Arterial Ammonia and Clinical Risk Factors for Encephalopathy and Intracranial Hypertension in Acute Liver Failure

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High circulating ammonia concentrations are common in patients with acute liver failure (ALF) and are associated with hepatic encephalopathy (HE) and intracranial hypertension (ICH). Other risk factors are poorly characterized. We evaluated the relation of the admission arterial ammonia concentration and other clinical variables with the development of HE and ICH. Arterial ammonia was measured on admission to the intensive care unit in 257 patients; 165 had ALF and severe HE, and there were 3 control groups: acute hepatic dysfunction without severe HE (n = 50), chronic liver disease (n = 33), and elective surgery (n = 9). Variables associated with ICH and HE were investigated with regression analysis. Ammonia was higher in ALF patients than controls. An independent risk factor for the development of severe HE and ICH, a level greater than 100 μmol/L predicted the onset of severe HE with 70% accuracy. The model for end-stage liver disease (MELD) score was also independently predictive of HE, and its combination with ammonia increased specificity and accuracy. ICH developed in 55% of ALF patients with a level greater than 200 μmol/L, although this threshold failed to identify most cases. After admission, ammonia levels remained high in those developing ICH and fell in those who did not. Youth, a requirement for vasopressors, and renal replacement therapy were additional independent risk factors. *Conclusion:* Ammonia is an independent risk factor for the development of both HE and ICH. Additional MELD scoring improved the prediction of HE. Factors other than ammonia also appear important in the pathogenesis of ICH. Ammonia measurements could form part of risk stratification for HE and ICH, identifying patients for ammonia-lowering therapies and invasive monitoring. (HEPATOLOGY 2007;46:1844-1852.)

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There is now strong evidence of a central role for ammonia in the pathogenesis of hepatic encephalopathy (HE) that defines acute liver failure (ALF) and the cerebral edema (CE) and intracranial hypertension (ICH) that contribute to the high mortality seen in this condition. Elevations in the circulating ammonia concentration are a frequent finding in experimental and human ALF and appear to be closely related to these complications.[1-3] Experimental studies have demonstrated ammonia-induced changes in neurotransmitter synthesis and release, neuronal oxidative stress, impaired mitochondrial function, and osmotic disturbances resulting from astrocytic metabolism of ammonia to glutamine.[4-6] The net result of these changes is a marked alteration in cerebral function and astrocytic swelling.[5-7]

Recent studies reporting circulating ammonia concentrations in patients with ALF have found levels higher than those seen in patients with HE accompanying chronic liver disease (CLD).[2,3,8,9] The magnitude of the elevation of ammonia, particularly if it is above 150 μmol/L, has been reported to be related to an increased risk of major cerebral complications, including reduced consciousness level, seizures, cerebral herniation (CH), and death.[2,3,8,10,11]

If confirmed, these findings have the potential to alter clinical practice; patients identified as being at high risk for HE and ICH in this way could be targeted with specific therapies to reduce the circulating ammonia concen-

Abbreviations: ALF, acute liver failure; AUROC, area under the receiver operating characteristic curve; CE, cerebral edema; CH, cerebral herniation; CI, confidence interval; CLD, chronic liver disease; CVVHF, continuous venovenous hemofiltration; HE, hepatic encephalopathy; ICH, intracranial hypertension; ICP, intracranial pressure; INR, international normalized ratio; LITU, liver intensive therapy unit; LRN, likelihood ratio negative; LRP, likelihood ratio positive; LT, liver transplantation; MELD, model for end-stage liver disease; MOF, multiple organ failure; ROC, receiver operator characteristic; SIRS, systemic inflammatory response syndrome.

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tration to interrupt disease progression. Furthermore, the monitoring of intracranial pressure (ICP) is associated with rare but definite risks of severe complications, and the use of ammonia measurement could aid the selection of patients most likely to benefit from this invasive procedure.[12]

The relation between other clinical factors and HE and ICH is not well understood. Although an association with systemic inflammatory response syndrome (SIRS) and infection has been suggested, little is known about the importance of other factors that could identify patients as being at high risk.[11,13,14] A recent report has suggested that in patients with acetaminophen-induced hepatotoxicity, model for end-stage liver disease (MELD) scores above 18 may predict the onset of HE and progression to ALF.[15] It is presently not known whether an additional measurement of ammonia could improve predictive accuracy in determining the risk of HE.

In this study, we investigated the prognostic value of arterial blood ammonia levels in a large cohort of patients with established or evolving ALF. We examined the relation between the arterial ammonia concentrations on admission to survival and to the risk of subsequent development of HE and ICH, making a comparison with other simultaneously measured clinical variables, including MELD scores.

Patients and Methods

The study was performed in a specialist liver intensive therapy unit (LITU) and included 4 patient groups with a total of 257 subjects (Table 1): 165 patients with ALF and severe HE of grade III or higher (group 1), 50 patients with acute hepatic dysfunction in the absence of CLD and without severe encephalopathy (less than grade III, group 2), 33 patients admitted to LITU with decompensated CLD (group 3), and 9 patients admitted following elective hepatobiliary surgery in the absence of cirrhosis (group 4).

ALF with Severe Encephalopathy. One hundred sixty-five patients with ALF and severe encephalopathy, admitted over the period of September 2001 to June 2006, were studied. ALF was defined with the criteria of O'Grady et al.,[16] and in all patients, the time from the onset of jaundice to encephalopathy was less than 12 weeks. One hundred thirty-three had HE of grade III or higher present on admission, and 32 developed severe HE after admission. With the exception of patients with an acute presentation of Wilson's disease, none had CLD. The causes of ALF were acetaminophen (n = 92), non–A-E hepatitis (n = 17), viral (n = 16; 10 hepatitis B, 3 Epstein-Barr, 2 hepatitis E, and 1 varicella), nonacetaminophen drug–induced (n = 13), Wilson's disease (n = 5), pregnancy-related (n = 3), malignant hepatic infiltration (n = 4), autoimmune (n = 2), Budd-Chiari syndrome (n = 1), ischemia (n = 1), and unknown (n = 11).

ALF patients were managed with standard protocols; noradrenaline was used as a primary vasopressor, and continuous venovenous hemofiltration (CVVHF) was instituted for renal failure, oliguria, and control of metabolic acidosis. Intravenous *N*-acetyl-cysteine was infused at a rate of 150 mg/kg for 24 hours until the international normalized ratio (INR) was less than 2 or for a maximum of 7 days. All patients received broad-spectrum antibacterial and antifungal therapy, and those with nonmalignant disease were considered for liver transplantation (LT) if they fulfilled standard Kings College Hospital criteria.[17]

Patients with HE of grade III or higher were sedated, intubated, and mechanically ventilated. Goals of care for ventilated patients included an arterial partial pressure of carbon dioxide between 4 and 5 kPa, a core temperature of 36°C, and a serum sodium level of 140-150 mmol/L. Patients intubated for HE were monitored with reverse jugular oximetry via a catheter inserted retrogradely into the jugular bulb. ICP monitoring was performed in 55 patients with the Camino extradural system; insertion was

Table 1. Characteristics of the Patient Study Groups

	ALF	Acute	Chronic	Surgical
Group	1	2	3	4
Number	165	50	33	9
Age (years)	38 (28–49)	34 (24–42)	50 (39–57)	56 (29–71)
Sex (female/male)	102/63	33/17	13/20	7/2
Admission				
INR	3.7 (2.5–6.2)	3.3 (2.0–4.1)	1.6 (1.4–2.2)	1 (1–1.5)
Bilirubin (μmol/L)	96 (56–237)	77 (56–101)	171 (87–355)	28 (11–34)
Creatinine (μmol/L)	162 (104–235)	138 (83–236)	146 (103–226)	73 (64–105)
Lactate (mmol/L)	3.8 (2.5–6.8)	2.4 (1.8–3.6)	2.3 (1.5–3.0)	1.7 (1.1–2.6)
Peak HE grade	3 (3–4)	0 (0–1)	2 (2–3)	0

NOTE. The data are medians (interquartile range).

performed in those who showed signs suggestive of ICH (including posturing, hypertonicity, dilated pupils with a sluggish reaction to light, pupillary asymmetry, and systemic hypertension) or reverse jugular oximetry abnormalities (saturations persistently <60% or >85%). Sustained elevations in ICP or other signs of ICH were treated with a protocolized treatment regimen of optimized sedation plus or minus paralysis and then bolus intravenous mannitol or hypertonic saline, with refractory cases treated with indomethacin and induced hypothermia (<34°C).

Controls. Control subjects were admitted to LITU over the period of March 2002 to June 2006. All patients in group 2 had acute liver dysfunction without severe HE and no clinical or radiological evidence of CLD and did not develop HE requiring ventilation. The causes of liver dysfunction were acetaminophen (n = 34), pregnancy-related (n = 7), nonacetaminophen drug–induced (n = 3), viral hepatitis (n = 2; 1 with acute hepatitis A and 1 acute hepatitis B), non–A-E hepatitis (n = 1), and Budd-Chiari syndrome (n = 3). Group 3 comprised 33 patients with decompensated cirrhosis; the causes were alcoholic liver disease (n = 17), viral (n = 8; 5 chronic hepatitis B virus and 3 hepatitis C virus), cryptogenic (n = 3), hemochromatosis (n = 1), autoimmune hepatitis (n = 2), and biliary cirrhosis (n = 2). The MELD score on admission for group 3 was 25 (18-32) with HE grade 2. (2-3) Group 4 comprised 9 patients admitted following elective hepatobiliary surgery in the absence of cirrhosis or previous transplantation.

Measurement of the Blood Ammonia. In all patients and controls, arterial blood was sampled soon after admission in preheparinized syringes from indwelling radial or femoral arterial catheters. Admission samples were taken within 24 hours of admission. Samples were also taken daily in the majority of group 1 patients who remained encephalopathic.

Ammonia was measured with Ammonia Test Kit II for the PocketChem BA device (Arkay, Inc., Kyoto, Japan). This measures ammonia in a 20-μL blood sample applied to a reagent strip. The continuous measurement range is 7-286 μmol/L; the normal blood ammonia level for healthy adults for this device is less than 54 μmol/L. The device was maintained in accordance with the manufacturer's specification, with daily internal and monthly external calibration. Testing was performed by trained technical staff immediately after collection.

Data Analysis. A comparison of admission arterial ammonia concentrations was made between group 1 patients and groups 2-4. To examine the relation between ammonia and HE, a comparison was made of the admission levels in groups 1 and 2 and of the prediction of HE for those patients in group 1 admitted without severe HE but who progressed to grade 3 HE and higher and for the patients of group 2 who did not.

Within group 1, the relation between the admission arterial ammonia concentration and the development of ICH was examined; the latter was defined as being present in those patients who developed pupillary abnormalities (dilated and sluggishly reactive to light) or had a sustained ICP of greater than 25 mm Hg (for those with ICP monitoring), the requirement for bolus therapy with mannitol, hypertonic saline, or indomethacin, or autopsy evidence of CE.[18]

Data are quoted as medians (interquartile range) or n values (%). For a comparison of categorical variables, chi-square and Fisher's exact tests were used, and for continuous variables, a Mann-Whitney test for unpaired data and a Wilcoxon rank sum test for paired data were used as appropriate. Correlations between variables were examined with a Spearman correlation. Optimal threshold values and test discrimination were determined with receiver operator characteristic (ROC) techniques.

The assessment of potential risk factors for the development of ICH and HE used Cox regression and Kaplan-Meier plots with log-rank testing; censoring was performed if patients died or underwent transplantation. Univariate Cox regression was used to estimate hazard ratios. These analyses were followed by a multiple Cox regression analysis to model the simultaneous effects of covariates and possible interactions. Models were generated from variables with $P < 0.25$ from the univariate analyses and used a backward variable-selection technique.

The examined variables included the age, sex, etiology of ALF (acetaminophen/nonacetaminophen), biochemical and hematologic values on admission to LITU, and the requirement for vasopressor or CVVHF support within the first 24 hours of the LITU stay. The components of SIRS were documented on admission as a temperature greater than 38°C or less than 36°C, a heart rate greater than 90 beats per minute, and a white blood cell count greater than 12×10^9/L or less than 4×10^9/L. As the majority of group 1 patients were ventilated, the partial pressure of carbon dioxide was not used as a SIRS component. Patients were considered to have SIRS if 2 or more components were present. The MELD score was calculated as follows: $\{[0.957 \times \text{Log}_e(\text{mg of creatinine/dL})] + [0.378 \times \text{Log}_e(\text{mg of bilirubin/dL})] + [1.120 \times \text{Log}_e(\text{INR})] + 0.643\} \times 10$. All data were prospectively entered on a daily basis into the LITU database and analyzed with SPSS version 14.0 (SPSS, Inc., Chicago, IL). As the study relied on measurements taken as part of

routine care, the Ethical Committee of Kings College Hospital waived the need for informed consent/assent.

Results

Admission Arterial Ammonia: Study Group and Outcome. Arterial ammonia on admission was significantly higher in group 1 patients [median: 113 μmol/L (74-164 μmol/L)] than controls [group 2, 72 μmol/L (43-95 μmol/L), $P < 0.0001$; group 3, 86 μmol/L (58-124 μmol/L), $P < 0.03$; and group 4, 29 μmol/L (15-41 μmol/L), $P < 0.0001$; Fig. 1]. Within group 1, there was no significant difference in the ammonia concentration between those admitted with severe HE [111 μmol/L (68-163 μmol/L), n = 133] and those who developed it after admission [115 μmol/L (76-164 μmol/L), n = 32]. In those with HE present on admission, the median time from onset to blood sampling was 1 day (0-2); 94 of 133 (71%) had ammonia measured within 24 hours, and 115 (86%) had it measured within 48 hours of the onset of grade III HE.

In group 1, the ammonia concentration correlated with the admission INR (Spearman's rho = 0.340, $P < 0.0001$), bilirubin (0.177, $P < 0.01$), lactate (0.151, $P < 0.03$), and MELD (0.223, $P < 0.003$). There were no significant differences between those who survived with medical management [n = 49, 103 μmol/L (67-161 μmol/L)], those who died without LT [n = 58, 117 μmol/L (70-169 μmol/L)], and those who underwent transplantation [n = 58, 116 μmol/L (82-166 μmol/L)].

Of the 58 patients who died without LT, CH was the primary cause of death in 17 (29%), and multiple organ failure (MOF) was the primary cause in the remainder. The admission ammonia concentration was 114 μmol/L (64-223 μmol/L) in the patients dying of CH and 116 μmol/L (70-151 μmol/L) in those with MOF.

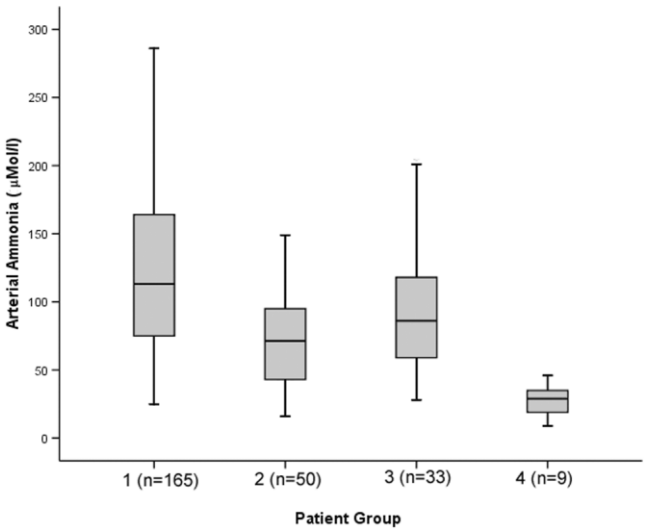

Fig. 1. Arterial ammonia concentration on admission in ALF patients and controls. The box plot shows the median, quartile, and extreme values. $P < 0.0001$ for group 1 versus group 2, $P < 0.03$ for group 1 versus group 3, and $P < 0.0001$ for group 1 versus group 4.

Table 2. Admission Characteristics of 82 Patients from Groups 1 and 2 Admitted Without HE with Respect to Subsequent Progression to Grade III-IV HE

	Progression	No Progression	P
Number	32	50	
Age	40 (33-46)	35 (24-43)	0.19
Sex (female/male)	18/14	34/16	0.31
Acetaminophen etiology	19 (59%)	33 (66%)	0.50
Ammonia (μmol/L)	114 (76-163)	72 (43-95)	<0.01
INR	4.2 (2.6-9.9)	3.3 (1.9-4.1)	<0.01
Lactate (mmol/L)	3.2 (2.5-4.8)	2.4 (1.8-3.6)	0.01
Bilirubin (μmol/L)	125 (81-314)	78 (57-103)	<0.01
pH	7.34 (7.27-7.4)	7.4 (7.36-7.4)	0.32
HCO_3 (mmol/L)	20.7 (18.2-22)	20.3 (18.4-22)	0.39
Sodium (mmol/L)	135 (131-139)	135 (134-139)	0.46
Creatinine (μmol/L)	111 (98-219)	143 (83-238)	0.64
Urine output (mL/24 hours)	125 (0-900)	1000 (200-1600)	0.74
MELD	37.3 (31.7-43)	28.9 (21.5-35.6)	<0.01
SIRS present	23 (72%)	26 (52%)	0.13
SIRS components	2 (1-3)	2 (1-2)	0.12
Vasopressors	2 (6%)	1 (2%)	0.33
CVVHF	17 (53%)	16 (32%)	0.07

NOTE. The data are medians (interquartile range) or n values (%).

Complete data for the calculation of the SIRS components were available for 209 of 215 (97%) patients from groups 1 and 2. Of the 162 patients from group 1, 122 (75%) fulfilled criteria for SIRS on admission versus 26 of 47 (55%) of group 2 ($P < 0.008$).

Arterial Ammonia and Risk Factors for the Development of Severe HE. Thirty-two patients from group 1 (19 acetaminophen and 13 nonacetaminophen) were admitted with HE of less than grade III but subsequently required intubation following its development at a median of 1 day after admission. These 32 were compared to the 50 group 2 patients who never developed severe HE (Table 2); the admission arterial ammonia was 114 μmol/L (76-163 μmol/L) in those who progressed to grade III and 72 μmol/L (43-95 μmol/L) in those who did not ($P < 0.0001$). Fourteen of 52 (27%) patients with an ammonia concentration lower than 100 μmol/L progressed to HE versus 13 of 25 (52%) of those with a concentration of 100-200 μmol/L and 5 of 5 (100%) of those with a concentration greater than 200 μmol/L ($P = 0.001$).

In a univariate Cox regression analysis, elevated ammonia, bilirubin, MELD, and lactate and prolonged INR were associated with the development of HE, as was the requirement for CVVHF (Table 3). In a multivariate

Table 3. Univariate and Multivariate Analyses of Variables Associated with Progression to Grade III-IV HE in 82 Patients from Groups 1 and 2

	Univariate			Multivariate		
Variable	HR	95% CI	*P*	HR	95% CI	*P*
Age	1.02	0.99–1.04	0.24			
Female Sex	0.78	0.38–1.58	0.49			
Acetaminophen etiology	1.20	0.58–2.47	0.62			
Ammonia (μmol/L)	1.01	1.01–1.02	<0.01	1.008	1.003–1.013	0.001
INR	1.11	1.03–1.20	<0.01			
Lactate (mmol/L)	1.25	1.06–1.49	<0.01			
Bilirubin (μmol/L)	1.00	1.01–1.01	<0.01			
pH	0.02	0–1.44	0.73			
HCO_3 (mmol/L)	1.02	0.94–1.1	0.66			
Sodium (mmol/L)	0.99	0.92–1.07	0.88			
Creatinine (μmol/L)	1.00	0.99–1.01	0.85			
Urine output (mL/24 hours)	0.99	0.99–1.01	0.70			
MELD	1.08	1.03–1.12	<0.01	1.06	1.01–1.11	0.01
SIRS components	1.69	0.77–3.67	0.18			
Vasopressors	3.39	0.80–14.4	0.10			
CVVHF	2.12	1.04–4.30	0.04			

NOTE. HR, hazard ratio (95% confidence intervals).

analysis, 2 variables remained independently significant: the ammonia and MELD score.

The area under the receiver operating characteristic curve (AUROC) for ammonia in the prediction of the development of severe HE was 0.785 [95% confidence interval (CI): 0.654-0.885]; the optimal threshold value for the identification of the development of HE of grade III or higher was 100 μmol/L. The Kaplan-Meier plot for this threshold is shown in Figure 2, and the test performance is shown later in Table 6.

AUROC for MELD was 0.764 (0.661-0.866). Only 6 of 82 (7%) patients had a MELD score lower than 18; scores above this threshold had 100% sensitivity but specificity of 12% (95% CI: 8-12) and diagnostic accuracy of 46% (41-46; shown later in Table 6).

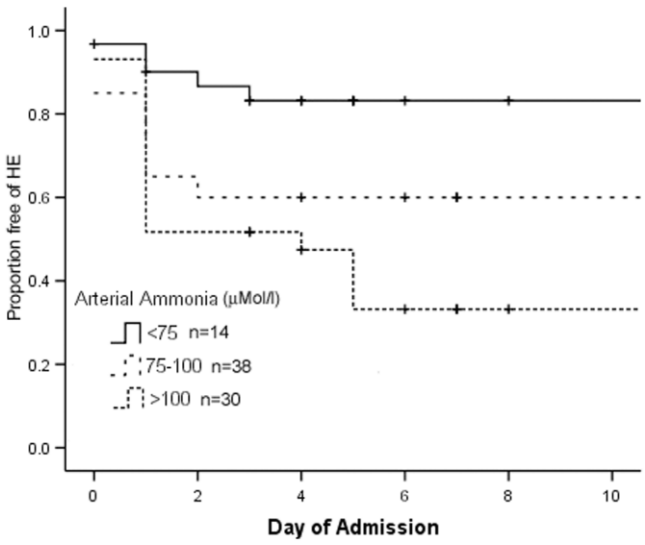

Fig. 2. Kaplan-Meier plot of HE in 82 patients admitted without HE according to the arterial ammonia concentration on admission. For the log-rank test, $P < 0.005$.

The optimal MELD threshold was 32; 9 of 39 (23%) with scores below this threshold progressed to severe HE versus 23 of 42 (55%) with scores above this threshold ($P < 0.005$). With a combination of an ammonia concentration greater than 100 μmol/L and a MELD score greater than 32, 3 of 26 (12%) patients without either criterion developed severe HE versus 15 of 39 (38%) with 1 and 14 of 17 (82%) with both ($P < 0.0001$). The use of either an ammonia concentration greater than 100 or a MELD score greater than 32 had higher sensitivity than either criterion alone but lower specificity and accuracy. A combination of an ammonia concentration greater than 100 and a MELD score greater than 32 had higher specificity and accuracy but lower sensitivity (shown later in Table 6). ROC curves are shown in Figure 3; AUROC for MELD plus ammonia was 0.834 (0.744-0.923). Hanley and McNeil comparisons of AUROC between criteria showed the following: ammonia versus MELD, $P = 0.72$; ammonia versus MELD plus ammonia, $P = 0.13$; and MELD versus MELD plus ammonia, $P < 0.05$.

Arterial Ammonia and Risk Factors for the Development of ICH. Forty-eight (29%) group 1 patients developed signs of ICH at a median of 2 (1-4) days after admission: 18 of 73 (25%) nonacetaminophen patients and 30 of 92 (33%) acetaminophen patients (Table 4). Thirty-five (64%) of 55 patients with ICP monitors showed evidence of ICH. The median peak ICP in those classified as having ICH was 36 mm Hg (30-42) versus 17 (13-22) in those who were not ($P < 0.00001$). Thirteen

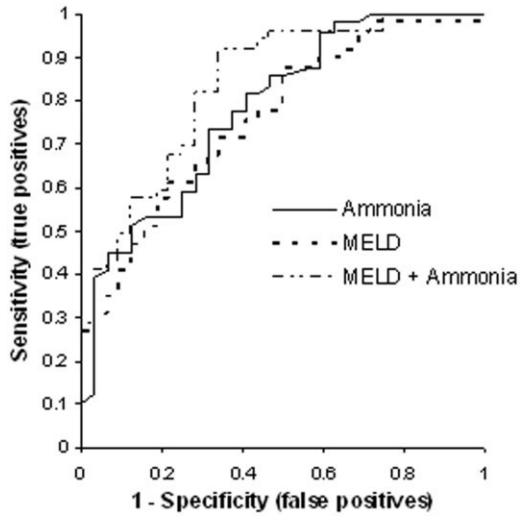

Fig. 3. ROC curves for MELD, admission ammonia, and admission ammonia plus MELD. The areas under the curves are as follows: ammonia, 0.785 (95% CI: 0.654-0.885); MELD, 0.764 (0.661-0.866); and MELD plus ammonia, 0.834 (0.744-0.923).

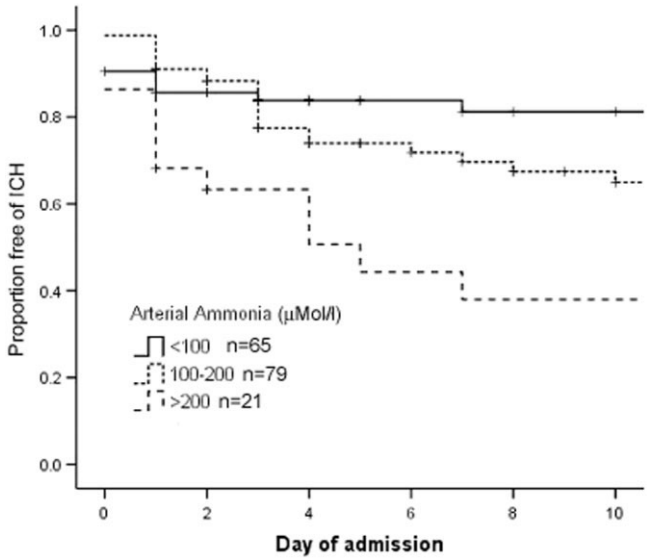

Fig. 4. Kaplan-Meier plot of ICH in 165 patients with ALF according to the arterial ammonia concentration on admission. For the log-rank test, $P < 0.01$.

patients were classified as having ICH without ICP monitoring; all had pupillary abnormalities and also received bolus therapy with mannitol, hypertonic saline, or indomethacin alone or in combination.

Arterial ammonia on admission was significantly higher in those who developed ICH than in those who did not [(121 (91-198) versus 109 (67-151), $P < 0.05$]. ICH developed in 13 of 64 (20%) patients with an ammonia concentration of less than 100 μmol/L, in 23 of 79 (29%) with an ammonia concentration of 100-200 μmol/L, and in 12 of 22 (55%) with an ammonia concentration greater than 200 μmol/L ($P < 0.03$; Fig. 4).

Table 4. Admission Characteristics of 165 Patients from Group 1 with Respect to the Subsequent Development of ICH

	ICH	No ICH	P
Number	48	117	
Age	35 (26-45)	39 (29-51)	<0.05
Sex (female/male)	34/14	68/49	0.13
Acetaminophen etiology	30 (63%)	62 (53%)	0.26
Ammonia	121 (92-198)	109 (69-151)	<0.05
INR	3.6 (2.7-7.4)	3.7 (2.4-5.6)	0.22
Lactate (mmol/L)	3.9 (2.8-7.3)	3.7 (2.4-6.7)	0.34
Bilirubin (μmol/L)	74 (47-215)	105 (60-250)	0.11
pH	7.33 (7.24-7.39)	7.36 (7.29-7.4)	0.03
HCO_3 (mmol/L)	20 (16-23)	21 (19-23)	0.09
Sodium (mmol/L)	136 (132-140)	137 (134-142)	0.08
Creatinine (μmol/L)	150 (104-200)	162 (104-246)	0.53
Urine output (mL/24 hours)	55 (0-425)	400 (0-1195)	0.02
MELD	35.1 (31.2-40.1)	34.2 (28.7-39.9)	0.56
SIRS present*	37 (80%)	85 (73%)	0.34
SIRS components	2 (2-3)	2 (1-3)	0.87
Vasopressors	24 (50%)	38 (33%)	0.03
CVVHF	41 (85%)	71 (61%)	<0.01

NOTE. The data are medians (interquartile range) or n values (%).
*n = 162 (46 with ICH and 116 without ICH).

Four variables were significant in the univariate Cox regression analysis: age, arterial ammonia, and INR on admission and a requirement for vasopressors and CVVHF (Table 5). On multivariate analysis, the risk for ICH was independently associated with a higher ammonia concentration and a requirement for vasopressors [adjusted hazard ratio, 2.02 (1.07-3.8); CVVHF hazard ratio, 3.33 (1.36-8.13); and hazard ratio for a young age (<45 years), 2.2 (0.99-4.8); Table 5].

AUROC for ammonia with respect to ICH was barely significant [0.598 (0.499-0.697), $P = 0.048$]; the identification of an optimal threshold value for the prediction of ICH was not possible. Values with a diagnostic accuracy greater than 50% had acceptable specificity but low sensitivity (Table 6). A threshold value of greater than 200 μmol/L had specificity of 92% (95% CI: 88-95) but sensitivity of 25% (17-33), failing to identify 36 of 48 (75%) patients who developed ICH.

Ninety-one patients from group 1 had further measurement of arterial ammonia performed at a median of 2 (1-3) days after admission. The median ammonia concentration was 135 mmol/L (91-178) at the first measurement and 104 (69-137) at the second. In the 69 patients who remained free of ICH, ammonia showed a significant reduction between measurements [133 (89-171) to 102 (71-135), $P < 0.0002$], and in the 22 (24%) patients who developed ICH, there was no significant change [142 (102-204) to 119 (64-178), $P < 0.15$].

Table 5. Univariate and Multivariate Analyses of Variables Associated with the Development of ICH in 165 Patients from Group 1

	Univariate			Multivariate		
Variable	HR	95% CI	*P*	HR	95% CI	*P*
Age	0.97	0.97–0.99	0.02	0.97	0.949–0.997	<0.04
Female sex	1.65	0.88–3.09	0.12			
Acetaminophen etiology	1.27	0.70–2.29	0.43			
Ammonia (μmol/L)	1.01	1.01–1.01	0.02	1.01	1.001–1.009	<0.03
INR	1.08	1.01–1.17	0.04			
Lactate (mmol/L)	1.05	0.98–1.11	0.20			
Bilirubin (μmol/L)	1.00	0.99–1.01	0.81			
pH	0.03	0.01–0.49	0.01			
HCO_3 (mmol/L)	0.91	0.85–0.98	0.01			
Sodium (mmol/L)	1.04	0.99–1.08	0.09			
Creatinine (μmol/L)	0.99	0.99–1.01	0.51			
Urine output (mL/24 hours)	1.00	0.99–1.00	0.05			
MELD	1.01	0.97–1.05	0.54			
SIRS components	1.00	0.73–1.38	0.99			
Vasopressors	2.18	1.23–3.88	<0.01	2.02	1.066–3.816	0.03
CVVHF	3.29	1.47–7.36	<0.01	3.33	1.363–8.131	<0.01

NOTE. HR, hazard ratio (95% confidence intervals).

Discussion

We found that in a large cohort of patients with evolving or established ALF, arterial ammonia concentrations in whole blood on admission to the intensive care unit were related to major cerebral complications. The ammonia concentration was an independent risk factor for the development of both encephalopathy and ICH. However, we could not confirm the value of 150 μmol/L as predictive of CH as shown in Clemmesen et al.'s study.[2] Although the risk of ICH was clearly increased in patients with an ammonia concentration greater than 200 μmol/L, this threshold failed to identify the majority of those who developed this complication. Factors other than the ammonia concentration appear important in its pathogenesis.

Ammonia was measured in whole blood and with a microdiffusion technique, without parallel measurements using enzymatic methods, and thus it is not possible to comment on the precision of the measurement with respect to other techniques. Both approaches have problems inherent in their use, although there is good agreement between the 2 methods and both are widely used.[19-21] The concentrations that we observed were closely comparable to those of studies using both methods, calculated whole blood levels, and those of patients with both ALF and CLD.[2,3,9,22]

In patients with established ALF, we found no relation between arterial ammonia measured on admission to the intensive care unit and survival, and this finding was in contrast to that of the recent report of Bhatia et al.[3] However, ICH occurred in only a minority of our patients, and MOF, not CH, was the leading cause of death. Unlike Bhatia et al.'s study, all our ALF patients had severe HE and were treated in a unit in which emergency LT was available, and over a third of our patients underwent transplantation. The full natural history of the condition as seen in nontransplant units was thus not observed, and the period during which patients were at risk of ICH was likely shorter. It may also be that the therapeutic strategies employed for our patients were successful in reducing the incidence of ICH.

Ammonia, MELD, and Risk of Severe Encephalopathy. The ammonia concentration on admission was strongly and independently predictive of the development of severe HE requiring intubation and ventilation. This observation and those of other recent studies of ALF and CLD confirm a close relation between the initial ammonia concentration and the severity of HE and provide further supportive evidence for the role of ammonia in its pathogenesis.[3,8,22] High MELD scores were also independently predictive of severe HE, although the severity of illness in our patients was such that few had scores below the recently proposed threshold score of 18.[15] The independent prognostic values of both the ammonia level and MELD suggest that a combined score may be clinically useful in assessing the risk of HE progression.

Ammonia and Risk of ICH. The relation between the ammonia concentration and ICH appears more complex. Although a high ammonia concentration was an independent risk factor for the development of ICH, particularly if sustained, its predictive accuracy was limited and was specific only at concentrations greater than 200 μmol/L. The majority of patients who developed ICH did so with admission and subsequent ammonia concen-

Table 6. Test Performance of the Ammonia Concentration and MELD Score Thresholds in the Prediction of Subsequent Encephalopathy and ICH

	x/n	N	Sensitivity	Specificity	Accuracy	LRP	LRN
Severe encephalopathy							
Ammonia (μmol/L)							
>100	30/82	19	59 (46-70)	78 (69-85)	70 (60-79)	2.6	0.5
MELD							
>18	76/82	32	100 (93-100)	12 (8-12)	46 (41-46)	1.1	0
>32	42/82	23	74 (61-85)	62 (54-69)	67 (56-75)	2.0	0.4
Combined							
>100 and MELD > 32	17/82	14	44 (35-50)	94 (87-98)	74 (66-79)	7.3	0.6
>100 or MELD > 32	56/82	29	91 (79-970	46 (39-50)	63 (54-68)	1.7	0.2
ICH							
Ammonia (μmol/L)							
>100	100/165	35	73 (61-83)	44 (40-48)	53 (46-58)	1.3	0.6
>150	49/165	19	40 (29-51)	74 (70-79)	64 (58-71)	1.5	0.8
>200	22/165	12	25 (17-33)	92 (88-95)	72 (67-77)	2.9	0.8

NOTE. 95% CIs are given in parentheses. LRN indicates likelihood ratio negative; LRP, likelihood ratio positive; N, number of patients fulfilling the criterion who developed the complication; and x/n, number of patients fulfilling the criterion/number of patients included in the analysis.

trations below this level. In their original study, Clemmensen et al.[2] reported that a cutoff value of greater than 150 μmol/L predicted CH, which occurred in more than 70% of patients above this threshold. All patients below this level remained free of CH. This report and most other studies have found only small differences and/or considerable overlap in the concentrations of those patients with ALF who did or did not develop ICH.[3,10,11] Ammonia determination should thus form only 1 component of the overall assessment of risk of ICH in patients with ALF. Our data suggest that this assessment should also take into account other factors.

We found that ICH was associated with a requirement for both CVVHF and vasopressors. Rather than causative effects, these associations may reflect the indications for the use of these supportive therapies. Both were required as a result of the development of extrahepatic organ failures: vasopressors for hypotension complicating systemic cardiovascular dysfunction and CVVHF after the development of renal failure or acidemia. This parallel development of extrahepatic organ failures with ICH supports observations that cerebral complications may arise as part of a systemic process.[11,23,24] In ALF as in other critical illness, MOF is associated with high circulating levels of proinflammatory cytokines and other modulators of vascular function;[25-27] the effects of these agents on cerebral endothelial and vascular function could be important factors in the pathogenesis of ICH.[5,28,29]

The observation of an increased incidence of ICH in the young was reported in the original description of this complication.[30] Although we confirmed this observation, we found no association between age and the development of HE. One explanation for these findings might be related to the changes in intracranial anatomy that occur with increasing age. Adulthood is associated with a progressive reduction in cerebral volume and a proportional increase in cerebrospinal fluid, even at a relatively young age.[31,32] As an acute reduction in cerebrospinal fluid volume is a protective homeostatic mechanism used to adapt to pathologic increases in ICP, in the young, the ability to compensate for increases in cerebral volume as a result of CE may be lower.[33] The risks of encephalopathy and CE may not be affected by age, but youth may confer susceptibility to the consequences of brain swelling with the development of ICH.

In conclusion, a number of pharmacological and nonpharmacological therapies are now available that may be employed to reduce circulating levels of ammonia.[5,34,35] Our data suggest that specific patient groups at high risk of HE and ICH might benefit from these therapies.

In patients admitted with acute hepatic dysfunction and sustained high levels of arterial ammonia (>100 μmol/L) and high MELD scores but without encephalopathy, progression to severe HE might be interrupted.

For those with established ALF and severe HE, the risk of ICH appears greatest in those with ammonia levels of greater than 200 μmol/L or with sustained high levels below this threshold. These patients might be appropriate targets for ammonia-reducing therapies and ICP monitoring. Younger patients and those with lower levels of ammonia but with concurrent renal dysfunction and a requirement for vasopressors appear to be at increased risk of ICH and may be additional groups to benefit from monitoring.

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