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Management of 35 critically ill hyperammonemic neonates: role of early administration of metabolite scavengers and continuous hemodialysis

Short title: Management of critically ill hyperammonemic neonates

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ABSTRACT

Neurological involvement is frequent in inherited metabolic disease of the intoxication type.

Hyperammonemic coma related to these diseases may cause severe neurological sequelae.

Early optimal treatment is mandatory combining metabolite scavengers (MS) and sometimes continuous veno-venous hemodialysis (CVVHD). We aimed to describe the therapeutic management of hyperammonemia in neonates upon diagnosis of their metabolic disease and to compare neonates managed with MS alone or with both MS and CVVHD.

We conducted a retrospective study including all neonates admitted for initial hyperammonemia to the pediatric intensive care unit of a Reference Center of Inherited Metabolic Diseases, between 2001 and 2012.

The study included 35 neonates. Before admission, MS were initiated for 11 neonates. At admission, the median ammonia levels were 391 $\mu\text{mol/L}$ and were significantly lower in neonates who received MS before admission. At admission, ammonia levels were 644 $\mu\text{mol/L}$ in dialyzed and 283 $\mu\text{mol/L}$ in non-dialyzed neonates. The median time to reach a 50% decrease of the initial ammonia levels was significantly shorter in dialyzed neonates; however, the normalization of ammonia levels was similar between dialyzed and non-dialyzed neonates. Hemodynamic disorders were more frequent in dialyzed neonates.

Conclusion: MS represent an effective treatment for hyperammonemia and should be available in all pediatric units to avoid the need for CVVHD. Although CVVHD enhances the kinetics of toxic metabolite decrease, it is associated with adverse hemodynamic effects.

KEYWORDS: Hyperammonemia, metabolite scavengers, hemodialysis, neurotoxicity, intoxication metabolic disease, intensive care medicine

ABBREVIATIONS

ASS: arginosuccinate synthetase
CPS: carbamoyl phosphate synthetase
CVVHD: continuous veno-venous hemodialysis
MS: metabolite scavengers
PICU: pediatric intensive care unit
PRISM: Pediatric Risk of Mortality
UCD: urea cycle disease
OA: organic acidurias
OTC: ornithine transcarbamylase

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1. INTRODUCTION

Hyperammonemic coma related to inherited metabolic diseases of the intoxication type may cause severe neurological sequelae and the prognosis is correlated with both the duration and intensity of the increased ammonia level [1-3]. Early adequate treatment is mandatory including (a) the removal of ammonia using metabolite scavengers (MS) and/or continuous veno-venous hemodialysis (CVVHD) and (b) the promotion of anabolism by providing adequate caloric intake (carbohydrates and lipids). Intravenous MS, such as sodium benzoate or sodium benzoate/sodium phenylacetate (AmmonulTM), reduce ammonia levels although perhaps not as quickly as intended [4-6]. MS associated with CVVHD should be started early according to the previous recommendations made for the management of urea cycle disorder (UCD) and organic acidurias (OA) [1,3]. CVVHD has been described in case reports as an efficacious treatment without adverse effects [7-9]. However, there are no data assessing the effective benefits of CVVHD compared with MS.

We aimed to describe the initial therapeutic management of hyperammonemic neonates upon diagnosis of their metabolic intoxication disease and to compare neonates treated with MS alone and those treated with both MS and CVVHD.

2. PATIENTS AND METHODS

This retrospective study was conducted at the Necker Hospital (Paris, France), a Reference Center of Inherited Metabolic Diseases. All hyperammonemic neonates (age <29 days, ammonia levels >100 $\mu\text{mol/L}$) with intoxication-type inherited metabolic disease admitted to

the pediatric intensive care unit (PICU) between 2001 and 2012 were included. The metabolic diagnosis was confirmed after admission by biochemical and molecular investigation. Two groups were formed: dialyzed neonates and non-dialyzed neonates. General and demographic characteristics were collected. Clinical data and management before PICU admission were recorded. Neurological, hemodynamic, and respiratory status was assessed at admission in order to establish the Pediatric Risk of Mortality (PRISM) score. Ammonia levels were collected at admission and during the PICU stay. The median time to reach a 50% decrease of the initial ammonia levels (t_{50}) was reported.

The MS administered were: sodium benzoate, sodium phenylbutyrate, AmmonulTM, carbamyl glutamate, arginine hydrochloride, and carnitine. We defined “late MS” when treatment was started after PICU admission and “early MS” when treatment was started before PICU admission. Side effects such as extravasation of the venous catheter, local inflammation, edema, and hematoma were recorded. CVVHD was initiated according to the guidelines for management of UCD and OA when the ammonia levels exceeded 500 $\mu\text{mol/L}$, or if the ammonia levels exceeded 250 $\mu\text{mol/L}$ with signs of metabolic encephalopathy, or if the ammonia levels increased quickly despite MS introduction or in case of very early onset of disease [1,3].

CVVHD was performed using renal replacement equipment and an HF20 set (polyarylethersulfone; Prismaflex, Hospital, Lyon, France) and was primed with albumin 30 mL (5%).

For each dialyzed neonate, the data and device type related to CVVHD were collected, such as the type of catheter, blood flow rate, and dialysis flow rate. We evaluated the time between onset of symptoms and the initiation of CVVHD. Finally, CVVHD complications including hemodynamic disorders (need for volume resuscitation and/or catecholaminergic support), catheter-related infections, thrombosis, and hemorrhage were reported.

A comparison between dialyzed and non-dialyzed patients was made for the total study population and after excluding patients with limitation of active care. A flowchart of the study is presented in Figure 1.

Statistical analysis

Data are expressed as median values (with range value) for continuous variables, and number and/or frequency (%) for binary or categorical data. A comparative analysis of data from dialyzed patients versus non-dialyzed patients was performed. The normality of the population was tested using the D'Agostino–Pearson test with an alpha risk of 5% and a significance level set at 5%. Fisher's exact test was used for qualitative variables and the Mann–Whitney test was used for quantitative variables. Statistical analyses were performed using the statistical software Graph Pad Prism 6.

3. RESULTS

3.1 Demographics, patient characteristics, and management:

We included 35 neonates with: (a) a male-to-female sex ratio of 1.3; (b) a term birth of 39 weeks' gestational age (34–42); (c) a birth weight of 3340 g (2000–4100); and (d) an admission weight of 3106 g (1900–4000) (**Table 1**).

Metabolic investigation facilitated the diagnosis of 19 UCD and 12 OA cases. Among the 19 UCD cases, there were four cases of ornithine transcarbamylase deficiency (OTC), 14 cases of arginosuccinate synthetase deficiency (ASS), and one case of carbamoyl phosphate synthetase deficiency (CPS). Among the 12 OA cases, there were five cases of methylmalonic aciduria, four cases of propionic aciduria, and three cases of isovaleryl aciduria. Among the

remaining four cases, there was one case of carbonic anhydrase deficiency and three cases of hyperammonemia without a diagnosis.

Age at onset of symptoms was 3 days (0–28) in the total study population (4 days for UCD, 3.5 days for OA, and 2.5 days for hyperammonemic patients without diagnosis). Age at admission was 6 days (1–32). The time between the first symptoms and PICU admission was 2 days (0.04–12) and the duration of transportation before admission was 40 min (0–436) (**Table 1**).

Coma or altered consciousness was observed in 29 neonates (82.9%), abnormal movements in 10 neonates (28.6%), and axial hypotonia in 27 neonates (77.1%). Hemodynamic and respiratory disorders (polypnea, apnea) were observed in 14 (40%) and 22 neonates (62.9%), respectively. Twelve patients were intubated (34.3%). The PRISM score at admission was 11 (0–32) (**Table 1**). Eight neonates died (22.8%) before PICU discharge, including four following withdrawal of care, because of (a) major hyperammonemia ($n = 3$) and (b) severe neurological damage with severe EEG abnormalities ($n = 1$).

Protein intake was stopped in 13 neonates (37.1%) before PICU admission, after which all neonates received intravenous high-caloric and protein-free intake providing glucose and lipids upon PICU admission. A total of 34 neonates (97.1%) had MS, 11 of whom (31.4%) received them before admission; 14 neonates (40%) had both MS and CVVHD during their PICU stay. The most commonly used MS was intravenous sodium benzoate in 30 neonates (88.6%; 250–500 mg/kg/day after a loading dose) and in combination with oral sodium phenylbutyrate (250–500 mg/kg/day) in 18 neonates (51.4%). AmmonulTM (250–500 mg/kg/day after a loading dose) was given to nine neonates (25.7%). Intravenous arginine (50–200 mg/kg/day) and oral glycine (250 mg/kg/day) were introduced following the diagnosis of a metabolic disorder. No side effects of MS were reported. The criteria for CVVHD ($n = 14$) initiation were respected in all cases: ammonia levels higher than 500

$\mu\text{mol/L}$ ($n = 10$), rapid elevation of ammonia levels despite initiation of MS ($n = 2$), and severe neurological features with ammonia levels higher than $250 \mu\text{mol/L}$ ($n = 2$). Among six neonates with initial criteria of CVVHD (ammonia levels above $500 \mu\text{mol/L}$) a withdrawal of active care was decided for five patients; and CVVHD could not be performed on one neonate due to technical difficulties (inaccessible venous pathway). Finally, five neonates were not dialyzed due to a favorable evolution following early administration of MS. The mean time between the onset of symptoms and the start of CVVHD was 31.5 h (2–75) and the mean time between PICU admission and the start of CVVHD was 7 h (2–36). Central venous catheter insertion sites were: jugular ($n = 7$), femoral ($n = 4$), and umbilical ($n = 2$) veins. Blood and dialysis flow rates were: 9.4 mL/kg/min (6.7–19.9) and 204.7 mL/kg/hour (24.4–917.4), respectively. Nine neonates received unfractionated heparin anticoagulants. The duration of CVVHD was 11 h (6–18). Hemodynamic disorders were observed during CVVHD in 12 neonates (necessitating volume expansion, $n = 12$; and vasopressor agents, $n = 5$). No catheter-related infection was observed. Catheter hemorrhage or thrombosis was reported in two neonates.

A comparative analysis between the dialyzed group and the non-dialyzed group according to patient characteristics and management is detailed in **Table 1** and **Table 2**: (a) The rate of MS administration before PICU admission tended to be lower in the dialyzed group than in the non-dialyzed group although this was not statistically significant; (b) the duration of transportation and time between symptoms and admission were similar between the dialyzed group and the non-dialyzed group; (c) the rate of intubation during PICU stay was significantly higher in the dialyzed group than in the non-dialyzed group ($p < 0.0001$); (d) the rate of hemodynamic disorders was significantly higher in the dialyzed group than in the non-dialyzed group ($p = 0.01$) during PICU stay.

Analysis of demographics, patient characteristics, and management was also performed in the study population after excluding patients with limitation of active care. Results are detailed in Table 3 and Table 4 (**Table 3, Table 4**). The results were similar except for invasive mechanical ventilation, which was significantly lower in the non-dialyzed group ($p = 0.01$).

Analysis was also performed comparing neonates with early and with late administration of MS. Clinical features before admission were similar in neonates with early and with late administration of MS. However, the PRISM score was significantly higher in neonates who did not receive early administration of MS (14 vs. 9, $p = 0.03$). The duration of transportation was significantly lower in late MS patients (98 vs. 30.5 min, $p = 0.02$) (**Table 5**).

3.2 Time course of ammonia levels during therapeutic management

The time course of ammonia levels according to the type of therapeutic management (early administration of MS vs. late administration of MS) and group (dialyzed neonates vs. non-dialyzed neonates) is detailed in **Figure 2 and Table 6**. Excluding patients with limitation of active care, ammonia levels before admission and at PICU admission were 440 $\mu\text{mol/L}$ (58–1347) and 391 $\mu\text{mol/L}$ (69–1247), respectively. Some patients had an initial ammonia level lower than 100 $\mu\text{mol/L}$ but it increased during management.

Before admission, ammonia levels were similar in the dialyzed group and the non-dialyzed group: 595.5 $\mu\text{mol/L}$ (58–1347) versus 347 $\mu\text{mol/L}$ (69–785; $p = 0.19$), respectively. At admission, ammonia levels were significantly higher in the dialyzed group: 644 $\mu\text{mol/L}$ (298–1247) versus 283 $\mu\text{mol/L}$ (69–919; $p < 0.001$), respectively (**Table 6**).

Although the rate of early administration of MS was not statistically different between the two groups, the ammonia levels were significantly lower at PICU admission in neonates with early administration of MS before admission to PICU (276 vs. 644 $\mu\text{mol/L}$, $p < 0.002$) (**Table 5**).

The t_{50} was calculated in both the dialyzed and the non-dialyzed groups. Patients with withdrawal or withholding of treatment (with very high ammonia levels of more than 1000 $\mu\text{mol/L}$ and/or with too severe neurological failure) were excluded from this analysis. The median t_{50} was 10 h (3–24) and was significantly shorter in dialyzed patients (5 vs. 12.5 h, $p = 0.006$). The last ammonia levels (59 $\mu\text{mol/L}$; 23–159) during therapeutic management were similar in the dialyzed group and the non-dialyzed group as well as for early and late administration of MS (**Table 6 and Figure 2**).

4. DISCUSSION

On the basis of our study of 35 critically ill hyperammonemic neonates, CVVHD decreases ammonia levels more quickly than the sole administration of MS but it is associated with increased adverse hemodynamic effects. Early administration of MS may be beneficial and should be available in all neonatal wards.

The design of our study differs from that of previous studies that only included dialyzed patients [2, 7, 10], thus allowing us to identify the possible therapeutic impact of CVVHD. The timeliness of the treatment regardless of the use of MS alone or MS in combination with CVVHD is the cornerstone of the management of metabolic disease of intoxication and particularly of comatose infants [7].

The rate of MS treatment before PICU admission was low (31.4%) although the effectiveness of MS in decreasing ammonia levels is well known. Accordingly, neonates with early MS treatment before PICU admission had significantly lower ammonia levels at admission than non-treated neonates. Also, five patients with an indication for CVVHD (hyperammonemia above 500 $\mu\text{mol/L}$ before admission) were not dialyzed due to a favorable development following early administration of MS. However, there was only a trend toward a need for

CVVHD in neonates who did not receive early MS, perhaps related to parameters other than ammonia levels that influence the indication for CVVHD.

No adverse effects were observed with the use of MS, which is consistent with the literature [6], although anorexia, vomiting, alteration of mental status, and dyspnea were difficult to distinguish from the symptoms of the disease itself. Furthermore, retrospective studies are not designed to report side effects, which may minimize their incidence MS can be used initially at an early stage via peripheral venous access, as sodium benzoate can be administered by a peripheral venous catheter. However, Ammonul^{MT} must be perfused only via a central catheter, which is associated with specific risks (sepsis, thrombosis, etc.). The low rate of early MS treatment in our cohort should alert practitioners to the need for better management of these metabolic intoxication diseases [6].

CVVHD is an effective treatment of hyperammonemia and allows for a significant and rapid decrease in ammonia levels. CVVHD is recommended for the treatment of severe metabolic diseases of intoxication [1, 3, 7, 11]. The time from PICU admission, dialysis initiation, and the duration of CVVHD in our study was lower compared with other published studies [7, 9]. The criterion for stopping dialysis in our study was mainly the ammonia level. The very short duration of hemodialysis could be explained by the dialysate flow rates used in our care unit that were different from those used in other studies. The duration of dialysis seemed to be sufficient, and no resumption of dialysis was described.

Hemodynamic disorders were more frequently observed in dialyzed patients, although they were transient as they commonly resolved following volume resuscitation and vasopressor agents. Arbeiter et al. described a rate of 41% of patients presenting with hemodynamic disorders, necessitating catecholamine support for 42% of them [12]. The rate in our cohort was higher (42.8% at PICU admission and 85.7% during CVVHD therapeutic management in the PICU). These adverse hemodynamic effects should be taken into account as they may

increase the risk of brain damage. Treatment by MS combined with CVVHD resulted in a more rapid normalization of ammonia levels than treatment by MS alone. This may be explained by the high ammonium clearance. Ammonium is a small molecule and is therefore likely to be eliminated through the dialysate filter and even more so under high dialysate flow rates, as we observed in our cohort (median of 204.7 mL/kg/h). However, the final ammonia levels were similar in the two groups – treatment by MS is less invasive than CVVHD and is associated with a lower risk of side effects. To avoid the need for CVVHD, MS should be started earlier in local hospitals before admission to more specialized hospitals with PICUs. Therefore, the availability of MS in all hospital pharmacies should be the rule [6].

Our study has some limitations due to its retrospective nature. The work does not provide evidence that early administration of ammonia scavengers can avoid CVVHD in all cases, which would require the ability to establish cause and effect. In addition, it would be interesting to assess the long-term neurological outcome of these neonates in order to assess the benefit of CVVHD. One question would be to assess whether dialysis changes the neurological prognosis.

5. CONCLUSION

We studied a large series of hyperammonemic neonates at the initial phase of diagnosis and treatment. MS are clearly effective treatments of hyperammonemia. However, administration of MS is often started late, which raises the question of the availability of MS in hospital pharmacies. CVVHD enhances the kinetics of decreasing toxic metabolites but is associated with adverse hemodynamic effects. Early administration of MS should be the rule for the treatment of suspected hyperammonemic metabolic disease of intoxication, since it may avoid use of CVVHD and the related adverse effects.

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Table 1: Clinical features before admission to PICU in total study population

	Dialyzed patients (<i>n</i> = 14)	Non-dialyzed patients (<i>n</i> = 21)	Total population (<i>n</i> = 35)	<i>p</i>
Type of disease	9 UCD 2 OA 3 others	10 UCD 10 OA 1 other	19 UCD 12 OA 4 others	
Age at admission to PICU days (range)	4 (3—32)	6 (1–22)	6 (1–32)	0.53
Time between the first symptoms and admission days (range)	1.1 (0.2—4)	2.1 (0.04–12)	2 (0.04–12)	0.07
Term GA (range)	39 (34–41.7)	39.3 (35.8–41.6)	39 (34–41.7)	0.81
Sex (M/F)	9/5	11/10	20/15	0.73
Admission weight g (range)	3207.5 (2040–3930)	2990 (1900–4000)	3106 (1900–4000)	0.66
PRISM score (range)	8 (0–26)	12.5 (2–32)	11 (0–32)	0.34
Coma <i>n</i> (%)	12 (85.7)	17 (80.9)	29 (82.9)	1.00
Axial hypotonia <i>n</i> (%)	11 (78.6)	16 (76.2)	27 (77.1)	1.00
Abnormal movements <i>n</i> (%)	4 (28.6)	6 (28.6)	10 (28.6)	1.00
Hemodynamic disorders <i>n</i> (%)	6 (42.8)	8 (38.1)	14 (40)	1.00

Invasive mechanical ventilation <i>n</i> (%)	7 (50)	5 (23.8)	12 (34.3)	0.15
Duration of transport min (range)	31 (6–271)	43 (0–436)	40 (0–436)	0.77
Protein intake disruption <i>n</i> (%)	4 (28.6)	9 (42.8)	13 (37.1)	0.48
MS administration <i>n</i> (%)	3 (21.4)	8 (38)	11 (31.4)	0.46

PICU: pediatric intensive care unit; F: female; GA: gestational age; M: male; MS: metabolite scavengers; *n*: number; PRISM: Pediatric Risk of Mortality; UCD: urea cycle disorder; OA: organic aciduria. The *p* value corresponds to the comparison between the dialyzed and non-dialyzed groups.

Table 2: Clinical features and management during PICU stay in total study population

	Dialyzed patients (<i>n</i> = 14)	Non-dialyzed patients (<i>n</i> = 21)	Total population (<i>n</i> = 35)	<i>p</i>
Protein intake disruption <i>n</i> (%)	14 (100)	21 (100)	35 (100)	1.00
MS administration <i>n</i> (%)	14 (100)	20 (95.2)	34 (97.1)	1.00
Intubation rate <i>n</i> (%)	14 (100)	9 (42.8)	23 (65.7)	0.0001**
Hemodynamic disorders <i>n</i> (%)	12 (85.7)	7 (36.8)	19 (57.6)	0.01 *
Seizures <i>n</i> (%)	2 (14.3)	6 (28.6)	8 (22.8)	0.43
Sepsis <i>n</i> (%)	3 (21.4)	8 (42.1)	11 (33.3)	0.28
Death <i>n</i> (%)	3 (21.4)	5 (23.8)	8 (22.8)	1.00

PICU: pediatric intensive care unit; MS: metabolite scavengers; *n*: number. The *p* value corresponds to the comparison between the dialyzed and non-dialyzed groups. ***p*<0.01; **p*<0.05

Table 3: Clinical features before admission after excluding patients with limitation of active care

	Dialyzed patients (n = 14)	Non-dialyzed patients (n = 15)	Total population (n = 29)	<i>p</i>
Type of disease	9 UCD 2 OA 3 others	7 UCD 7 OA 1 other	16 UCD 9 OA 4 others	
Age at admission to PICU days (range)	4 (3–32)	7 (1–22)	6 (1–32)	0.28
Time between the first symptoms and admission days (range)	1.1 (0.2–4)	2 (0.04–12)	1.5 (0.04–12)	0.17
Term GA (range)	39 (34–41.7)	40.4 (35.8–41.6)	39.7 (34–41.7)	0.43
Sex (M/F)	9/5	8/7	17/12	0.71
Admission weight g (range)	3207.5 (2040–3930)	3210 (2400–4000)	3210 (2040–4000)	0.65
PRISM score (range)	8 (0–26)	10.5 (2–16)	10 (0–26)	0.77
Coma n (%)	12 (85.7)	12 (80)	24 (82.7)	1.00
Axial hypotonia n (%)	11 (78.6)	11 (73.3)	22 (75.8)	1.00
Abnormal movements n (%)	4 (28.6)	4 (26.6)	8 (27.6)	1.00

Hemodynamic disorders <i>n</i> (%)	6 (42.8)	4 (26.6)	10 (34.5)	0.45
Invasive mechanical ventilation <i>n</i> (%)	7 (50)	1 (6.7)	8 (27.6)	0.01*
Duration of transport, min (range)	31 (6–271)	52 (0–436)	40 (0–436)	0.77
Protein intake disruption, <i>n</i> (%)	4 (28.6)	8 (53.3)	12 (41.4)	0.26
MS administration, <i>n</i> (%)	3 (21.4)	7 (46.7)	10 (34.5)	0.24

PICU: pediatric intensive care unit; F: female; GA: gestational age; M: male; MS: metabolite scavengers; n: number; PRISM: Pediatric Risk of Mortality; UCD: urea cycle disorder; OA: organic aciduria. The *p* value corresponds to the comparison between the dialyzed and non-dialyzed groups. **p*<0.05; **

Table 4: Clinical features and management during PICU stay after excluding patients with limitation of active care

	Dialyzed patients (<i>n</i> = 14)	Non-dialyzed patients (<i>n</i> = 15)	Total population (<i>n</i> = 29)	<i>p</i>
Protein intake disruption <i>n</i> (%)	14 (100)	15 (100)	29 (100)	1.00
MS administration <i>n</i> (%)	14 (100)	15 (100)	29 (100)	1.00
Intubation rate <i>n</i> (%)	14 (100)	4 (26.7)	18 (62)	< 0.0001**
Hemodynamic disorders <i>n</i> (%)	12 (85.7)	5 (33.3)	17 (58.6)	<0.01*
Seizures <i>n</i> (%)	2 (14.3)	1 (6.7)	3 (10.3)	1.00
Sepsis <i>n</i> (%)	3 (21.4)	6 (40)	9 (31)	0.43
Death <i>n</i> (%)	3 (21.4)	1 (6.7)	4 (13.8)	0.32

PICU: pediatric intensive care unit; MS: metabolite scavengers; *n*: number. The *p* value corresponds to the comparison between the dialyzed and non-dialyzed groups. ** *p*<0.01; * *p*<0.05

Table 5: Clinical features, management, and time course of ammonia level during therapeutic management in early MS and late MS patients

	Early MS (<i>n</i> = 11)	Late MS (<i>n</i> = 24)	<i>p</i>
Age at admission to PICU days (range)	7 (3–32)	4.5 (3–25)	0.24
Term GA (range)	39 (34–41.5)	39.3 (36.8–41.7)	0.28
Admission weight g (range)	2740 (2040–3900)	3182.5 (1900–4000)	0.40
PRISM score (range)	9 (0–13)	14 (2–32)	0.03*
Coma <i>n</i> (%)	9 (81.8)	20 (83.3)	1.00
Abnormal movements <i>n</i> (%)	2 (18.2)	8 (33.3)	0.44
Duration of transport min (range)	98 (0–395)	30.5 (6–436)	0.02 *
Ammonium level before admission μmol/L (range)	347 (58–1347)	560.4 (94–1422)	0.1
Ammonemia at admission μmol/L (range)	276 (69–1247)	644 (94–1889)	<0.01**
Hemodialysis rate <i>n</i> (%)	3 (27.3)	11 (45.8)	0.46

PICU: pediatric intensive care unit; F: female; GA: gestational age; M: male; MS: metabolite scavengers; *n*: number; PRISM: Pediatric Risk of Mortality. The *p* value corresponds to the comparison between early MS and late MS patients. ***p*<0.01; **p*<0.05

Table 6: Time course of ammonia level during therapeutic management in dialyzed and in non-dialyzed patients

	Dialyzed patients (<i>n</i> = 14)	Non-dialyzed patients (<i>n</i> = 15)	Total population (<i>n</i> = 29)	<i>p</i>
Ammonium level before admission μmol/L (range)	595.5 (58–1347)	347 (69–785)	440 (58–1347)	0.19
Ammonemia at admission μmol/L (range)	644 (298–1247)	283 (69–919)	391 (69–1247)	0.0004 **
<i>t</i> 50 ^a (h)	5 (3–12)	12.5 (5–24)	10 (3–24)	0.006**
Last ammonemia μmol/L (range)	52 (25–150)	60.5 (23–159)	29 (23–159)	0.76

^aTime to reach a 50 % decrease of the initial ammonia level.

***p*<0.01; *p* value corresponds to the comparison between the dialyzed and non-dialyzed groups.

Figures:

Figure 1: Flowchart of the patient distribution

OA: organic aciduria; UCD: urea cycle disorder

Figure 2: Time course of ammonia level decrease during the first 24 h of therapeutic management.

Early MS without HDF = Early treatment by metabolite scavengers started before admission to PICU

Late MS without HDF = Late treatment by metabolite scavengers started after admission to PICU

Early MS + HDF = Early treatment by metabolite scavengers started before admission to PICU and continuous veno-venous hemodialysis

Late MS + HDF = Late treatment by metabolite scavengers started after admission to PICU and continuous veno-venous hemodialysis

Figure 1:

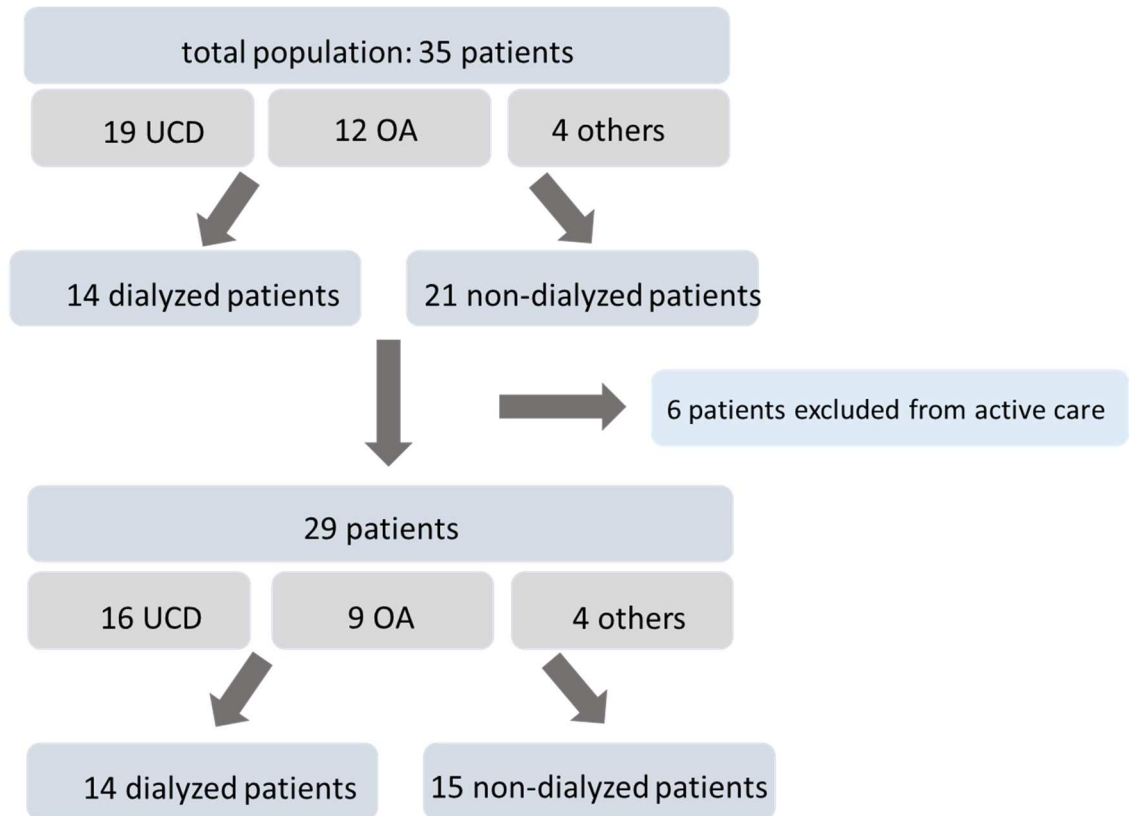


Figure 2:

