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What every Intensivist should know about the role of ammonia in liver failure

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ABSTRACT

Purpose: Acute liver failure (ALF) or acute-on-chronic liver failure (ACLF) patients have high short-term mortality and morbidity. In the context of liver failure, increased serum ammonia is associated with worse neurological outcomes, including high-grade hepatic encephalopathy (HE), cerebral edema, and intracranial hypertension. Besides its neurotoxicity, hyperammonemia may contribute to immune dysfunction and the risk of infection, a frequent trigger for multi-organ failure in these patients.
Material and methods: We performed a literature-based narrative review. Publications available in PubMed® up to June 2023 were considered.
Results: In the ICU management of liver failure patients, serum ammonia may play an important role. Accordingly, in this review, we focus on recent insights about ammonia metabolism, serum ammonia measurement strategies, hyperammonemia prognostic value, and ammonia-targeted therapeutic strategies.
Conclusions: Serum ammonia may have prognostic value in liver failure. Effective ammonia targeted therapeutic strategies are available, such as laxatives, rifaximin, L-ornithine-L-aspartate, and continuous renal replacement therapy.

1. Why serum ammonia increases with liver failure?

The liver is paramount for ammonia metabolism during balanced homeostasis (Fig. 1A). Ammonia (NH_4^+/NH_3) reaches the liver mainly through the portal vein, 50% from endogenous glutamine conversion in the enterocytes and 50% from the gut lumen, by degradation of nitrogen substrates from diet or bacteria [1]. In the hepatocytes, ammonia is converted to urea or glutamine. Other organs such as the brain, the kidneys, and the muscle also participate in the ammonia metabolism. The kidneys not only produce, from endogenous glutamine, but also excrete ammonia in the urine [1].

With liver failure, the loss of viable hepatocytes leads to impaired metabolism of ammonia. Therefore, these patients often develop hyperammonemia.

2. How increased serum ammonia affects liver failure patients?

Hyperammonemia is a fundamental driver of hepatic encephalopathy (HE) [1]. Its accumulation in the astrocytes, among other molecules, may lead to cerebral edema, intracranial hypertension, and brain stem herniation (Fig. 1B) [2]. Besides its neurotoxicity, hyperammonemia may contribute to immune dysfunction and infection, a common trigger of multi-organ dysfunction in these patients [3].

3. Which differences in the ammonia metabolism are there between acute liver failure and acute-on-chronic liver failure patients?

Liver cell death is often greater and faster in acute liver failure (ALF) than in acute-on-chronic liver failure (ACLF). Therefore, serum ammonia frequently reaches higher levels in ALF than in ACLF (Table 1).

Abbreviations: ACLF, acute-on-chronic liver failure; ALF, acute liver failure; CRRT, continuous renal replacement therapy; IHD, intermittent hemodialysis; HE, hepatic encephalopathy; LOLA, L-ornithine-L-aspartate.

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Brain osmotic compensatory mechanisms are more evolved in ACLF than ALF patients [4]. Kidney dysfunction, both common in ALF and ACLF, and sarcopenia, more common in ACLF than ALF, also contribute to hyperammonemia.

4. What is the diagnostic and prognostic value of serum ammonia in liver failure patients?

In ALF patients, hyperammonemia (arterial ammonia levels >150 μmol/l) has been associated with an increased risk of major cerebral complications, including HE, cerebral edema, intracranial hypertension, and mortality [2]. In ACLF patients, while the risk of cerebral edema is

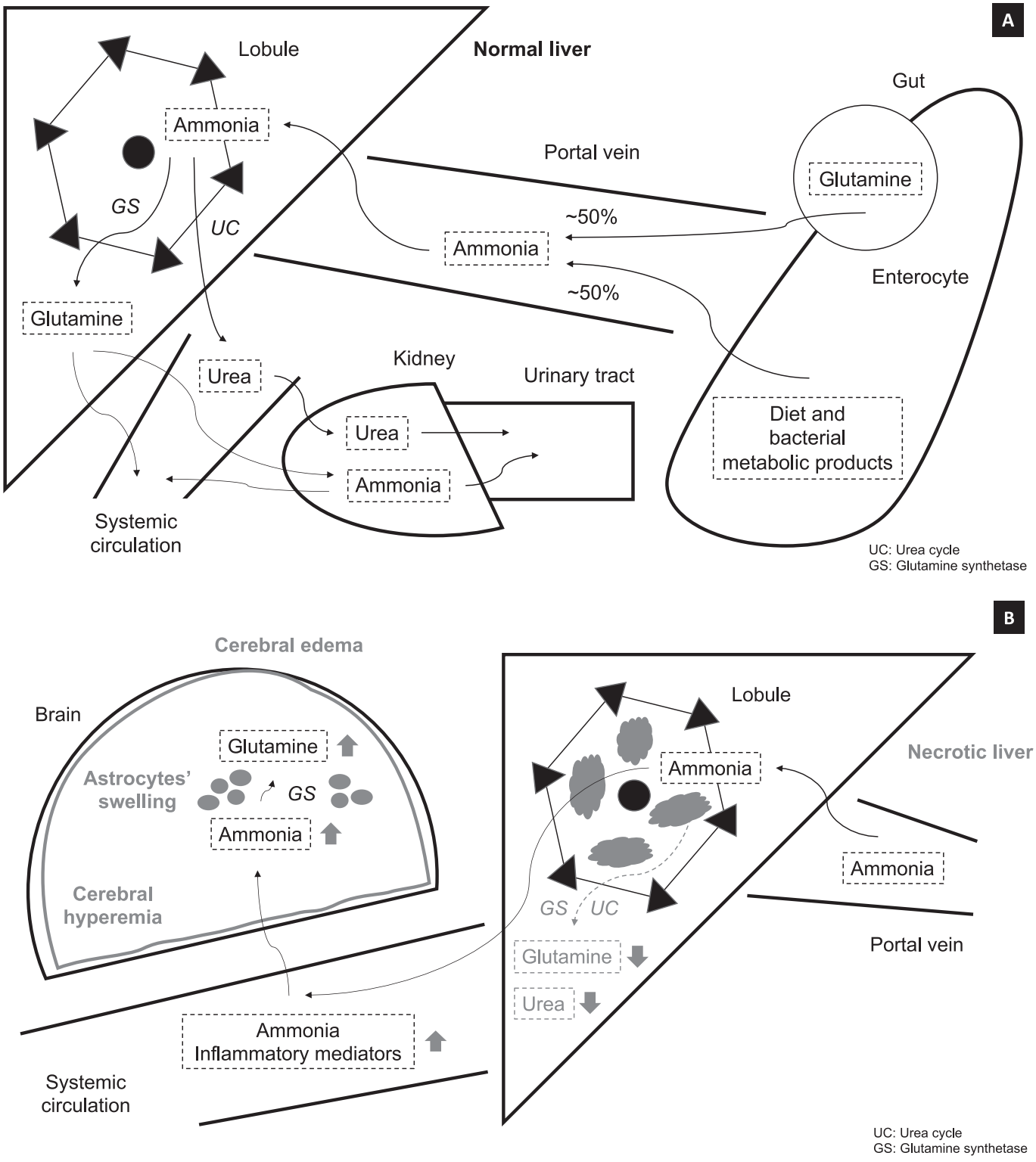

Fig. 1. Overview of interorgan ammonia metabolism. *Panel A: ammonia metabolism under normal homeostasis. Panel B: ammonia metabolism following liver necrosis and the pathway to cerebral edema.*

Table 1
Schematic differences among patients with acute liver failure and acute-on-chronic liver failure.

	Acute liver failure	Acute-on-chronic liver failure
Average patient characteristics[#]		
Age (years)	40–45	55–60
Comorbidities	Uncommon	Common
Cirrhosis	No	Yes
Portal hypertension	None or uncommon	Common
Serum ammonia	High	High or moderate
Cerebral edema	Uncommon	Uncommon
Intracranial hypertension	Uncommon	No
Kidney dysfunction	Common	Common
Sarcopenia	Uncommon	Common
Liver transplant	25–50%	<25%
Hospital mortality	20–40%	40–60%
Therapeutic strategies effectiveness at reducing serum ammonia		
Lactulose, lactitol, or polyethylene glycol	Unclear	Effective*
Rifaximin	Unclear	Effective*
L-ornithine-L-aspartate	Unclear	Effective*
L-ornithine-*L*-phenylacetate	Unclear	Unclear
Renal replacement therapy	Effective**	Unclear
Liver support dialysis	Unclear	Unclear
Plasma exchange	Effective*	Unclear

[#] While this review considers average patients with liver failure as those in typical western countries (North America, Europe, and Australasia), epidemiology may be different in other regions.
[*] Evidence from clinical trials.
[**] Evidence from multicenter observational studies.

lower than in ALF patients, hyperammonemia has been associated with increased risk of extra hepatic organ failures and mortality [3].

5. How should we measure serum ammonia in the intensive care unit?

Serum ammonia levels may vary with protein intake, brain and muscle (sarcopenia), uptake, kidney dysfunction, infection, or gastrointestinal bleeding.

Arterial ammonia better reflects acute changes in nitrogen metabolism than venous ammonia [1]. The upper limit of normal of serum ammonia levels ranges frequently from 50 to 70 μmol/l. Fresh blood samples are preferred to frozen ones [5]. Serial arterial ammonia measurements may be more informative than time-specific single determinations [6]. Normal serum ammonia levels have shown high negative predictive value for HE [1].

6. Which therapeutic strategies are there to modulate serum ammonia?

1. Laxatives

Nonabsorbable disaccharides (eg. lactulose and lactilol) remain the first line options for HE treatment and prevention in cirrhosis patients [7]. Their therapeutic effect in ALF patients remains unclear.

Lactulose mechanisms of action are multiple: (1) colonic acidification promoting the conversion of NH_3 to non-absorbable NH_4^+; (2) inhibition of ammoniagenic bacteria growth; (3) inhibition of intestinal glutamine absorption; and (4) reduction of ammonia absorption time and increase in fecal nitrogen excretion [7]. Other laxatives (eg. polyethylene glycol) have also improved HE [7].

2. Rifaximin

Rifaximin is a nonabsorbable gut-selective oral antibiotic recommended as an adjunct HE treatment in cirrhosis patients [8]. Its mechanisms of action are several: (1) suppression of gut microbiome oralisation and mucin-degrading bacteria; (2) promotion of augmented responses to pathobionts and gut barrier repair; and (3) reduction of serum proinflammatory cytokine levels and infection [8].

3. Metabolic scavengers

L-ornithine-L-aspartate (LOLA) may reduce serum ammonia by promoting conversion of ammonia to urea in the liver. Additionally, ammonia may be further converted to glutamine in the liver or the skeletal muscle. LOLA may be safe and effective in HE treatment and prevention in cirrhosis patients [9]. However, LOLA did not seem to improve serum ammonia or HE in ALF patients.

L-ornithine-*L*-phenylacetate may reduce serum ammonia by promoting its renal excretion as phenylacetylglutamine [9]. Although its safety profile has been tested both in cirrhosis and ALF patients, its effect on HE remains unclear.

4. Extracorporeal circulation

Ammonia is a small (17 Da) water-soluble molecule with a low volume of distribution and minimal protein binding [4]. Although ammonia resembles urea structurally, its dialysis clearance is 30–50% of urea's [4].

5. Renal replacement therapy

During intermittent hemodialysis (IHD), higher blood flow and dialysate rates and dialyzer surface were associated with higher ammonia, glutamine, and urea clearance [4]. In ALF patients on continuous renal replacement therapy (CRRT), higher effluent flow rate and greater cumulative dose were associated with higher ammonia clearance [10]. There was no difference in ammonia clearance between different CRRT modalities [11]. Adsorptive filters, such as Cytosorb® or Oxiris®, have not led to effective ammonia clearance [12].

Overall, CRRT results in greater ammonia clearance than IHD since it is deployed for 24-h periods. In ALF patients, while CRRT has shown to be associated with better survival, IHD has been associated with worse survival [6]. Potentially, IHD may lead more often to hemodynamic derangements [13].

While CRRT initiated early and extended for longer time may be a useful adjunctive hyperammonemia treatment in ALF patients, that remains unclear in ACLF patients [6,10,11].

6. Liver support dialysis

Among several liver support dialysis devices developed, Prometheus® (fractioned plasma plus adsorption) and MARS® (albumin dialysis plus adsorption) have been the most studied. However, their impact on ALF and ACLF patients' outcomes remains unclear [14]. While Prometheus® has shown higher urea clearance than MARS®, that was not as significant for ammonia [14].

7. Plasma exchange

Plasma exchange in ALF patients, whether with high (8-12 l) or standard (1.5–2 times the plasma volume) volumes, has decreased serum ammonia levels at least as efficiently as CRRT [15]. Potential similar data for ACLF patients is lacking.

7. Practice implications and future directions

In liver failure patients, especially in those sedated, serum ammonia monitoring may anticipate the risk of brain complications. The use of laxatives or rifaximin may be hindered by ileus. Thus, CRRT constitutes

a safe and effective strategy for hyperammonemia control, especially in ALF patients [6,11,12].

Future studies, both in ALF and ACLF patients, could explore hyperammonemia as an independent indication for CRRT initiation. Moreover, novel treatments with serum ammonia lowering potential, such as fecal microbiota transplantation, still require further validation.

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Tiago Duarte: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. **Pedro Fidalgo:** Conceptualization, Investigation, Writing – original draft, Writing – review & editing. **Constantine J. Karvellas:** Writing – review & editing. **Filipe S. Cardoso:** Conceptualization, Investigation, Writing – original draft, Writing – review & editing.

Declarations of interest

None.

References

[1] Wright G, Noiret L, Olde Damink SW, Jalan R. Interorgan ammonia metabolism in liver failure: the basis of current and future therapies. Liver Int 2011;31(2):163–75.
[2] Bernal W, Hall C, Karvellas CJ, Auzinger G, Elizabeth Sizer, Wendon J. Arterial ammonia and clinical risk factors for encephalopathy and intracranial hypertension in acute liver failure. Hepatology 2007;46:1844–52.
[3] Cardoso FS, Kim M, Pereira R, Bagulho L, Fidalgo P, Pawlowski A, et al. Early serum ammonia variation in critically ill patients with cirrhosis: a multicentre cohort study. Aliment Pharmacol Ther 2023. https://doi.org/10.1111/apt.17650. Epub ahead of print. PMID: 37470277.
[4] Naorungroj T, Yanase F, Eastwood GM, Baldwin I, Bellomo R. Extracorporeal ammonia clearance for hyperammonemia in critically ill patients: a scoping review. Blood Purif 2021;50(4–5):453–61.
[5] Bajaj JS, Bloom PP, Chung RT, Hassanein TI, Padilla-Martinez M, Kayali Z, et al. Variability and lability of ammonia levels in healthy volunteers and patients with cirrhosis: implications for trial design and clinical practice. Am J Gastroenterol 2020;115(5):783–5.
[6] Cardoso FS, Gottfried M, Tujios S, Olson JC, Karvellas CJ, US Acute Liver Failure Study Group. Continuous renal replacement therapy is associated with reduced serum ammonia levels and mortality in acute liver failure. Hepatology 2018;67(2):711–20.
[7] Rahimi RS, Singal AG, Cuthbert JA, Rockey DC. Lactulose vs polyethylene glycol 3350–electrolyte solution for treatment of overt hepatic encephalopathy: the HELP randomized clinical trial. JAMA Intern Med 2014;174(11):1727–33.
[8] Patel VC, Lee S, McPhail MJW, Da Silva K, Guilly S, Zamalloa A, et al. Rifaximin-α reduces gut-derived inflammation and mucin degradation in cirrhosis and encephalopathy: RIFSYS randomised controlled trial. J Hepatol 2022;76(2):332–42.
[9] Butterworth RF. Ammonia removal by metabolic scavengers for the prevention and treatment of hepatic encephalopathy in cirrhosis. Drugs R D 2021;21(2):123–32.
[10] Warrillow S, Fisher C, Bellomo R. Correction and control of Hyperammonemia in acute liver failure: the impact of continuous renal replacement timing, intensity, and duration. Crit Care Med 2020;48(2):218–24.
[11] Fisher C, Baldwin I, Fealy N, Naorungroj T, Bellomo R. Ammonia clearance with different continuous renal replacement therapy techniques in patients with liver failure. Blood Purif 2022;51(10):840–6.
[12] Liebchen U, Paal M, Gräfe C, Zoller M, Scharf C, Cyto-SOLVE Study Group. The cytokine adsorber Cytosorb® does not reduce ammonia concentrations in critically ill patients with liver failure. Intensive Care Med 2023;49(3):360–2.
[13] Davenport A, Will EJ, Davidson AM. Improved cardiovascular stability during continuous modes of renal replacement therapy in critically ill patients with acute hepatic and renal failure. Crit Care Med 1993;21(3):328–38.
[14] Krisper P, Haditsch B, Stauber R, Jung A, Stadlbauer V, Trauner M, et al. In vivo quantification of liver dialysis: comparison of albumin dialysis and fractionated plasma separation. J Hepatol 2005;43(3):451–7.
[15] Larsen FS, Schmidt LE, Bernsmeier C, Rasmussen A, Isoniemi H, Patel VC, et al. High-volume plasma exchange in patients with acute liver failure: an open randomised controlled trial. J Hepatol 2016;64(1):69–78.