Research Article

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Threshold for toxicity from hyperammonemia in critically ill children

Bruno Ozanne, John Nelson, Jocelyne Cousineau, Marie Lambert, Véronique Phan, Grant Mitchell, Fernando Alvarez, Thierry Ducruet, Philippe Jouvet*

CHU Sainte-Justine, Soins Intensifs, 3175 Chemin de la Côte Sainte-Catherine, Montréal (QC), Canada H3T 1C5

Background & Aims: Hyperammonemia results from reduction of hepatocyte function or enzyme of urea cycle deficiency. Hyperammonemia contributes to cerebral edema that may lead to cerebral herniation. The threshold of toxicity of ammonemia is unknown.

Methods: We conducted a retrospective observational study in our pediatric intensive care unit. All children who developed hyperammonemia from January 2000 to April 2009 were included. Clinical and laboratory data at admission, specific treatments implemented, and ammonemias the first 7 days after inclusion were collected. The outcome assessed was 28 day mortality. Risk of mortality was estimated by a logistic regression model.

Results: Ninety patients with liver failure (63.3%) and primary or secondary urea cycle defect (23.3%) were included. Patients with urea cycle defects were more likely to receive ammonia scavengers than patients with liver failure (47.6% *versus* 3.5%). The 28 day mortality rate was 31.1%. Risk of mortality increased according to the ammonemia within 48 h: odds ratio 1.5, 1.9, 3.3, 2.4 for ammonemia above 100, 150, 200, and 300 μmol/L, respectively. Peak ammonemia $\geqslant$200 μmol/L within the first 48 h was an independent risk factor for mortality, with greater risk found in liver failure than in urea cycle defect.

Conclusions: Our study identifies a threshold of exposure to ammonia ($\geqslant$200 μmol/L) above which mortality increases significantly, especially in liver failure. Specific treatments of hyperammonemia are rarely used in liver failure when compared with urea cycle defect even though use of ammonia scavengers may help to decrease ammonemia.

Introduction

Hyperammonemia is an acute life threatening situation encountered in the pediatric intensive care unit (PICU). Reduction in hepatocyte number or function in liver failure (LF) and inhibition or primary defect of urea cycle enzymes in inborn errors of metabolism (urea cycle defect UCD) are the main causes of hyperammonemia in children [1,2]. Ammonia has been shown to affect brain function, to modulate both excitatory and inhibitory neurotransmission, and to contribute to cerebral edema. The pathophysiology of disabling symptoms associated with hyperammonemia is not fully understood, but various mechanisms have been observed in patients and experimental models: higher ammonia permeability of the blood brain barrier leading to changes in cellular pH, alteration of response to neurotransmitters, astrocyte swelling through glutamine accumulation, mitochondrial dysfunction with changes in cerebral energy metabolism, and reduced ATP concentration [3,4]. Ammonia induces oxidative and nitrosative stress that lead to apoptosis. These effects, coupled with an increase of cerebral blood flow can lead to cerebral edema [5]. There are several demonstrations of a link between hyperammonemia and death or encephalopathy in either LF or UCD with threshold for risk of toxicity ranging from 120 μmol/L up to 500 μmol/L [6–12]. However, the exact threshold for toxicity from hyperammonemia according to specific etiology is unknown. Pediatric data are scarce because of the small number of patients and the various therapeutic strategies used to treat high ammonia levels.

We, therefore, studied hyperammonemia episodes in a group of critically ill children in order to identify risk factors for death, treatments implemented, interaction with the underlying etiology, and to determine a threshold for toxicity of hyperammonemia.

Patients and methods

Population

We performed a retrospective longitudinal study in the 24-bed multidisciplinary, pediatric ICU of a tertiary care university-affiliated hospital in Montréal, Québec, Canada. The unit is a medical-surgical PICU that admits all critically ill children including cardiac surgery and organ transplantation patients.

All consecutive episodes of hyperammonemia in patients less than 18 years old between January 2000 and April 2009 were included, unless they met one of the exclusion criteria. A hyperammonemia episode was defined as arterial plasma ammonia above 80 μmol/L in children under 1-year and above 55 μmol/L in older children, on two successive samples within 24 h in order to minimize false positives (previously published definition [13]). Blood samples were collected in heparin tubes and put on ice immediately. Ammonia concentrations were measured on a Beckman Coulter LX-20 automat using a spectrophotometric enzymatic method with Beckman reagents [13]. Exclusion criteria were brain death and decision to withdraw or withhold therapy at PICU admission.

Data source and study variables

Retrospective identification of patients was done by cross-referencing the laboratory database with the PICU database. Possible risk factors for death were identified and selected from the medical literature before the initiation of the study by

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*Corresponding author. Tel.: +1 514 345 4931/4927; fax: +1 514 345 7731.
E-mail address: philippe.jouvet@umontreal.ca (P. Jouvet).

two investigators (JN, PJ). Time zero for inclusion was defined as time of the first report of hyperammonemia. The presence or absence of each potential risk factor was assessed for each case, using data extracted from the hospital medical chart. Data collected included sex, age, weight, patients' underlying condition and etiology of hyperammonemia, biological characteristics at inclusion, clinico-biological severity scores for death (PIM 2 score [14]) and for organ dysfunction, including hepatic and renal dysfunction (PELOD score [15]), treatment implemented for hyperammonemia (i.e. inhibitors of intestinal production, ammonia scavengers, extra-corporeal removal therapies, liver transplant). LF was defined as underlying hepatic disease diagnosis with an abnormal INR in the absence of disseminated intravascular coagulation. Plasma ammonia concentration at inclusion, maximum ammonia concentration within 48 h (48 h-NH_3) and 7 days (7 d-NH_3) post inclusion, and all other ammonia values measured during the first 7 days following inclusion were noted. Included cases were categorized according to their survival status at 28 days and 90 days after inclusion.

Data analysis and statistics

All episodes of hyperammonemia in our PICU were recorded but only the first episode of hyperammonemia per patient was considered for analysis. Data are quoted as median (interquartile range (IQ)) and n values as percentages. Categorical variables were analyzed using Chi square and Fisher's exact tests. Continuous variables were analyzed using Wilcoxon rank sum test when appropriate. Correlations between variables were examined with a Spearman's coefficient correlation. Optimal threshold values and test discrimination were determined with receiver operator characteristic (ROC) techniques. Kaplan–Meier curves were drawn to display survival.

The assessment of potential risk factors for the development of death used a logistic regression model; censoring was performed according to primary outcome (28 days mortality). Univariate regression was used to estimate odds ratios. These analyses were followed by a multiple logistic regression analysis to model the simultaneous effects of covariates and possible interactions. Maximum likelihood was assessed to test the possible interaction between etiology, hyperammonemia, and death and sub-group analysis according to the etiology was made. Models were generated from variables with p <0.10 from the univariate analyses, variables of interest, excluding confounding variables and variables with more than 5% missing data. Continuous data were dichotomized for analysis of risk factors according to clinical based considerations and data distribution. Data were analyzed with SAS software, version 9.2 (SAS Institute). A p value $\leqslant$0.05 was regarded as statistically significant.

Results

We identified 103 episodes of hyperammonemia. Among them, 90 patients presented a first episode during the study period and were considered for analysis. Hyperammonemia was secondary to UCD in 21 (23.3%) patients, LF in 57 (63.3%) patients, and other causes in 12 (13.3%). Baseline clinical and biochemical characteristics of patients and etiology of hyperammonemia are summarized in Table 1.

Pharmacological treatments implemented in order to decrease ammonia levels were mainly inhibitors of intestinal production of ammonia: 31 (34.4%) patients received antibiotics including metronidazole, or disaccharides, or both. Ammonia scavengers were used in 12 (13.3%) patients, renal replacement therapies were initiated in 22 (24.4%) patients and 10 (11.1%) patients underwent liver transplantation. Patients with LF were more likely to be treated with inhibitors of intestinal production, whereas patients with UCD were treated more likely with ammonia scavengers. Renal replacement therapy was used in a similar proportion of both patients groups, LF or UCD (28.1% *versus* 28.6%). The range of treatments implemented is reported in detail in Table 2.

At 28 days, 28 patients (31.1%) had died; at 90 days, 37 patients (41.1%) had died. Causes of death at 28 days were: withdrawal of life support due to neurological impairment in 11 patients (39.3%), non-septic multiple organ dysfunction (MODS) in 10 patients (35.7%), cerebral herniation in four patients (14.3%), septic MODS in three patients (10.7%). The median length of PICU stay was 8 days (IQR 4; 18 days). Median time to death was 11 days (IQR 6; 36 days). In patients with LF, 28 day mortality was 35.1% (20/57), 90 day mortality was 49.1% (28/57), and length of PICU stay was 10 days (IQ 6; 21 days). In patients with UCD, 28 day mortality and 90 day mortality was 33.3% (7/21), median time to death was 4 days (IQ 4; 8 days), and length of PICU stay 4 days (IQR 3; 7).

Median initial ammonia value was 101.5 μmol/L (IQR 74; 156 μmol/L), median max7 d-NH_3 was 129.5 μmol/L (IQR 88; 203 μmol/L), median max48 h-NH_3 was 113 μmol/L (IQR 84; 180 μmol/L), median area under curve for first 48 h (48 h-AUC) was 91. Max7 d-NH_3 was strongly correlated with max48 h-NH_3 (Spearman's correlation coefficient = 0.90, p <0.0001). Although there were no statistically significant differences, median values for initial NH_3, max7 d-NH_3, max48 h-NH_3, and 48 h-AUC NH3 were higher in non survivors than in survivors

Table 1. Characteristics at inclusion for first episode of hyperammonemia (n = 90).

Age (month) median (IQR)	15.3 (3.5; 75.2)
Sex (F/M) n (%)	38 (42)/52 (57)
Weight (kg) median (IQR)	10 (4.8; 24.5)
PIM 2 median (IQR)	20.6 (6.6; 36.2)
PELOD median (IQR)	11 (2.0; 22.0)
Etiology* n (%)	
Liver failure	57 (63.3)
Primary hepatic disease	38 (42.2)
Biliary atresia	12 (13.3)
Congenital	4 (4.4)
Post-viral	5 (5.6)
Auto-immune	5 (5.6)
Toxic	5 (5.6)
Tumoral	2 (2.2)
Other	5 (5.6)
Secondary to MODS of extra-hepatic origin	19 (21.1)
Urea cycle defect	21 (23.3)
Primary urea cycle defect	9 (10)
Other urea cycle inhibition	12 (13.3)
Others	12 (13.3)
Biochemical parameters	
Lactate (mmol/L) median (IQR)	4.2 (2.5; 8.7)
HCO_3 (mmol/L) median (IQR)	23.5 (20.4; 27.2)
INR median (IQR)	2.6 (1.6; 3.9)
Bilirubin (μmol/L) median (IQR)	70.0 (25.0; 216.0)
ASAT (IU/L) median (IQR)	404.5 (94.5; 2773.5)
GammaGT (IU/L) median (IQR)	52.0 (29; 77)

PIM 2: pediatric index of mortality 2; PELOD: pediatric logistic organ dysfunction score; MODS: multiple organ dysfunction syndrome. * Details of the etiologies: (a) causes of congenital disease: (hemochromatosis, fructosemia, galactosemia, cystic fibrosis); (b) causes of toxic diseases (acetaminophen, chemotherapy); (c) causes of tumoral (lymphoma, hepatic tumor); (d) other causes (veino occlusive diseases, unknown); (e) causes of primary urea cycle defects (carbamyl phosphate synthase, ornithine transcarbamylase, arginine synthase lyase, argino-succinate synthase, N acetylglutamate synthase); (f) causes of other urea cycle inhibition (organic aciduria, β-oxidation defect, respiratory chain defect); and (g) others (valproïc acid toxicity, etc.).

Table 2. Treatments implemented in order to lower plasma ammonia.

	All patients n = 90	Liver Failure n = 57	Primary or secondary Urea Cycle Defect n = 21
Inhibitors of intestinal production n (%)	31 (34.4)	29 (50.9)	2 (9.5)
Antibiotics	20	18	2
Disaccharides	20	20	0
NH_3 scavengers n (%)	12 (13.3)	2 (3.5)	10 (47.6)
Sodium benzoate	12	2	10
Phenyl acetate	11	2	9
Phenyl butyrate	0	0	0
Arginine	9	1	8
Carglumic acid	2	0	2
Citrullin	1	0	1
Renal replacement therapy n (%)	22 (24.4)	16 (28.1)	6 (28.6)
Continuous VenoVenous therapies	16	14	6
Peritoneal dialysis	4	4	0
Intermittent hemodialysis	2	2	0
Liver transplant n (%)	10 (11.1)	10 (17.5)	0 (0)
None n (%)	35 (38.9)	16 (17.8)	9 (10)

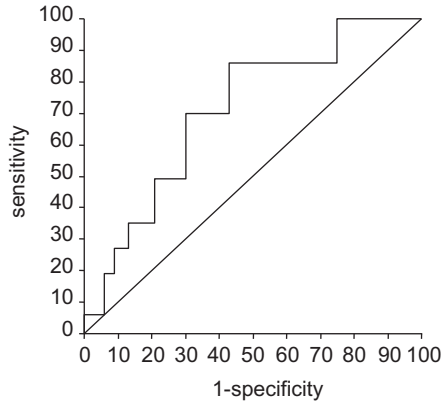

Fig. 1. Plasma ammonia concentration within the first 48 h (max48 h-NH_3) ROC curve for 28 day mortality.

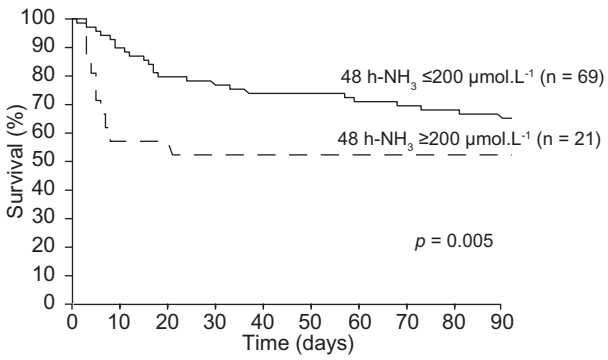

Fig. 2. Kaplan–Meier plot of survival in patients according to maximum ammonia concentration within the first 48 h after inclusion (48 h-NH_3).

(Table 2). ROC curve for max48 h-NH_3 as a predictor for 28-day mortality is shown in Fig. 1. Area under ROC curve was 0.63 (Table 3). The optimal threshold value for prediction of 28-day mortality was 200 µmol/L with a specificity of 80% and a sensitivity of 35%.

The 28 day mortality in patients with a max48 h-NH_3 $\geqslant$ 200 µmol/L was 11/21 (52.3%) versus 17/69 (24.6%) in patients with a max48 h-NH_3 <200 µmol/L. Kaplan–Meier survival curve for patients according to this threshold is shown in Fig. 2 (log-rank test, $p = 0.005$). Among patients with LF and max48 h-NH_3 $\geqslant$ 200 µmol/L, 28 day mortality was 6/8 (75%). Among patients with UCD and max48 h-NH_3 $\geqslant$ 200 µmol/L, 28 day mortality was 5/13 (38.5%). Kaplan–Meier survival curve according to the etiology in patients with max48 h-NH_3 $\geqslant$ 200 µmol/L is shown in Fig. 3 (log-rank test, $p = 0.08$).

Univariate analysis of risk factors for death showed that PIM 2 score above 10 and max48 h-NH_3 $\geqslant$ 200 µmol/L were significant risk factors for death at 28 days (Table 4). Odds ratio for PIM 2 >10 was 4.23 (95% CI: 1.30–13.78, $p = 0.016$), and it was 3.36 (95% CI: 1.22–9.30, $p = 0.019$) for max48 h-NH_3 $\geqslant$ 200 µmol/L. Confounding factors (PELOD score) and factors with more than 5% of data missing (lactate) were removed for multivariate logistic regression. After adjustment for covariates (age, sex, max48 h-NH3, diagnostic group) patients with PIM 2 $\geqslant$ 10 were five times more likely to die within 28 days of admission than patients with PIM 2 <10. Similarly, after adjustment for covariates (age, sex, PIM 2, diagnostic group) patients with max48 h-NH_3 $\geqslant$ 200 µmol/L were also five times more likely to die within 28 days of admission than patients with max48 h-NH_3 <200 µmol/L (Table 4). Adjusted odds ratio for etiology of hyperammonemia did not reach statistical significance (Table 4), and maximum likelihood was not significant ($p = 0.36$). In a subgroup analysis, patients with

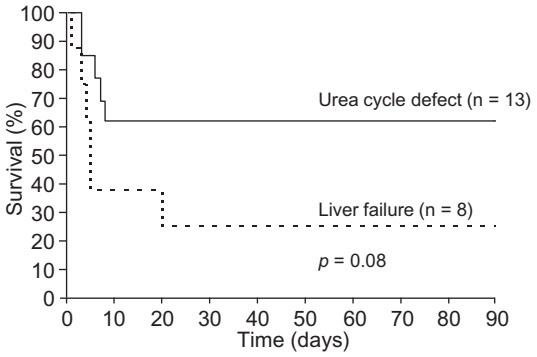

Fig. 3. Kaplan–Meier plot of 28-day mortality in patients with peak blood ammonia concentration within the first 48 h above 200 µmol L^{-1}, according to the etiology of hyperammonemia.

LF and 48 h-NH_3 ⩾ 200 µmol/L had a significantly higher risk for death at 28 days (Table 5).

Among patients with 48 h-NH_3 ⩾ 200 µmol/L, those with LF were more likely to receive inhibitors of intestinal production of ammonia (n = 6 (75%)) than those with UCD (7.7%). Conversely, 2 (25%) patients with LF and max48 h-NH_3 ⩾ 200 µmol/L received ammonia scavengers compared with 9 (69.2%) patients with UCD and max48 h-NH_3 ⩾ 200 µmol/L.

Discussion

Our study identifies a threshold ammonia level (200 µmol/L) above which risk of death is greatly increased in children (five fold). The increased risk was even greater in the subgroup of patients with hyperammonemia secondary to LF (eight fold). Ammonemia above 200 µmol/L within 48 h post-inclusion was an independent risk factor for death.

These findings are consistent with previous studies in adult patients with LF. Clemmesen *et al.* [7], in a retrospective study, found that in patients with acute LF and hepatic encephalopathy, high arterial ammonia levels within the first 24 h after onset of encephalopathy were associated with cerebral herniation. Patients who later developed cerebral herniation presented with median serum ammonia levels of 230 µmol/L versus 118 µmol/L in patients who did not. Bhatia *et al.* [8], in a prospective study exploring the link between hyperammonemia and death in patients with acute LF, reported that patients with ammonemia

Table 3. Plasma ammonia concentrations at inclusion, maximum levels during the first 48 h and the first 7 days following inclusion, area under curve (AUC) of plasma ammonia concentrations for the first 48 h after inclusion.

	All patients n = 90	Survivors n = 62	Non survivors n = 28	
	Median (IQR)	Median (IQR)	Median (IQR)	*p*
Initial NH_3 value (µmol/L)	101.5 (74; 156)	100.5 (72; 135)	123 (74.5; 206)	0.17
Max 48 h NH_3 value (µmol/L)	113 (84; 180)	107.5 (82; 163)	156 (95; 206)	0.067
Max 7 day NH_3 value J7 (µmol/L)	129.5 (88; 203)	110.5 (85; 172)	174.5 (99.5; 327.5)	0.099
AUC NH_3 first 48 h	91 (69; 128)	88 (69; 115)	103 (69; 232)	0.055

Table 4. Univariate and multivariate analysis (logistic regression model) of risk factors for 28 day death.

Variable	n	Missing data	Univariate				Multivariate			
			Odds Ratio	95% CI		*p*	Odds Ratio	95% CI		*p*
Sex (M/F)	38/90	0	1.19	0.48	2.96	0.70	1.18	0.42	3.27	0.76
Age ≤1 year	71/90	0	1.03	0.35	3.06	0.96	1.39	0.37	5.21	0.62
PIM 2 ≥10	57/86	4	4.23	1.30	13.78	0.017	4.93	1.35	18.08	0.016
PELOD ≥10	51/89	1	2.42	0.92	6.33	0.07				
Lactate ≥4 mmol/L	42/81	9	2.5	0.95	6.55	0.06				
INR ≥2	52/82	8	0.7	0.27	1.81	0.46				
Bilirubin ≥30 µmol/L	62/87	3	1.74	0.61	5.00	0.30				
ASAT ≥260 IU/L	49/88	2	1.09	0.44	2.70	0.85				
GammaGT ≥40 IU/L	51/85	5	1.39	0.53	3.62	0.50				
Etiology = LF *vs.* UCD	57/78	0	1.08	0.37	3.11	0.14	1.84	0.41	8.22	0.14
48 h-NH_3 value ≥200 µmol/L	21/90	0	3.36	1.22	9.30	0.019	5.07	1.22	21.02	0.025

PIM: pediatric index of mortality; PELOD: pediatric logistic organ dysfunction; LF: liver failure; UCD: urea cycle defect.

Table 5. Risk factor for 28 day mortality in patients with max 48 h-NH_3 ⩾200 μmol/L, according to the etiology.

Etiology	Odd ratios	95% CI		p	Adjusted odd ratios	95% CI		p
LF (n = 57)	7.3	1.3	40.55	0.02	8.3	1.3	52.5	0.02
UCD (n = 21)	1.9	0.3	13.2	0.53	1.0	0.1	13.7	0.99
All patients (n = 90)	3.4	1.2	9.3	0.02	4.0	1.0	15.6	0.04

LF: liver failure; UCD: urea cycle defect.

above 124 μmol/L were ten times more likely to die than those whose levels were below this threshold. In this study, no ammonia lowering therapies were used and liver transplant or liver assist devices were not available. In our study, the threshold for a significant increase in mortality was higher (200 μmol/L). This may be due to the heterogeneity of our population, with different etiologies to those encountered in adult LF (where LF is mostly a consequence of chronic liver diseases), and to the impact of the treatment on outcome.

Several reports [10–12,16] in children with urea cycle defects have shown that the degree of hyperammonemia is associated with the severity of outcome, but the threshold value for toxicity remains unclear. This threshold seems to be higher than in patients with LF. In fact, death was quite rare (less than 2%) in patients reported by Enns *et al.* at levels below 500 μmol/L. In a retrospective study by Bachmann *et al.* [11], no patient with UCD and peak serum ammonia above 480 μmol/L had a normal neuro-developmental outcome. In patients with UCD described by Uchino *et al.* [12], when the ammonemia exceeded 350 μmol/L during the first hyperammonemic crisis, patients died or had severe neurological deficits. None of these papers studied the precise link between ammonia toxicity and its concentration.

In patients with ammonia levels above 200 μmol/L, risk of death was higher in patients with LF although we could not show a significant interaction between etiology and ammonia concentration. This result can be explained by the small number of subjects in the UCD group. A sub-group multivariate analysis was not possible due to the small number of patients with each etiology. The risk of death in hyperammonemic patients with LF is probably greater because ammonia is not the only toxic substance that accumulates during liver failure, as opposed to UCD. Even if ammonia plays a key role in pathogenesis of hepatic encephalopathy, a panel of multiple precipitating factors are involved: the most relevant are probably inflammatory cytokines and natural benzodiazepine [4,5,17]. Our study clearly shows that ammonia was a marker of risk of death, but its role as a causative agent was not addressed.

The other major confounding factors in the analysis of the relationship between hyperammonemia and death are the treatments provided to control ammonemia. The descriptive data shown in Table 2 may explain, at least partially, differences observed between UCD patients and LF patients in the context of hyperammonemia. Patients with LF, who were more likely to die, received mainly inhibitors of gut ammonia production whereas patients with UCD received mainly ammonia scavengers such as sodium benzoate, sodium phenylacetate, or arginine.

Targeting gut production of ammonia may be too slow and ineffective in lowering ammonia level and modulating its cerebral effects, in patients sufficiently ill to require PICU admission. The use of antibiotics remains controversial in the management of hepatic encephalopathy and the effects on ammonia remain uncertain. While some proof exists regarding the efficacy of rifamixin [18,19], administration of other antibiotics, such as metronidazole, used in our population, shows no evidence of proven value [20], with only a few studies conducted on small samples of patients [21]. Furthermore, there is no high-quality evidence to support the use of non-absorbable disaccharides and a recent Cochrane systematic review [22] questions its beneficial effects and use as standard therapy in hepatic encephalopathy. At best, its effect on ammonia level is minor.

Ammonia scavengers are now widely used in patients with UCD, and seem to improve outcome by efficient lowering of ammonia levels [23]. In our study, patients with LF received few treatments activating alternative pathways of ammonia metabolism (3.5%).

The literature shows that few molecules have been tested in hyperammonemia due to LF. Possible treatment could include oral sodium benzoate [24], L-ornithine used in combination with L-aspartate [25], and phenylacetate [26,27]. We think that it is of high priority to identify patients who might benefit from such treatments. Given the potential risk of side effects, only patients whose risk for death is high should be considered eligible for these treatments.

Our study provides new data on toxicity from hyperammonemia, with an exhaustive review of all cases encountered in a single PICU. False identification of hyperammonemia was avoided by selecting episodes where hyperammonemia was confirmed on two samples. Our study cohort is very large considering the rarity of this entity in PICU. The association between early exposure to hyperammonemia and death suggests that there is a link between both, although absolute proof cannot be ascertained from a retrospective study.

Several limitations prevent making definitive conclusions. Etiologies of hyperammonemia were varied with few patients suffering from UCD. Nevertheless, this heterogeneous distribution of underlying diagnoses reflects what is observed in a PICU population. Our focus was on death as the main outcome and we did not include neurological impairment as an end point, since the design of the study did not allow us to make a diagnosis of neurocognitive disability. Using 48 h-NH_3 as a test for predicting death is weakened by the low area under ROC curve (0.63) and its sensitivity may increase with an outcome including neurological disability.

A non negligible number of our patients presented with LF as a component of MODS, and death may have been precipitated by other systemic factors (hemodynamic, respiratory, etc.) in addition to hyperammonemia and LF. As non neurologic organ dysfunction in patients with life threatening neurologic illness may arise as a direct result of brain injury [28], we included deaths due to MODS, assuming that hyperammonemia contributed, at

least partially, to death in the context of MODS. This hypothesis is suggested in many neurological illnesses and further research is needed to show that hyperammonemia has an impact on non neurologic organ dysfunction.

In conclusion, our study identified a group of children with an increased risk of death when ammonia levels higher than 200 μmol/L, and with greater length of exposure to these high levels. This association is stronger in patients with LF than UCD suggesting an additional effect of other toxicity due to liver dysfunction. A prospective study assessing neurological outcome as well as death could improve the identification of the threshold for poor outcome and may further define the causal link between plasma ammonia level and neurological outcome. These patients might benefit from efficient ammonia lowering therapies such as ammonia scavengers, or the use of innovative therapies for neuroprotection.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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