Undifferentiated Hyperammonemia Cheat Sheet

Work up and initial management of refractory and/or unexplained (non- Liver Failure) Hyperammonemia:

Please confirm NH3 elevation is real with a repeat test on ice/cold water sent immediately to the lab.

R/o Liver disease if not done – LFT, INR, Factor V, VII & VIII, RUQ Ultrasound/CT

- If significant Transaminitis (>1000) is noted – Call Hepatology for ALF consult, check acute hepatitis panel, acetaminophen level and HSV PCR. (This is a Liver emergency)
- When there is disproportionate hyperammonemia to transaminitis in ALF, consider the possibility of heat stroke with rhabdomyolysis, mitochondrial toxin or microvescicular steatosis (Hypoglycin- Ackee fruit, fatty liver of pregnancy, Reye syndrome)
- If known diagnosis of Cirrhosis or suspected diagnosis but with disproportionately elevated NH3, aspects of work up and management below may be applicable. Disproportionately elevated NH3 in cirrhosis occurs in concomitant renal failure, cachexia, large portosystemic shunts, GI bleed, NASH, infection or bowel ischemia.

If no clear evidence of Cirrhosis or ALF :
Obtain history

- Hx of toxindrome? – Valproate therapy/ overdose, Salicylate, Ackee fruit ingestion, ASA in a child, overlapping Alcohol intake, OTC supplement, Chemotherapeutic agents, Topamax, Organic acids intoxication i.e. Ethylene Glycol, Methanol
- Hx of weight loss causing catabolism or risk of bacterial overgrowth? – Post Roux-en-y gastric bypass (RYGB) (usually a few years post RYGB), short gut, malnutrition, recent pregnancy, malignancy (especially multiple myeloma) *Steatosis on CT scan may be due to starvation and not necessarily MAFLD/MASH
- Is the patient pregnant → Acute fatty liver of pregnancy
- Hx of aversion to meat with a family history of early death from unexplained coma or elevated NH3 (Inborn Errors of Metabolism)
- Hx of fever and chills, ongoing infections or immunosuppression/transplant
- Hx of muscle rigorous muscle activity or muscle breakdown – prolonged seizure, myoclonus i.e. serotonin syndrome, heat stroke, rhabdomyolysis
- Hx of recent cardiac arrest - After cardiac arrest, ATP depletion drives ADP→AMP buffering; excess AMP is deaminated to IMP, releasing ammonia, while hepatic ATP failure limits urea-cycle clearance making hyperammonemia a marker of global ischemic energy collapse. Usually peaks hours after ROSC and rapidly if liver function is preserved.
- Hx of bowel/mesenteric ischemia – i.e. unexplained abdominal pain, aortic dissection/repair, mesenteric/acute portal vein thrombosis, cocaine induced vasospasm of bowel, ECMO (watershed/mixing zone ischemia).

See More detailed mechanisms for hyperammonemia in Appendix Table 1

Consider the following tests to evaluate and monitor NH3:

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1. Serial Plasma NH3 Q6 hours

2. Basic Micronutrients: Whole blood Thiamine Level, Plasma B6 level, Free and Total Carnitine Level.

3. If hx of RYGB or Short gut or Severe Malnutrition suspected, see Appendix 1 for extended/ comprehensive micronutrient laboratory. Also refer to separate cheat sheet tailored to management of **Malnutrition Associated Hyperammonemia**

5. TSH, Free T4

6. Comprehensive urine drug screen, Blood salicylate level,

7. Evaluate for Possible Renal or intrabdominal abscess 2/2 to urea splitting organism that produces ammonia (i.e. Proteus) by producing the Urease. Obtain **Blood and U/A with urine culture** + Imaging if abscess suspected.

8. If immune suppressed (especially if transplant patient) – Infections by atypical Urease or Arginine Deaminanse producing organisms should be considered.
   i. Check Blood culture - Consider broad spectrum antibiotics Urease Producers → i.e. *Proteus, Some Klebsiella, Nocardia, S. Saprophyticus, S. Epidermidis.*
   ii. Check Serum Cryptococcal antigen -Disseminated *Cryptococcus Neoformans or Gattii* and renal failure is associated with hyperammonemia.
   iii. **Ureaplasma/Mycoplasma PCR** in Urine and BAL (ARUP Labs) and Blood (Mayo Clinic Test ID **URBRP**). Ensure it is PCR. Ureaplasma culture has a low yield. Ureaplasma/Mycoplasma will not show up on routine blood cultures due to absence of a cell wall. Ureaplasma produces Urease while Mycoplasma produces Arginine Deaminase. Both cause hyperammonemia. If suspicion is high and on immunosuppression or post solid organ transplant with unexplained hyperammonemia, start IV **Doxycycline +/- IV Azithromycin**. If response is suboptimal, may consider adding or swapping Azithromycin for **IV Levaquin** due possibility of antimicrobial resistance in Ureaplasma.
   *Acquired Glutamine Synthase Deficiency has been reported in post lung transplant patients however there is no easy way test for this deficiency without a liver biopsy and a specialized center to process it. Treatment remains supportive.

9. Consider MRI/MRA Abdomen with and without GAD to evaluate for spontaneous portosystemic shunts and liver malignancy if hemodynamically stable for travel. If known hematologic malignancy, perform portal vein and hepatic artery dopplers ultrasound for venoocclusive disease.

10. Obtain MRI brain with and without contrast (non contrast is also acceptable) to evaluate for hyperammonemic brain injury. This should ideally be done once NH3 is controlled.

11. Urea Cycle Disorder Work up :

- Plasma amino acid

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- Urine orotic acid
- Urine amino acids
- Urine organic acid
- Blood Acylcarnitine Profile

If urea cycle disorder suspected → call your regional pediatric hospital genetics/metabolic specialist who can help review amino acid/metabolic panel to determine if UCD genetic panel should be performed.

Management options for Hyperammonemia:

Goal of Management is to bring NH3 quickly down to < 150 µmol /L and eventually if possible to < 100 µmol/L

1) If uptrending NH3 >150 µmol/L, will need to initiate CRRT if not responsive to other medical management. Early initiation of CRRT is preferred. The later CRRT is initiated, the possibility of fluid shifts driven by and osmolar gap may be higher. Recommend adding hypertonic saline if exceeding standard dialysate flow rates (Total effluent rate > 20 ml/kg/hr). Some centers may preferentially use IHD over CRRT. Caution when IHD in obtunded patient or late in hyperammonemia due to dialysis disequilibrium syndrome. If IHD being used, consider higher sodium concentration in dialysate fluid which will raise serum sodium by 5meq/L from baseline by the end of IHD.

2) If NH3 >200mcmol/L or If the patient is a late presenter with evidence of brain edema from hyperammonemia or has a large osmolar gap (> 20) (presumably from Urea, Glutamine, Inflammatory mediators, Toxic alcohols), consider hypertonic saline 23.4 NACL 120 – 240 meq Q4hrs If running CRRT simultaneously. 3% continuous infusion for initial goal sodium 145-150meq/L is an easier alternative. Rate of 3% is dependent on dialytic dose and should be discussed with nephrology.
3) **Anticipate and Rx hypophosphatemia aggressively** when running CRRT at elevated effluent flow rates in an already malnourished patient. Rather than decreasing effluent flow rates before goal NH3, consider a continuous phosphate infusion or Q6 hour infusions. Check phosphate levels Q6 hours
4) Consider Rifaximin 550mg PO Q12 (Use especially in cirrhosis)
5) Consider Lactulose 30cc Q6hrs and titrate to 3 bowel movements(Use especially in cirrhosis**).** **Hold lactulose if ileus, abdominal distension, high dose vasopressors**. May consider using lactulose rectally if concerned about airway protection or small bowel distension. *No studies to support the use of Lactulose and Rifaximin outside of liver failure as enteral bacterial contribution to hyperammonemia is likely less significant. If used outside of liver failure, consider a short course if safe.

6) IV Metronidazole 250mg Q8hrs (7 day course) high suspicion for bacterial overgrowth (i.e blind loop /Roux Limb) Make sure there is a stop date as Metronidazole can cause CNS demyelination especially in liver and renal failure (Limit use to 7-10days). (especially in cirrhosis)
7) D20 Dextrose at 20cc/hr with insulin drip – to promote anabolism
8) Levocarnitine IV 500mg Q6 hours
9) Thiamine 100mg IV daily. If Wernickes suspected, use 500mg IV Q8 hours.
10) Biotin 5mg NG daily
11) Initiate IV B6 (pyridoxine) supplementation 100mg -200mg IV Q12
12) Sodium benzoate+ Sodium phenylacetate (Ammonul) infusion – requires adequate urine output with good renal clearance (Urine output > 3cc/kg/hr with Creat <2.0). Oral Buphenyl (Sodium Phenylbutyrate) is an alternate option in less severe undifferentiated hyperammonemia. Consult nutrition and metabolic/genetic team if using this. Requires pharmacy assistance for dosing. (Use especially if urea cycle disorder suspected)

13) Consider induced hypothermia to 34 -35C as a bridge to ammonia reduction especially in profound or refractory hyperammonemia. Cooling may slow down metabolic insult to the brain reduce NH3 production by slowing catabolism and slowing bacterial metabolism. Removing warmer on CRRT will quickly cool the patient. Use surface counter warming to prevent shivering as profound muscle activity can increase ammonia production. Rewarm once NH3< 150 and down trending*Disclamer : This recommendation for targeted temperature management is not supported by any strong evidence.

14) If in a catabolic state from malnutrition, use D10 or D20 infusion until the following is initiated :
    a. Parenteral Nutrition Approach : High calorie (carbohydrate and fat) and No protein (initially) parenteral nutrition (1.5X the daily weight based calorie requirement) is initiated. Only use low protein pre-dialytic tube feeds (i.e. Suplena) as trophic feed only. Only add protein to TPN once CRRT effluent flow rate has been weaned to reasonable level i.e. **25-30ml/kg/hour** and plasma NH3 remains ≤ 100µmol/L **.** Monitor NH3 more frequently initially (Q6Hours to Q8 hours) as protein is increased slowly in parenteral nutrition. If ammonia remains at acceptable levels <100µmol/L during increments in parenteral protein, consider suspending parenteral nutrition and advancing enteral nutrition. Once tolerating goal tube feeds without rebound in NH3 or the need for CRRT to control NH3, can consider increasing to higher protein tube feeds. May decrease frequency of plasma ammonia checks to Qday if no rebound in levels noted.
    b. Enteral Nutrition approach: Only use low protein pre-dialytic tube feeds (i.e. Suplena) initially as trophic feed only and run D20 at 20cc/hr or D10 at 40cc/hr infusion while monitoring electrolytes. Add insulin SSI or infusion if hyperglycemic. Increase tube feeds rate once CRRT effluent flow rate has been weaned to reasonable level i.e. **25-30ml/kg/hour** and plasma NH3 remains ≤ 100µmol/L **.** Monitor NH3 more frequently initially (Q8Hours to Q12 hours) as tube feeds are slowly increased to goal. One

tolerating goal tube feeds without rebound in NH3 or the need for CRRT to control NH3, can consider increasing to higher protein tube feeds. May decrease frequency of plasma ammonia checks to Qday if no rebound in levels noted.

***Emory Has a separate dedicated Parenteral macro and micronutrient protocol for severe malnutrition associated hyperammonemia. Contact Prem Kandiah premkandiah@emoryhealthcare.org or the Nutrition support Team for this protocol.**

15) If immunosuppressed (especially if transplant recipient) without a clear cause for hyperammonemia, start IV **Doxycycline +/- IV Azithromycin**. If suspicion for urease producing infection is high, start Acetohydroxamic acid (urease Inhibitor) if available at your institution. Dose of Acetohydroxamic Acid (Lithostat) is 250 mg, tablet, oral, (q6h or q8h frequency options) Patients with serum creatinine ≤1.8 mg/dL. 250 mg, tablet, oral, q12h for patients with serum creatinine >1.8 mg/dL to ≤2.5 mg/dL. Contraindicated in renal failure. Limit Acetohydroxamic acid to ≤ 5 days to minimize toxic effects (Marrow suppression). If Ureaplasma is confirmed by PCR and response to antibiotics is suboptimal, may consider adding or swapping Azithromycin for **IV Levaquin** due possibility of antimicrobial resistance in Ureaplasma.

16) If serum Cryptococcal antigen is positive or fungal elements on microscopy – initiate therapy with Amphotericin and Flucytosine**. (A subset of this information is repeated in diagnostic section intentionally to avoid oversight)**

There remain undiscovered causes for clinically significant hyperammonemia. If using our cheat sheet does not reveal a diagnosis, you may be dealing with one. Please feel free to give Dr. Kandiah a call/text for clarification on any part of this work up/ management or to discuss a case.

Please call with Questions:

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Appendix 1:

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Micronutrient Laboratory Testing for severe malnutrition in RYGB or Short gut.

Folic Acid (B9), Red Cell Folate
Cobalamin (B12), Methylmalonic acid (MMA)
Thiamine (B1) Level
Free and total carnitine levels
Pyridoxine (B6) level
Essential Fatty acid Panel (Serum) Mayo Clinic Test ID: FAPEP https://www.mayocliniclabs.com/test-catalog/overview/82426 Specimen: Red Top Tube
Ceruloplasmin Level
Serum Copper level
Selenium
Iron, TIBC Ferritin
Vit D
Vitamin A
Vitamin E
Vitamin C
Zinc

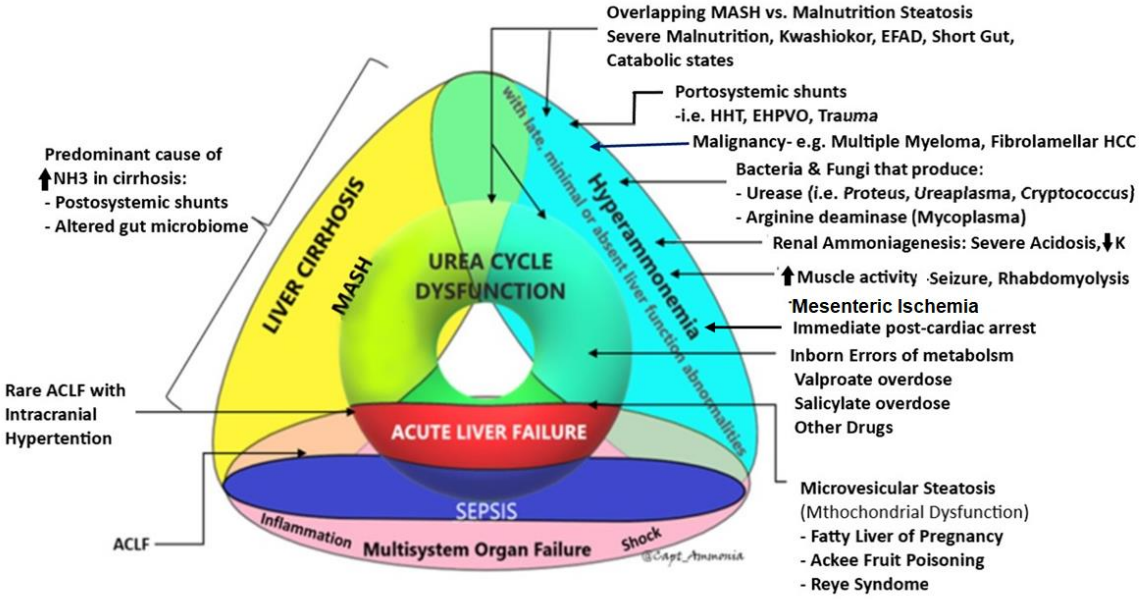
Appendix Table 1: Etiology and mechanism of hyperammonemia.

Etiology of Hyperammonemia	Pathophysiology
Transient/self limiting Hyperammonemia – Focus on underlying cause	
Ammonia drawn hours after cardiac arrest	After cardiac arrest, ATP depletion drives ADP→AMP buffering; excess AMP is deaminated to IMP, releasing ammonia, while hepatic ATP failure limits urea-cycle clearance making hyperammonemia a marker of global ischemic energy collapse. Usually peaks hours after ROSC and rapidly clears after ROSC if liver function is preserved. Correlates with outcomes in out of hospital cardiac arrest.
Bowel/mesenteric ischemia	In early gut ischemia, enterocyte ammonia production persists because glutaminase (GLS1) continues to deamidate glutamine without ATP, while ATP-dependent CPS1 fails, uncoupling ammonia generation from its consumption in citrulline synthesis. With progression to late ischemia, epithelial barrier collapse, functional porto-systemic shunting, lymphatic drainage, and hepatic ATP failure allow gut-derived ammonia to bypass first-pass detoxification and enter the systemic circulation. Consider in unexplained abdominal pain, aortic dissection/repair, mesenteric/acute portal vein thrombosis, cocaine induced vasospasm of bowel, ECMO (watershed/mixing zone ischemia).
Renal ammonia genesis	Acidosis and hypokalemia increase renal ammoniagenesis via glutamine metabolism and Rh transport to buffer acid; severe

	metabolic acidosis warrants evaluation for toxic alcohol ingestion (ethylene glycol, methanol).
Intense muscle activity, Seizure, rhabdomyolysis	Exercise-, seizure-, and rhabdomyolysis-related hyperammonemia reflects transient muscle AMP deamination and amino-acid catabolism with preserved hepatic clearance, rather than impaired ammonia detoxification. However, is Heat Shock, the overlap of rhabdomyolysis and shock liver can cause profound hyperammonemia.
Constipation and dehydration in elderly	In the elderly, constipation converts the colon into a high-ammonia bioreactor while age-related reductions in hepatic, renal and muscle clearance (sarcopenia) allow systemic accumulation.
Impaired Urea cycle function	
Post-bariatric surgery/ severe malnutrition associated hyperammonemia	Reversible urea cycle dysfunction secondary to severe macro and micronutrient deficiency, overlapping catabolism from severe weight loss and contribution from bacterial overgrowth. Most commonly occurring years after Roux-en-Y gastric bypass (RYGB). Often accompanied by malnutrition associated hepatosteatosis that is reversible with macro & micro-nutrient replacement (distinct from MAFLD).
Toxidrome	Functional urea-cycle inhibition due to mitochondrial toxicity, N-acetylglutamate depletion, or direct suppression of CPS1/OTC, most commonly triggered by valproate, salicylates, topiramate, alcohol, chemotherapeutic(5-FU, Oxplatin, Asparaginase) agents, or hypoglycin-containing toxins such as Ackee fruit poisoning. Dihydropyridine dehydrogenase (DPD) deficiency increase risk of hyperammonemia in 5-FU therapy.
Inborn Errors of Metabolism	Most common undiagnosed adult-onset urea cycle disorder is OTC deficiency.
Acute Fatty Liver of Pregnancy	Mitochondrial disfunction Presents as acute liver failure however hyperammonemia can be pronounced and precede other liver function abnormalities.
Shunting	
Large portosystemic shunt	Congenital, traumatic, parasitic, or iatrogenic extrahepatic portosystemic shunts (including EHPVO, HHT-related AVMs, trauma, schistosomiasis, and surgical or spontaneous shunts) cause hyperammonemia by bypassing hepatic first-pass ammonia detoxification despite intact liver function.
Malignancy	
Malignancy	Most notorious: Multiple Myeloma and Fibrolamellar HCC Arises either from excessive ammonia production by metabolically active tumors (e.g., multiple myeloma) or from functional urea-cycle disruption within tumor-altered liver tissue (e.g., fibrolamellar HCC).

Infection	
Bacteria (blood/fluid culture positive)	Urease Producing Bacteria: Proteus mirabilis, Morganella morganii, Pseudomonas aeruginosa, Klebsiella pneumoniae, Corynebacterium spp. Image for abscess if source unclear.
Bacteria (blood/fluid culture negative) Mollicutes	Urease producing: Ureaplasma Urelyticum / Parvum (Post Lung Transplant & immunocompromised), Arginine Deiminase Producing Organism -*Mycoplasma* pneumoniae infection Requires PCR for detection in urine, BAL, Blood or Joint fluid.
Bacteria - Acid Fast Bacilli. Slow growing in culture	*Mycobacterium genavense (Immunocompromised patients)* *May require 16s Ribosomal testing/NGS* *Mechanism of hyperammonemia remains unclear*
Fungus	Cryptococcus Neoformans/Gatii

Etiology of Hyperammonemia



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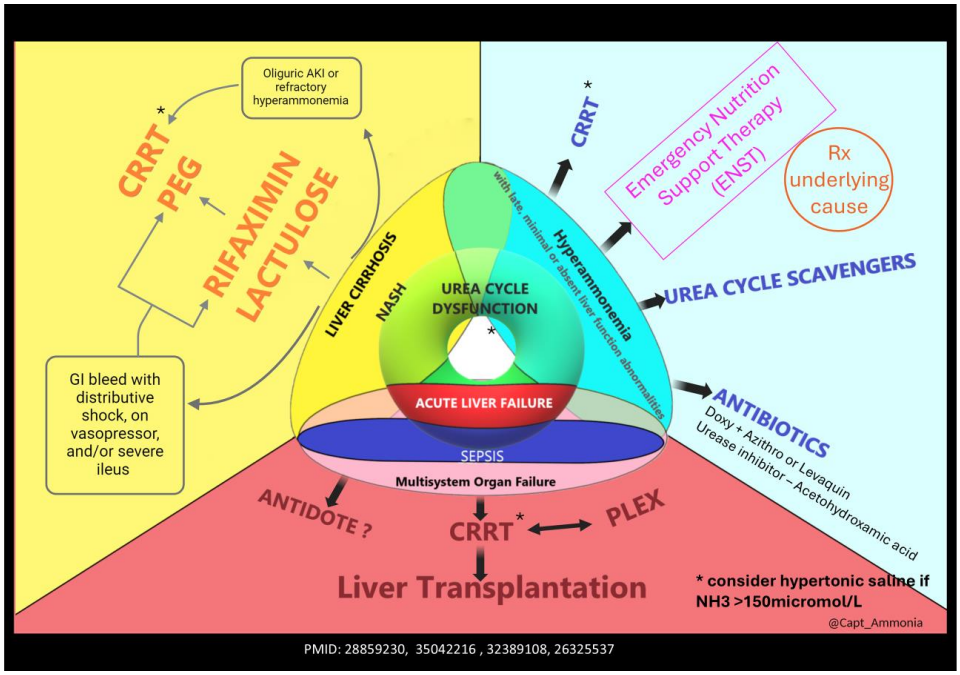
Summary of Management of Hyperammonemia



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