Pediatr Nephrol (2001) 16:862–867

ORIGINAL ARTICLE

Stefano Picca · Carlo Dionisi-Vici · Damiano Abeni
Anna Pastore · Cristiano Rizzo · Marcello Orzalesi
Gaetano Sabetta · Gianfranco Rizzoni
Andrea Bartuli

Extracorporeal dialysis in neonatal hyperammonemia: modalities and prognostic indicators

Received: 8 February 2001 / Revised: 9 July 2001 / Accepted: 10 July 2001

Abstract We investigated the prognostic indicators in ten hyperammonemic neonates: four treated by continuous arteriovenous hemodialysis (CAVHD), four with continuous venovenous hemodialysis (CVVHD), and two with hemodialysis (HD). Plasma ammonium levels decreased significantly within the first 24 h irrespective of dialysis modality (from 1419 to 114 µmol/l, median values; $P<0.0001$). CVVHD achieved the highest ammonium clearance. HD provided highest ammonium extraction but clearance was hampered by severe hemodynamic instability. Five patients had a good outcome (normal at follow-up of 9–59 months), five had poor outcome (four died and one has severe neurological damage). Total coma duration was shorter in patients who had a good outcome (47±11 vs 78±13 h; $P=0.02$). Remarkably, only coma duration before dialysis determined this difference (22.2±10.1 vs 48.8±11.2 h; $P=0.02$). In cases with good outcome, coma duration was <33 h, whereas the others exceeded this limit. The prognosis was not related to dialysis modality, rapidity in reducing ammonium levels or to the underlying metabolic defect. In conclusion, results showed CVVHD to be the optimal modality for extracorporeal ammonium detoxification. However, the most relevant indicator for prognosis was coma duration before the start of dialysis. Therefore, major efforts should be made to refer patients quickly to highly specialized centers.

Keywords Hyperammonemia · Urea cycle defects · Organic acidurias · Hemodialysis · Continuous arteriovenous hemodialysis · Continuous venovenous hemodialysis

S. Picca (✉) · G. Rizzoni
Division of Nephrology and Dialyses,
Bambino Gesù Children Research Hospital,
Piazza S. Onofrio 4, 00165 Rome, Italy
e-mail: picca@opbg.net
Tel.: 39-06-68592393, Fax: 39-06-68592602

C. Dionisi-Vici · G. Sabetta · A. Bartuli
Division of Metabolism,
Bambino Gesù Children Research Hospital, Rome, Italy

D. Abeni
Epidemiology Unit, Istituto Dermopatico dell'Immacolata,
Rome, Italy

A. Pastore · C. Rizzo
Division of Clinical Biochemistry,
Bambino Gesù Children Research Hospital, Rome, Italy

M. Orzalesi
Division of Neonatalogy,
Bambino Gesù Children Research Hospital, Rome, Italy

Introduction

Ammonium is a strong neurotoxic metabolite that accumulates in neonates with primary urea cycle disorders. In addition, excess glutamine is generated in the cytosol of astrocytes from ammonium and glutamate by the action of glutamine synthetase [1]. This leads to cell swelling and brain edema due to the osmotic action of glutamine [1]. In organic acidurias, intramitochondrial accumulation of acyl-CoA esters produces secondary inhibition of urea cycle enzymes, resulting in severe hyperammonemia [2]. In most of these cases, hyperammonemia develops in the neonatal period and clinical features include feeding refusal, vomiting, abnormal muscle tone, lethargy, seizures and coma leading to death within a few days. Recommended guidelines for the initial medical management include protein avoidance, adequate caloric support, supply of arginine and carnitine, and pharmacological priming of alternative pathways for nitrogen excretion [3, 4, 5]. Poor response to pharmacological therapy requires prompt exogenous removal of toxic compounds to prevent permanent brain damage or death. Exchange transfusion provides only transient, if any, ammonium reduction [6, 7, 8, 9]. Better results, often anecdotally reported, were obtained with different dialysis modalities including peritoneal dialysis [6, 7, 8, 9, 10, 11, 12, 13]. After the introduction of techniques and devices suitable for very small children [14, 15], continuous hemofiltration [16, 17, 18, 19], intermittent HD [6, 8, 20, 21, 22, 23], continuous hemodiafiltration [24] and

continuous HD [13] have been employed for ammonium detoxification in the newborn. HD, CAVHD and CVVHD have been claimed to provide maximal efficiency in ammonium removal, when compared with peritoneal dialysis [6, 13, 25].

In 1984, Msall et al. reported improved long-term neurological outcome in a large series of neonates with urea cycle disorders treated with pharmacological therapy alone when the duration of coma lasted less than 3 days, regardless of the ammonium levels [26]. In addition, the rapidity of detoxification obtained with dialysis has been found to significantly affect survival and prognosis of hyperammonemic neonates [13].

Our aim was to study the indicators of the outcome in ten neonates with hyperammonemic coma, four treated with CAVHD, four with CVVHD and two with HD, and to evaluate the efficacy of three different dialysis modalities.

Patients and methods

Patients

Ten of twenty neonates who were referred to our Neonatal Intensive Care Unit from peripheral hospitals for hyperammonemic coma, and who did not respond to pharmacological therapy alone, were treated by extracorporeal dialysis. Biochemical investigations on admission included measurement of plasma amino acids and urinary organic acids, orotate and amino acids. Plasma ammonium was measured enzymatically by a Cobas Fara II centrifugal analyzer (Roche Diagnostics System, Hoffmann La Roche Ltd., Switzerland). Simultaneously, the initial management included avoidance of nitrogen intake, adequate caloric intake (80–120 kcal/kg per day), and intravenous administration of arginine (250–500 mg/kg per day), carnitine (250–500 mg/kg per day), hydroxycobalamin (1 mg/day), and biotin (10 mg/day). Energy was supplied as parenteral glucose and, whenever possible, with nasogastric infusion of protein-free formulas. Insulin was added to maintain blood glucose levels between 100 and 200 mg/dl. Intravenous sodium benzoate (250–500 mg/kg per day) was given only after establishing a primary urea cycle defect. Patients 6 and 7 also received peroral phenylbutyrate (250 mg/kg per day).

In five patients, medical treatment was started elsewhere before admission to our hospital. In the other five patients treatment outside our hospital was limited to the time necessary to provide first care and vascular access. The median pre-dialysis pharmacological treatment time was 8.5 h (range 2–19). Except for patient 1, diagnosis was obtained within 2–12 h.

Duration of coma was evaluated by periodic neurological assessment and was defined as the number of hours spent in coma stage III (unconsciousness, decerebrate posture with reduced response to painful stimuli) or stage IV (flaccid tone with dilated pupils and no response to painful stimuli) [26]. Total coma duration was not available for patient 6, who died without coma resolution, or for patient 7, who required pharmacological maintenance of coma for a pulmonary hemorrhage. Mental Developmental Index (MDI) score of patients with good outcome was periodically evaluated at 12-month intervals using the Bayley scale of infant development (second edition) [27] (normal range 85–114).

All patients required mechanical ventilation before the start of dialysis, and intravenous therapy remained unchanged during dialysis. According to individual diseases, some of the pharmacological supply was interrupted after establishing the diagnosis. Protein intake (human milk) was reintroduced only after stabilization of plasma ammonium levels below 150 µmol/l.

The characteristics of the individual patients are detailed in Table 1.

Dialysis modalities

In CAVHD, vascular access was obtained through a femoral artery and vein, using 18G single lumen catheters (Abbocath-T; Abbott Ltd., Sligo, Ireland). In CVVHD, a femoral vein was cannulated with a 6.5F, 7.5 cm double lumen neonatal catheter (Hemoaccess; Hospal, Bologna, Italy). In HD, vascular access was the same as for CAVHD in patient 9 and as for CVVHD in patient 10.

In CAVHD, a 0.08 m^2 polysulfone hemofilter (Amicon Minifilter Plus; Grace Co. Amicon Division, Beverly, Mass., USA) with arterial and venous lines provided by the manufacturer was utilized (total priming volume including filter 15 ml). A dialysate flow of 0.5 l/h was achieved using two volumetric infusion pumps placed pre- and post-filter [28]. The pumps used were IVAC 591 and IVAC 560 (IVAC Corporation, San Diego, Calif., USA), and Lifecare Abbott (Abbott Laboratories, North Chicago, Ill., USA), all of which have a declared error from the manufacturer of 2–5% of total delivered volume. Effluent dialysate was collected every hour and compared with the post-filter pump display for corrections. Blood flow was measured by priming solution displacement time [29].

In CVVHD, the Amicon Minifilter Plus was used in patient 5 with a blood monitor utilizing a roller pump and equipped with neonatal bloodlines (BSM32IC; Hospal, Italy; total priming volume including filter 38 ml). In patients 6, 7 and 8, a 0.3 m^2 polysulfone hemofilter (PSHF 400; Minntech Corporation, Minneapolis, Minn., USA) equipped with pediatric blood lines (total priming volume including filter 89 ml) was used with the BM25 system (Baxter, McGraw Hill, Ill., USA). This integrated double-module machine, available in our unit since 1998, allowed fluid balance accuracy of ±0.5%. Dialysate flow was 2 l/h.

In both CAVHD and CVVHD, a lactate-free solution containing calcium and bicarbonate (Solubag 30; Sifra, Italy) was used as dialysate (Na^+ 140, K^+ 1.5, Ca^{2+} 4, Mg^{2+} 1.5, CH_3COO^- 4, HCO_3^- 30 mEq/l, glucose 0.1%). Potassium chloride was added according to plasma potassium levels.

HD was performed using an AK100 monitor (Gambro AB, Lund, Sweden) with a dialysate flow of 500 ml/min. A Pro100 dialyzer (Gambrane membrane, 0.3 m^2. Gambro Italia, Parma, Italy) equipped with pediatric blood lines (total priming volume: about 110 ml) was used. The ultrafiltration rate control system showed a maximum error of ±1%. A minimum ultrafiltration rate of 100 ml/h was required by the monitor to avoid back-filtration. Dialysate composition (mmol/l) was: Na^+ 140, K^+ 4, Cl^- 111.5, Ca^{2+} 1.75, Mg^{2+} 0.5, CH_3COO^- 4, HCO_3^- 34.

In all procedures, the circuit was pre-primed with concentrated red blood cells and saline in order to keep the hematocrit of the priming solution around 30%. No citrate anticoagulant was present in the priming solution. In order to maintain the activated clotting time between 150 and 200 s, heparin (0–20 IU/kg per h) was administered according to the patient's coagulation status. Protamine was infused immediately before the inlet catheter at a ratio of 1:1–1.5. In all patients, intravenous therapy and glucose infusion were maintained unchanged throughout the dialysis procedure. Ultrafiltration was modulated according to fluid intake, and phosphate loss was corrected with intravenous phosphate salts.

Ammonium clearance calculation

In CAVHD, 24-h collection of effluent dialysate and urine were evaluated in patient 2, 4 and 5 in order to calculate ammonium urinary and dialysis mass removal and clearance. Both urinary and dialysis clearances (K, ml/min) were calculated according to the formula: $K = U \times V/P$, where U is solute concentration, V is volume of dialysate or urine and P is the mean plasma concentration during volume collection time [30].

In CVVHD (patients 6, 7 and 8) and HD (patients 9 and 10), ammonium clearance (K, ml/min) was calculated, according to the formula: $K = Q_b \times (C_i - C_o)/C_i$, where Q_b is blood flow (ml/min), C_i is solute concentration at filter inlet, and C_o is solute concentration at filter outlet [31].

Table 1 Characteristics of ten neonates with neonatal hyperammonemia treated with extracorporeal dialysis (*CPS* carbamylphosphate synthetase deficiency, *PA* propionic acidemia, *AS def* argininosuccinic synthetase deficiency, *AL def* argininosuccinic lyase deficiency, *MMA* methylmalonic acidemia, *CAVHD* continuous arteriovenous hemodialysis, *CVVHD* continuous venovenous hemodialysis, *HD* hemodialysis)

Patient	Age at start of dialysis (days)	Weight (kg)	Disease	Dialysis modality	Plasma ammonium (μmol/l)		Dialysis duration (h)	Time to 50% ammonium reduction (h)	Coma duration (h)		Present age, outcome and mental development index (MDI)
					At start of dialysis	At end of dialysis			Total	Before dialysis	
1	4	2.8	CPS	CAVHD	1482	117	60	0.85	92	56	6 years; severe motor and mental delay
2	7	2.6	PA	CAVHD	1170	49	33	1.74	49	18	4 years 11 months; normal development (MDI 102)
3	21	3.1	PA	CAVHD	1357	93	37	1.46	84	46	24 days; died, pulmonary hemorrhage
4	2	2.9	AS def	CAVHD	1534	211	39	9.45	72	48	5 days; died, cardiac arrest
5	4	2.7	AL def	CVVHD	1714	106	42	9.29	55	33	2 years; normal development (MDI 88)
6	3	3.0	CPS	CVVHD	4531	111	23	3.93	–	35	31 days; died, cerebral infarction
7	3	4.0	AS def	CVVHD	729	143	9	2.10	99[a]	14	10 months; normal development (MDI 92)
8	7	3.1	PA	CVVHD	785	82	5.5	1.84	31	13	9 months; normal development (MDI 92)
9	3	2.7	MMA	HD	1726	224	7.5	1.34	63	53	14 days; died, cardiac arrest
10	4	2.4	MMA	HD	1099	361	9	1.89	54	31	2 years 1 month; normal development (MDI 106)

[a] Prolonged pharmacological coma

Dialysis filtration fraction (FF, as percentage) was calculated according to the formula: $FF=K/Q_b \times 100$, where K is clearance (ml/min) and Q_b is blood flow (ml/min). A filtration fraction of 100% was considered as maximal ammonium extraction.

Statistical methods

Plasma ammonium concentrations recorded during dialysis were used to fit a first order decay curve and the time to 50% reduction was calculated for each patient. The Mann-Whitney test was used to assess differences between two groups and the Kruskal-Wallis test was used among three groups. Non-parametric Spearman rank correlation was used to assess possible association between two sets of measures. Statistical analyses were performed with the SPSS statistical package (SPSS Inc., Chicago, Ill., USA).

Results

Within the first 24 h, all dialysis procedures provided a significant decrease of median plasma ammonium concentration from 1419 (range 729–4531) to 114 μmol/l (range 49–361) (P=0.0001). Plasma glutamine levels were available only for seven patients and showed a similar trend to decline from a median value of 1580 (range 1310–3640) to 800 μmol/l (range 448–1000) (P=0.001).

Paralleling the decrease in ammonium and glutamine, there was an improvement of the neurological picture, with reappearance of spontaneous movements and of response to painful stimuli in all patients with the exception of patient 6, who had the highest ammonium levels and was later diagnosed with a cerebral infarction.

As shown in Table 1, five patients had a good outcome (normal at follow-up), while the remaining five had a poor outcome (four died and one has severe neurological impairment). The short-to-medium term outcome was not related to the dialysis modality. The most recent MDI scores for patients with good outcome are also reported in Table 1.

Total coma duration was significantly shorter in patients with good outcome than in those with poor outcome (47±11 h vs 78±13 h, P=0.02). Remarkably, by sub-dividing this time, we found that the true determinant for the prognosis was the duration of coma before the beginning of dialysis (22±10 h in good outcome patients vs 49±11 h in poor outcome patients, P=0.02), rather than total coma duration. Indeed, no difference was found between the two groups in the duration of coma following the beginning of dialysis (25±11 h vs 23±6 h). In all patients with good outcome the pre-dialysis coma duration

Table 2. Ammonium clearance and filtration fraction using different dialysis modalities (Q_b blood flow, Q_d dialysate flow, *b.wt.* bodyweight, *CAVHD* continuous arteriovenous hemodialysis, *CVVHD* continuous venovenous hemodialysis, *HD* hemodialysis)

Patient	Type of dialysis	Q_b (ml/min)	Q_d (ml/min)	Ammonium clearance (ml/min)	Ammonium clearance (ml/min per kg b.wt.)	Ammonium filtration fraction (%)
2	CAVHD	16	8.3	2.86	0.97	14.3
4	CAVHD	10	8.3	2.50	0.87	12.5
5	CVVHD	20	8.3	2.61	0.95	13.1
6	CVVHD	20	33.3	11.6	3.90	58.0
7	CVVHD	20	33.3	10.6	2.65	53.0
8	CVVHD	40	33.3	21.5	6.80	53.8
9	HD	15	500	14.4	5.37	96.0
10	HD	10	500	9.5	3.95	95.0

was less than 33 h, while those exceeding this limit invariably presented an unfavorable outcome.

There was a borderline difference of peak plasma ammonium levels between patients with poor outcome and those with good outcome (median values 1534 vs 1099 µmol/l, range 1357–4531 and 729–1714, respectively; P=0.05).

Peak ammonium levels and pre-dialysis coma duration were also correlated (P=0.03).

No differences were found in the time (hours) to 50% ammonium reduction between the two groups of patients (3.4±3.6 vs 3.4±3.3 h), or among the different dialysis modalities (CAVHD 3.4±4.1 h, CVVHD 4.3±3.5 h, HD 1.6±0.4 h). By dividing our series into patients with urea cycle defects and those with organic acidurias, no significant differences were found for the interval between the appearance of first symptoms and dialysis initiation, predialysis ammonium or glutamine levels, or 50% ammonium reduction time.

In CAVHD, the average blood flow was 14±7 ml/min (range 8–31), whereas in the CVVHD group blood flow was 20 ml/min in patients 5, 6 and 7 and 40 ml/min in patient 8. In the two neonates treated with HD, blood flow was between 10 and 15 ml/min. In Table 2, ammonium clearance and extraction are compared according to the dialysis type and to different parameters. In the three patients studied (2, 4 and 5), the urinary ammonium excretion was 802±147 µmol/day whereas the dialytic mass removal was 3811±306 µmol/day (P=0.0001).

Treatment with CAVHD and CVVHD did not cause cardiovascular intolerance except in patient 4, who had two cardiac arrests before the initiation of CAVHD. Both HD-treated patients showed severe hypotension requiring repeated plasma and blood transfusions, increase of inotropic support and suspension of dialysis in one case (patient 10). The system of infusion pumps used in patients 1–5 caused a fluid loss ranging from 20 to 75 ml/h, which required repeated adjustments.

A transitory ischemia of the limb after cannulation of femoral vessels was observed in all cases, and microsurgical repair of the femoral artery was required in patient 1. Two cases (patients 1 and 5) had transient thrombocytopenia. Patient 3 died of pulmonary hemorrhage during CAVHD. Patient 1 had a delayed relapse of hyperammonemia at the age of 45 days that required further dialysis.

Discussion

Our report shows that the three dialysis techniques used resulted in a striking reduction of blood ammonia levels within a few hours. These results are consistent with those reported by others [8, 13, 20, 21, 22, 24]. However, in our series of patients the rapidity of dialysis treatment per se did not seem to influence the outcome. In contrast with the report of Schaefer et al. [13], who found a correlation between rapidity of detoxification and prognosis, in our series the 50% ammonium reduction time did not significantly differ between patients with good and poor outcome. At the extremes, one HD-treated patient with a 50% ammonium reduction time of 1.3 h died, whereas one CVVHD-treated patient with a 50% ammonium reduction time of 9.3 h is alive and well.

An association between total coma duration and outcome was evident in our series of patients, as already reported in non-dialyzed hyperammonemic neonates [26]. However, we found that the limiting factor for prognosis was the duration of coma before the start of dialysis, and not the total coma duration. It is important to note that a pre-dialysis coma duration exceeding 33 h was the limit invariably associated with a poor outcome. This may represent a useful prognostic indicator to take into consideration when a dialysis treatment is initiated in these patients.

In the study by Msall and colleagues, no correlation was found between ammonium levels and neurological outcome [26]. It is likely that the difference we found in patients with good or poor outcome is a time-related effect rather than the cause of the condition sustaining the different outcome, as is also supported by the significant correlation between peak ammonium levels and coma duration.

Since different metabolic defects led to hyperammonemia, it cannot be excluded that the outcome in our patients could also be influenced by the natural history of the individual disease. However, it must be noted that in both groups of diseases (urea cycle defects and organic acidurias) predialysis ammonium and glutamine levels as well as the rate of detoxification were comparable. Therefore, given that our series does not include male newborns with ornithine carbamoyltransferase deficiency whose prognosis is invariably fatal, this study

shows that the type of metabolic defect does not seem to have influenced the early outcome. Concerning the long-term outcome, it must be remembered that the prognosis may be influenced by relapses of life-threatening metabolic decompensation occurring later in the patients' lives.

Despite the small sample size, as often happens in study of rare diseases, our results indicate that rapidity of treatment can be meaningless if prompt identification of hyperammonemia and simultaneous start of therapy are not guaranteed, regardless of the mode of dialysis. This implies that success of the treatment is mostly time-dependent and that patients' prognosis relies on rapidly referring patients to centers with expert metabolic clinicians and full dialysis facilities, rather than on the dialysis characteristics. This point becomes crucial in deciding the treatment strategy when duration of hyperammonemia exceeds the limit beyond which the prognosis is invariably poor. Therefore, a relevant ethical issue is raised by the use of an aggressive treatment in hyperammonemic newborns with a coma duration that is too prolonged.

Based on the efficacy of pharmacological therapy alone in 50% of our hyperammonemic newborns (personal observation), our present attitude is to monitor closely the initial response and the plasma ammonium trend, and to limit this approach in non-responsive patients to the time necessary solely to provide first care and vascular access, before starting dialysis.

HD provided the highest ammonium extraction with a dialysate flow of 500 ml/min. However, ammonium clearance was lower than with CVVHD, since blood flow was hampered by severe hypotension (see Table 2). This complication has already been reported in 64% of neonates treated with HD [22], and in our patients it limited the efficacy of dialysis. In CAVHD and CVVHD, when dialysate delivery was regulated by the double pump system, we refrained from increasing the dialysate flow in order to avoid further unpredictable fluid loss [32, 33]. Nonetheless, the dialytic mass removal of ammonium was almost five times that of diuresis, which explains the plasma ammonium decrease. Using the BM25 system, a higher blood flow was obtained because of good cardiovascular stability. Moreover, the better precision of fluid balance allowed us to increase the dialysate flow up to 33.3 ml/min (2 l/h), thus obtaining an ammonium clearance 3–4 times higher. We therefore recommend use of this system for dialysate flow and fluid balance control in neonatal CVVHD. No patient treated with CVVHD at a dialysate flow of 2 l/h showed ammonium extraction close to 100%. Since there are no in vivo studies on ammonium extraction with CVVHD at different dialysate and blood flow rates, dialysate flows higher than 2 l/h should be investigated in order to reach maximal CVVHD in vivo ammonium clearance.

In conclusion, our study confirms the efficacy of dialysis in neonatal hyperammonemia. Since the prognosis depends on coma duration preceding the start of dialysis rather than on dialysis modality, the success of treatment in the short-to-medium term is strongly related to the rapid identification of patients and to the time taken to refer them to centers with metabolic clinicians and full dialysis facilities. Once the decision for dialysis is made, we recommend the use of CVVHD equipped with a high-precision dialysate delivery system and with high dialysate flow.

References

1. Brusilow SW, Horwich AL (1995) Urea cycle enzymes. In: Scriver CR, Beaudet AL, Sly WS, Valle D (eds) The metabolic and molecular bases of inherited disease, 7th edn. McGraw-Hill Inc., New York, pp 1187–1232
2. Coude FX, Sweetman L, Nyhan WL (1979) Inhibition by propionylCoA of N-acetylglutamate synthetase in rat liver mitochondria. J Clin Invest 64:1544–1548
3. JV Leonard (1995) Urea cycle disorders. In: Fernandes J, Saudubray JM, van den Berghe G (eds) Inborn metabolic diseases. Springer-Verlag, Berlin, pp 167–176
4. Bachmann C (1984) Treatment of congenital hyperammonemias Enzyme 32:56–64
5. Ogier H, Saudubray JM (1995) Emergency treatment. In: Fernandes J, Saudubray JM, van den Berghe G (eds) Inborn metabolic diseases. Springer-Verlag, Berlin, pp 47–56
6. Wiegand C, Thompson T, Bock GH, Mathis RK, Kjellstrand CM, Mauer SM (1980) The management of life-threatening hyperammonemia: a comparison of several therapeutic modalities. J Pediatr 96:142–144
7. François B, Cornu G, de Meyer R (1976) Peritoneal dialysis and exchange transfusion in a neonate with argininosuccinic aciduria. Arch Dis Child 51:228–231
8. Donn SM, Swartz RD, Thoene JG (1979) Comparison of exchange transfusion, peritoneal dialysis, and hemodialysis for the treatment of hyperammonemia in an anuric newborn infant. J Pediatr 95:67–70
9. Snyderman SE, Sansaricq C, Phansalkar SV, Schacht RG, Norton PM (1975) The therapy of hyperammonemia due to ornithine transcarbamylase deficiency in a male neonate. Pediatrics 56:65–73
10. Brusilow SW, Daney M, Waber LJ, Bathshaw M, Burton B, Levitsky L, Roth K, McKeethren C, Ward J (1984) Treatment of episodic hyperammonemia in children with inborn errors of urea synthesis. N Eng J Med 310:1630–1634
11. Siegel NJ, Brown RS (1973) Peritoneal clearance of ammonia and creatinine in a neonate. J Pediatr 82:1044
12. Gortner L, Luepold D, Pohlandt F and Bartmann P (1989) Peritoneal dialysis in the treatment of metabolic crises caused by inherited disorders of organic and amino acid metabolism. Acta Paediatr Scand78:706–711
13. Schaefer F, Straube E, Oh J, Mehls O, Mayatepek E (1999) Dialysis in neonates with inborn errors of metabolism. Nephrol Dial Transplant 14:910–918
14. Kjellstrand CM, Shideman JR, Santiago EA, Mauer M, Simmons RL, Buselmeier TJ (1971) Technical advances in hemodialysis of very small pediatric patients. In: Schreiner GE (ed) Proc Clin Dial Transplant Forum 1:124–132
15. Ronco C, Brendolan A, Bragantini L, Chiaramonte S, Feriani M, Fabris A, Dell'Aquila R, La Greca G (1986) Treatment of acute renal failure in newborns by continuous arterio-venous hemofiltration. Kidney Int 29:908–915
16. Ring E, Zobel G, Stockler S (1990) Clearance of toxic metabolites during therapy for inborn errors of metabolism. J Pediatr 117:349–350
17. Thompson GN, Butt WW, Shann FA, Kirby DM, Henning RD, Howells DH, Osborne A (1991) Continuous venovenous hemofiltration in the management of acute decompensation in inborn errors of metabolism. J Pediatr 118:879–884

18. Sperl W, Geiger R, Maurer H, Guggenbichler JP (1990) Continuous arteriovenous haemofiltration in hyperammonemia of newborn babies Lancet 336:1192–1193
19. Ring E, Zobel G (1992) Hamofiltration bei akuten neonatalen Stoffwechselkrisen. Wien Klin Wochenschr 104:674–677
20. Rutledge SL, Havens OL, Haymond MW, McLean H, Kan JS, Brusilow SW. (1990) Neonatal hemodialysis: effective therapy for the encephalopathy of inborn errors of metabolism. J Pediatr 116:125–128
21. Summar M, Pietsch J, Deshpande J, Schulman G (1996) Effective hemodialysis and hemofiltration driven by an extracorporeal membrane oxygenation pump in infants with hyperammonemia. J Pediatr 128:379–382
22. Sadowski RH, Harmon EH, Jabs K (1994) Acute hemodialysis of infants weighing less than five kilograms. Kidney Int 45:903–906
23. Tuchman M, Mauer SM, Holzknecht RA, Summar ML, Vnencak-Jones CL (1992) Prospective versus clinical diagnosis and therapy of acute neonatal hyperammonaemia in two sisters with carbamyl phosphate synthetase deficiency. J Inher Metab Dis 15:269–277
24. Falk MC, Knight JF, Roy LP, Wilcken B, Schell DN, O'Connell AJ, Gillis J (1994) Continuous venovenous haemofiltration in the acute treatment of inborn errors of metabolism. Pediatr Nephrol 8:330–333
25. Wong KY, Wong SN, Lam SY, Tam S, Tsoi NS (1998) Ammonia clearance by peritoneal dialysis and continuous arteriovenous hemodiafiltratrion. Pediatr Nephrol 12:589–591
26. Msall M, Batshaw ML, Suss R, Brusilow SW, Mellits ED (1984) Neurologic outcome in children with inborn errors of urea synthesis. New Eng J Med 310:1500–1505
27. Bayley N (1993) Bayley Scales of Infant Development, 2nd edn. Psychological Corporation, New York, pp 35–60
28. Peachey TD, Ware RJ, Eason JR, Parsons V (1988) Pump control of continuous arteriovenous haemodialysis. Lancet 2:878
29. Kaplan AA (1996) Continuous arteriovenous haemofiltration and related therapies. In: Jacobs C, Kjellstrand CM, Koch KM, Winchester JF (eds) Replacement of renal function by dialysis, 4th edn. Kluwer Academic Publishers, Dordrecht, pp 390–417
30. Semama DS, Huet F, Gouyon JB, Lallement C, Desgres J (1995) Use of peritoneal dialysis, continuous arteriovenous hemofiltration and continuous arteriovenous hemodiafiltration for removal of ammonium chloride and glutamine in rabbits. J Pediatr 126:742–746
31. Hoenich NA, Woffindin C, Ronco C (1996) Hemodialysis and associated devices. In: Jacobs C, Kjellstrand CM, Koch KM, Winchester JF editors. Replacement of renal function by dialysis, 4th edn. Kluwer Academic Publishers, Dordrecht, pp 188–230
32. Roberts M, Winney RJ (1992) Errors in fluid balance with pump control of continuous hemodialysis. Int J Artif Organs 15:99–102
33. Jenkins R, Lee T, Arnold D, Funk J (1991) Accuracy of IV pumps in CAVHD. ASAIO Abstracts 20:78