a special circuit for neonates and a circuit warmer. Authors concluded that CVVHDF is safe and effective for hyperammonemia
Chan et al 2002[15]	CVVH	To present the case of a neonate with CPS deficiency who presented with hyperammonemic coma and respiratory failure, and was successfully	1 neonate with CPS deficiency who was treated with CVVH	Case report	The authors showed that rapid detoxification was successfully achieved with CVVH, with an ammonia clearance greater than 20 mL/min/m^2

		treated with CVVH			
Rajpoot et al 2004[16]	Intermittent HD	To assess the feasibility of HD in low-weight neonates, the rate of ammonia decrease, and complications	4 patients weighing <4 kg, (2 with transient hyperammonemia, 1 with OTC deficiency, 1 with MMA) who were treated with HD	Retrospective review of a single institution from 1999 to 2002	All 4 patients tolerated HD well, with hemodynamic instability in the first 2 hours that subsequently improved w/ normal saline, inotropes, and albumin. HD reduced ammonia levels by 71% within 3-4 hrs. Authors concluded HD was tolerated by this small subset of patients with low birthweight
Haller et al 2005[17]	CVVHDF	To present the case of a newborn with citrullinemia who clinically improved once CVVHD was initiated	1 neonate with citrullinemia treated with CVVHDF	Case report	CVVHDF at blood flow rates of 45-65 ml/min, dialysate flow rates of 1000 ml/hr resulted in a significant decrease in ammonia levels, with improved neurologic outcomes longterm at 22 months of age
McBryde et al 2006[18]	CVVHD	To determine whether RRT could correct hyperammonemia associated with IEM and to analyze risk factors for mortality when using RRT	18 patients with IEM , all of whom were treated with CVVHD	Retrospective review of a single institution from 1991-2000	11 of the 18 patients died before hospital discharge. Follow-up data showed that 5 patients remained alive at 2 years. Time to RRT >24 hrs was associated with increased risk of mortality
Lai et al	CVVH, CAVH,	To determine whether CVVH could be used in	8 children with IEM in	Case series at a single	Authors concluded that CVVH had good clearance of ammonia when applying high-volume hemofiltration (>35 ml/kg/h), and

2007[19]	CVVHD, intermittent HD, PD	place of other methods of dialysis to remove ammonia	whom different RRTs were applied (n =7 for CVVH, n =2 for CAVH, n= 1 for CVHD, n = 1 for HD, n =2 for PD)	institution	could therefore be considered as an alternative therapy if infant HD was not available
Bunchman et al 2007[20]	Intermittent HD followed by HF	To present the case of a newborn with a suspected IEM who was treated with sequential HD followed by HF and to determine whether dialysis would clear phenylacetate and sodium benzoate therapy	1 neonate with a suspected IEM and hyperammonemia who was treated with HD followed by HF	Case Report	The sequential use of HD and HF rapidly reduced ammonia concentrations and prevented rebound in ammonia levels after HD discontinuation. Though HD and HF significantly cleared phenylacetate and sodium benzoate, therapeutic levels could still be obtained
Pela et al 2008[21]	PD	To evaluate outcomes of patients treated with PD	7 neonates with IEM who all received PD	Retrospective analysis of single institution from 1994 to 2002	6 out of 7 patients survived acute neonatal hyperammonemia, but 2 died later on due to complications. Authors postulated that total coma duration influenced outcome and that early initiation of PD in patients could be considered if implemented in a timely fashion
Ishida et al	CVVHDF	To describe the case of a neonate with suspected	1 neonate with	Case	With the initiation of CVVHD, ammonia level decreased rapidly and the patient's hemodynamics improved. After discharge,

2009[22]		CPS-1 deficiency who was treated initially with CVVHDF and then underwent liver transplantation	suspected CPS-1 deficiency	Report	patient developed transient hyperammonemia several times and underwent liver transplantation, with normalization of ammonia level and normal neurologic development
Arbeiter et al 2010[23]	PD, CVVHD	To determine safety of CVVHD, whether reduction in ammonia depends on technical parameters, and how long it takes to achieve nontoxic levels of ammonia with PD vs. CVVHD	21 children with IEM, 17 of whom received CVVHD and 4 who received PD	Retrospective analysis of a single institution, from 1996 to 2008	CVVHD was safe, and nontoxic plasma levels were achieved more quickly with CVVHD compared with PD. Blood and dialysate flows correlated with ammonia clearance. There were higher rates of survival without mental retardation in CVVHD patients
Westrope et al 2010[24]	CVVH	To assess the efficacy of CVVH in the reversal of hyperammonemia in neonates and to determine which variables correlated with survival	14 neonates (7 with urea cycle defect, 7 with organic acidemias)	Retrospective review from single center between 1997 and 2007	Pretreatment level of serum ammonia, rapidity of ammonia clearance, and duration of CVVH therapy did not differ between survivors and non-survivors. Pre-CVVH physiologic condition and use of cardio-active medications were main determinants of outcome
Stojanovic et al 2010[25]	CVVHDF	To present a case of a neonate with transient hyperammonemia whose ammonia levels normalized with CVVHDF	1 neonate with transient hyperammonemia	Case report	Serum ammonia levels normalized 30 hours after initiation of CVVHDF; patient survived till discharge and at 4 months, neurologic development was normal when corrected for age

Fleming et al 2012[26]	CVVH, CVVHD, CAVHD	To determine whether CRRT can be used for indications other than AKI (including IEM) and to determine how the modality of CRRT and dose delivered affected survival	334 patients enrolled in the Prospective Pediatric Continuous Renal Replacement Therapy Registry. IEM subgroup consisted of 21 CRRT patients (11 underwent CVVHD, 3 whom underwent CVVH, and 8 of whom underwent CAVHD)	Retrospective data from multiple centers from 2001 to 2005	Authors determined that CRRT was a viable option for detoxification in pediatric patients with other disorders such as IEM and TLS. Acute detoxification could be accomplished with CRRT alone without the need for intermittent HD. The modality of CRRT did not affect survival outcomes

Vargha et al 2012[27]	CVVHD	To present a case of CVVHD performed along with therapeutic hypothermia in a newborn with IEM	1 neonate with suspected urea cycle disorder	Case report	The combination of pharmacologic treatment, hypothermia, and CVVHD reduced ammonia levels from 2320 µmol/L to 224 2320 µmol/L, with 8 month follow up showing improved neurologic outcomes
Pirojsakul et al 2013[28]	CVVH	To present a case of CVVH performed in a neonate with OTC deficiency	1 neonate with OTC deficiency who was treated with CVVH	Case report	Authors reported successfully performing CVVH using umbilical vein as a vascular access site for ammonia removal
Spinale et al 2013[29]	CRRT	To ascertain whether high dose CRRT can effectively decrease ammonia levels in infants with hyperammonemia, and to determine the optimal RRT prescription	2 infants with ornithine transcarbamylase deficiency who were treated with high dose RRT	Case report	Rapid ammonia clearance was achieved with high dose CRRT within 4 hours. Authors recommended dialysis planning when ammonia levels >400 µmol/L with flow rates of 30-50 ml/min, until ammonia levels are <100-200 µmol/L
Picca et al 2014[30]	PD, CVVHD, CAVHD, HD	To analyze the association between different modes of dialysis and determine	45 neonates with IEM who underwent	Retrospective analysis of 6 Italian centers	Decay rate of ammonia was greatest in patients on HD. There was an increase in odds ratio for death associated with ECT as compared to PD. Risk of neurologic sequelae was equivalent with both HD and PD. Initiating PD ~10 hrs after diagnosis was

		short term outcomes (survival, neurologic sequelae) among infants with IEM	PD or ECT for hyperammonemia	between 1990-2011	equivalent to initiating HD ~20 hrs after diagnosis of hyperammonemia

HD: hemodialysis; PD: peritoneal dialysis; ECT: ectracorporeal treatment; CRRT: continuous renal replacement therapy; CVVH: continuous veno-venous hemofiltration; CVVHD: continuous veno-venous hemodialysis; CAVHD: continuous arteriovenous hemodialysis; CVVHDF: continuous venovenous hemodiafiltration; IEM: inborn errors of metabolism; CPS: carbamoyl phosphate synthetase; OTC: *o*rnithine transcarbamylase: MMA: methylmalonic acid; TLS: tumor lysis syndrome

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