

NICU: NEONATAL HYPERAMMONEMIA

Emergent Management of Acute Neonatal Hyperammonemia (NH)

ALGORITHM

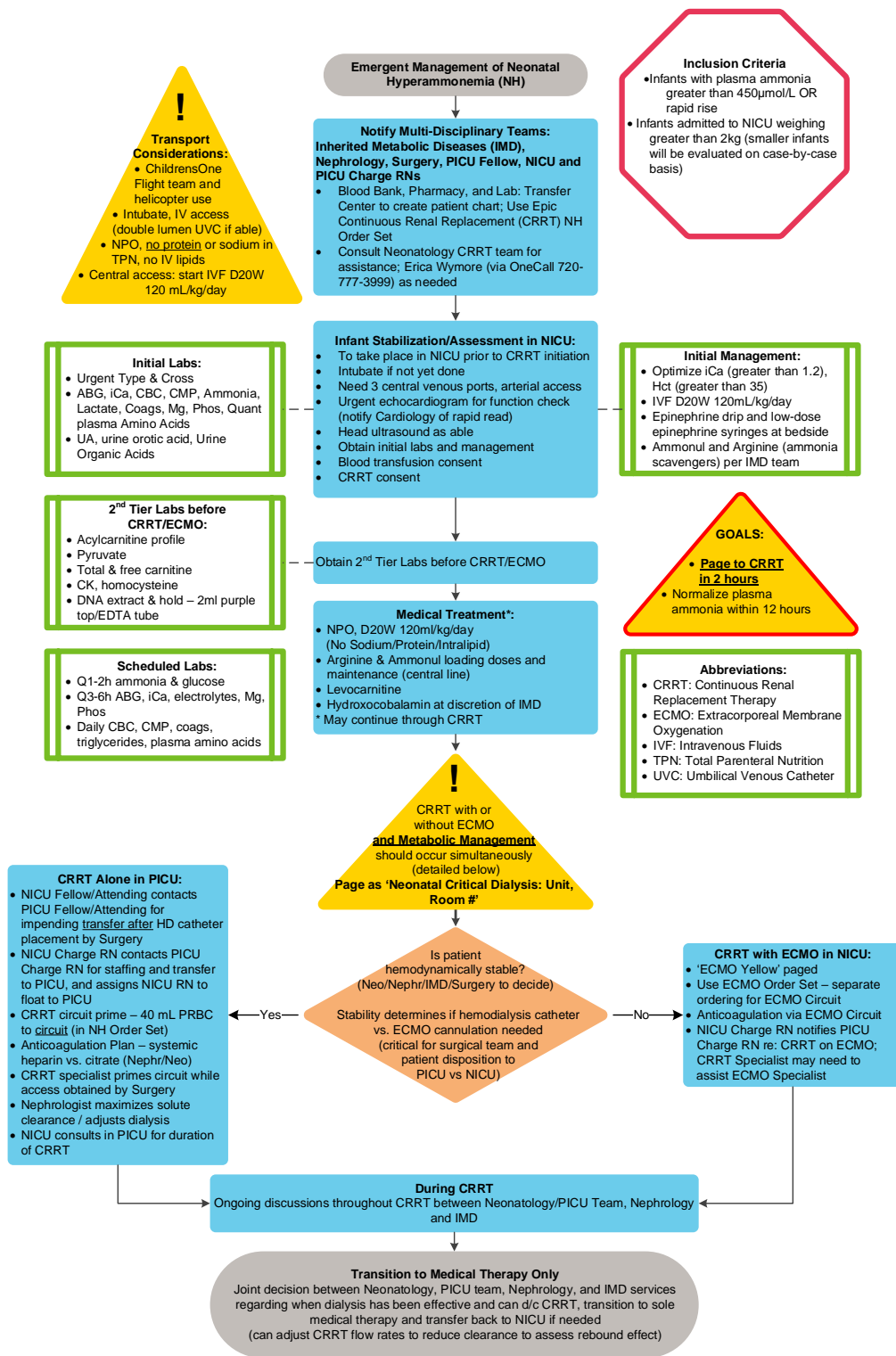


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TARGET POPULATION

Inclusion Criteria

- Infants with plasma ammonia level **greater than** 450 μ mol/L **OR** rapid rate of rise, suspicious for inborn error of metabolism.
- Infants admitted to NICU, weighing greater than 2kg (smaller infants determined on case-by-case basis)

BACKGROUND | DEFINITIONS

Background

This multidisciplinary clinical pathway has been developed to improve neurologic outcomes in the rare presentation of neonatal hyperammonemia (NH) due to inborn errors of metabolism, such as urea cycle defects (UCD), organic acidemias (OA) and fatty acid oxidation disorders (FAOD). The duration and level of the state of hyperammonemia determines the extent of neurologic injury and degree of long-term neurologic disability - a true **Metabolic Emergency**.

Objectives

- Prioritize and coordinate efforts by a multidisciplinary team including Neonatology, Nephrology, Surgery, Inherited Metabolic Diseases (IMD) and Pediatric Critical Care caring for infants in the NICU to:
 - Critical care stabilization and obtain rapid central vascular access (in NICU)
 - Initiate Continuous Renal Replacement Therapy (CRRT) for ammonia removal
 - Initiate metabolic therapy for ammonia scavengers
- Interventions to occur concomitantly
- Decision to CRRT in 2 hours, with hospital-wide response to page '**Neonatal Critical Dialysis: NICU Unit, Room Number**' similar to ECMO Yellow
- Once on CRRT, normalize plasma ammonia (to less than 100 μ mol/L) within 12 hours

Abbreviations

- ABG: Arterial Blood Gases
- BP: Blood Pressure
- CBC: Complete Blood Count

- CK: Creatine Kinase
- CMP: Comprehensive Metabolic Panel
- CRRT: Continuous Renal Replacement Therapy
- DNA: Deoxyribonucleic Acid
- Echo: Echocardiogram
- ECMO: Extracorporeal Membrane Oxygenation
- EDTA: Ethylenediaminetetraacetic acid
- Epi: Epinephrine
- FAOD: Fatty Acid Oxidation Disorders
- HCT: Hematocrit
- HUS: Head Ultrasound
- iCa: Ionized Calcium
- IMD: Inherited Metabolic Diseases
- IVF: Intravenous Fluids
- Mg: Magnesium
- NH: Neonatal Hyperammonemia
- NPO: Nothing by Mouth
- OA: Organic Acidemias
- Phos: phosphorus
- PRBC: Packed Red Blood Cell
- TPN: Total Parenteral Nutrition
- UA: Urinalysis
- UCD: Urea Cycle Defects
- UVC: Umbilical Venous Catheter

INITIAL EVALUATION

Neonatology Considerations for Transport

- a. Helicopter use if able - emergent transport
- b. Intubation if not done already (ChildrensOne Flight team or referring provider)
- c. Obtain IV access - prefer UVC double lumen but should not delay transport
- d. NPO, no parenteral nutrition (PN), remove all protein intake, no IV lipids
- e. If UVC access – dextrose 20% (D20W) at 120ml/kg/day; if PIV- dextrose 12.5% (D12.5W) at 180 ml/kg/day (GIR 16 mg/kg/min)
- f. Obtain electrolytes prior to transport (if not done already/recently)

Neonatology Pre- CRRT Clinical Considerations

- Notification of multi-disciplinary team regarding pending patient: IMD, Nephrology, Surgery; NICU Charge RN to notify PICU Charge RN of infant admission and presumptive diagnosis; PICU fellow to be notified of possible pending transfer of patient to PICU after HD catheter placement for use of CRRT with PrisMax (if ECMO not

needed). Text NICU CRRT clinical champion, Dr. Erica Wymore, (720-777-3999), for patient tracking and assistance.

- a. Urgent central venous (3 ports) and arterial access - for metabolic medications, monitoring
 - b. Prioritize correction of hypocalcemia/anemia: iCa greater than 1.2 mmol/L, Hct goal greater than 35%
 - c. Urgent echocardiogram to assess ventricular function- request rapid read from Cardiology
 - d. Notify Pharmacy, Laboratory and Blood Bank regarding plans for CRRT
 - e. Epinephrine (continuous drip and low-dose epinephrine syringes) ordered to bedside, in-line, in preparation for BP changes on CRRT; calcium chloride boluses ordered to bedside
- Cranial ultrasound to document pre-CRRT/ ECMO evaluation for intracranial hemorrhage, but should never delay therapy

CLINICAL MANAGEMENT I THERAPEUTICS

All three sections of Vascular Access, CRRT, and Metabolic Management detailed below, to occur simultaneously

1. Vascular Access

Contact Pediatric Surgery Attending on call: 720-777-3999

- Urgent placement of CRRT access expeditiously, at the bedside or in the OR if readily available (within 30 minutes):
 - If delay is expected (greater than 30 minutes), contact back-up surgeon for urgent bedside placement
 - For CRRT without ECMO: 7 Fr double lumen hemodialysis catheter, Right Internal Jugular percutaneous placement preferred to cutdown**
 - **OR** ECMO cannulation, if needed
 - CXR or echocardiography (surgeon preference) to verify position of catheters for use
 - ** Catheters will be heparin locked when not in use for dialysis, refer to CRRT policy for care
- Notify Nephrology on call regarding planned start time for placement of CRRT/ECMO vascular access to facilitate CRRT initiation; CRRT circuit should be primed while access is being obtained to avoid delays in initiation of therapy.
- Notify Nephrology once vascular access obtained and position verified for use
- Peripheral arterial access for hemodynamic monitoring required
- Additional priority vascular access: minimum of 3 central venous access ports needed for all medications and therapy (performed by Neonatology) separate from CRRT or ECMO catheters; these procedures should be performed expeditiously and not delay therapy.

2. CRRT with or without ECMO

Consult Nephrology Provider on call: 720-777-3999

Hemodynamic stability and evaluation of infant's ability to tolerate CRRT will determine infant location for undergoing CRRT via PrisMax.

- Rapid echocardiography for cardiac functional assessment - notify Cardiology fellow for rapid review by Cardiology attending (concise function assessment, not full anatomic echo unless warranted; Cardiology consult in order set to promote rapid study interpretation)
- PrisMax with HF20 filter will be utilized to allow for more rapid ammonia clearance and/or tandem use with ECMO if warranted.

If infant is hemodynamically stable, without evidence of impending cardiovascular compromise, proceed to HD catheter placement by Surgery, with **infant transfer to PICU for CRRT by PrisMax**.

If infant demonstrates refractory hypotension and/or severe ventricular dysfunction, proceed to ECMO with CRRT for ammonia detoxification and **infant remains in NICU**.

CRRT without ECMO- infant will transfer to PICU after HD catheter placement for CRRT initiation

- NICU Provider will contact PICU Admission Provider to arrange patient transfer to PICU once HD catheter placed and position verified for use. PICU bed availability should not delay initiation of CRRT.
- NICU Charge Nurse will contact PICU Charge Nurse to arrange for staffing.
- CRRT Specialist staffing for PrisMax CRRT
- NICU RN staffing for patient while in the PICU
- PrisMax CRRT is not performed in the NICU. Patient is stabilized in NICU and then transferred to PICU for initiation of PrisMax CRRT.
- If PICU bed not immediately available, patient may be initiated on PrisMax in NICU and then transported to PICU on CRRT.
- Expected total preparation time for CRRT circuit is 90 minutes - should be initiated at time of '**Neonatal Critical Dialysis**' page and primed while access being obtained by Pediatric Surgery; goal to initiate CRRT as soon as vascular access obtained and position verified for use
- CRRT circuit preparation requires 40 ml PRBCs (to be ordered by Neonatology service for circuit prime)
- Anticoagulation plan (heparin - systemic vs citrate - regional) made between Nephrologist & Neonatology attending based on overall clinical status, hepatic function, risk for intraventricular hemorrhage/bleeding
 - Note that systemic heparin anticoagulation is used most commonly
 - Citrate can cause severe hypocalcemia - optimization of iCa greater than 1.2 mmol/L is critical before CRRT
- Nephrology will maximize solute clearance to address hyperammonemia, and will adjust dialysate/replacement fluid as clinically indicated
 - Suggested starting dose of dialysis with a dialysis/replacement flow rate of 8,000 ml/1.73 m²/hr (1,000 ml/h). Assuming blood flow of 30 mL/min or greater this dose should provide clearance equivalent to intermittent hemodialysis.
 - Concerns regarding recalcitrant hyperammonemia or insufficient ammonia clearance should be discussed with Nephrology and IMD
- Need for continuation of ammonia scavenger medications **during** dialysis to prevent rebound hyperammonemia will be determined by IMD attending
- Neonatology will consult and round for duration of infant's stay in PICU
 - Infant will be transferred back to NICU once PrisMax CRRT therapy is complete.

CRRT with ECMO- infant remains in NICU

- Notify Neonatal ECMO Director - Dr. Jason Gien or Dr. John Kinsella (contact via OneCall 720-777-3999); NICU provider to update Nephrology regarding clinical status warranting ECMO
- ECMO order set in Epic for CRRT orders, lab schedule, etc. Note blood for priming ECMO circuit is separate from blood required for CRRT circuit prime. Transfusion of blood products occurs per ECMO standing orders.
- NICU Charge Nurse will update PICU Charge Nurse regarding ECMO need with CRRT
- If patient is on CRRT with ECMO, patient will remain in NICU and not transfer to PICU for PrisMax
- Expected total preparation time for CRRT circuit is 90 minutes – preparation should be initiated at time of NH page and performed while access being obtained by Pediatric Surgery

- Utilize protocol in place for CRRT in tandem with ECMO circuit, anticoagulation occurs via ECMO circuit
- Concerns for recalcitrant hyperammonemia or insufficient ammonia clearance/detoxification on ECMO should be discussed with Nephrology and ECMO team leaders, to optimize blood flow rates and CRRT/ECMO configuration

Joint decision between Neonatology, Nephrology and IMD services regarding when dialysis support can be terminated and transition to sole medical therapy is appropriate. Option to also adjust CRRT flow rates to reduce clearance while still on CRRT to assess rebound effect (preferable to discontinuing CRRT and requiring re-initiation with a new circuit).

3. Metabolic Management

Consult IMD Attending on call: 720-777-3999

Basic steps in initial management should be discussed with IMD attending, including during infant transport.

Intravenous Fluids and Medications- recommendations for fluids/TPN to be initiated during transport as able, metabolic medications to be initiated upon NICU admission and central venous access.

- NPO - to halt protein and fat intake
- High caloric IV intake = **Goal 120 kcal/kg/day** to avoid catabolic state which increases protein catabolism and ammonia production
 - Maintenance IV fluids with dextrose 20% (D20W) or greater: total fluid rate at least 120 ml/kg/day to achieve caloric goal
 - Given potential for cerebral edema in setting of hyperammonemia, avoid fluid overload
 - Serum glucose 120-170 mg/dl may be needed to promote anabolism; consider insulin if needed (especially in organic acidemias, may be associated with recalcitrant hyperglycemia)
 - Hold sodium in maintenance IV fluids and follow sodium in serum: ammonia scavengers have high sodium content; may be preferable to use maintenance IV fluids with minimal sodium to maintain sodium in normal/high normal range
 - Acid-base status: respiratory alkalosis is a common finding in UCD (ammonia is a primary respiratory stimulant); metabolic acidosis is typically the prominent feature in OA. Acidosis should correct as hyperammonemia corrects and should not be routinely treated e.g., sodium bicarbonate
 - No protein in TPN: typical approach to exclude natural protein for first 18-24 hours of ammonia detoxification, with gradual reintroduction of protein as guided and at the discretion of the IMD physician and IMD nutritionist
 - Lipid emulsion (Intralipid): clinical need determined by IMD attending (await acylcarnitine profile and other biochemical test results to rule out) - start 20% lipid emulsion at 2g/kg/day and may increase in setting of urea cycle defect or organic acidemia
- Give IV Arginine
 - Loading dose 200 mg/kg IV over 90 minutes
 - Maintenance dose 200 mg/kg IV over 24 hours immediately after completion of loading dose
 - Note **hypotension** as common side effect
 - Central line recommended for infusion, compatible with sodium benzoate/sodium phenylacetate (Ammonul) and dextrose 10% (D10W), verify with Pharmacy
 - May continue to administer through CRRT
- Give IV Sodium Benzoate/Sodium Phenylacetate (Ammonul)
 - Loading dose 250 mg/kg IV over 90 minutes
 - Maintenance dose 250 mg/kg IV over 24 hours immediately after completion of loading dose

- Central line recommended for infusion, compatible with arginine and dextrose 10% (D10W), verify with Pharmacy
- May continue to administer through CRRT
- d. Give Levocarnitine 200-400 mg/kg/day, at discretion of IMD attending
- e. Consider Hydroxocobalamin 1 mg IM/SC once daily, especially if high or emerging suspicion of organic academia/disorder of cobalamin metabolism, at discretion of IMD attending
- f. Pressor support that should be readily available due to CRRT and/or arginine effects
 - Epinephrine drip
 - Low-dose epinephrine syringes available at bedside
 - Calcium chloride bolus available at bedside
 - If infant arrives/escalates to pressor support prior to CRRT, anticipate 2nd and 3rd line pressor support and order to bedside to be in-line prior to CRRT initiation

Additional Considerations

Dependent upon specific etiology of metabolic disorder:

Initiation of lipid emulsion after FAOD excluded, or if UCD/OA more strongly suspected

- Intralipid 20% at 2g/kg/day to start and may increase as needed for high caloric goal intake; follow triglyceride levels and lipase levels if receiving high dose lipids
- Consider abdominal ultrasound with Doppler of portal vein for evaluation of portosystemic shunt or thrombosis, in possible transient hyperammonemia of the newborn (THAN), especially with unexpectedly slow ammonia clearance despite optimal therapy and optimization of CRRT/ECMO circuit

Timing and method of reintroduction of enteral or parenteral protein is at the discretion of the IMD physician and dietitian on service.

LABORATORY STUDIES | IMAGING

Laboratory Studies

Notify laboratory of frequent samples to be performed urgently

1. Admission Studies

Utilize iSTAT for ABG/iCa/HCT

- a. Order STAT blood type and crossmatch - needed for CRRT/ ECMO priming
- b. ABG, CBC with differential, CMP, ammonia, lactate, magnesium, phosphorus, ionized calcium, coagulation studies; quantitative plasma amino acids
 - IMD team to notify Biochemical Genetics Laboratory (720-777-0525) to expedite plasma amino acids and urine organic acids. Data from these tests will be of diagnostic help in differentiating between OA, UCD, and FAOD, and for differentiating between different subtypes of UCD, which may affect dosing of ammonia scavengers (see Haberle et al. 2012 or Ammonul package insert). Low or low normal glutamine is often seen in OA, but very high glutamine is more likely in UCD
- c. Urinalysis (for ketones), urine organic acids, urine orotic acid

2. Second Tier of Laboratory Investigation

Please draw before initiating ECMO and/or CRRT

- a. Acylcarnitine profile

- b. Pyruvate
- c. Total and free carnitine
- d. CK, homocysteine
- e. Blood for Molecular Consultation - formerly known as "Extraction and hold DNA" to allow for genetic testing if needed; 2ml purple top/EDTA tube

3. Laboratory Schedule

- a. Q1-2h plasma ammonia initially and glucose, to be spaced per IMD service
- b. Q3-6h blood gas, electrolytes, phosphorus, magnesium, calcium
- c. Daily CBC and coagulation studies
- d. Daily CMP, triglycerides
- e. Plasma amino acids (holding enteral/intravenous protein sources for 2 hours prior to sampling)
- f. Consider daily lipase if on high dose lipid emulsion or possible emerging clinical features of acute pancreatitis

Imaging

See [imaging considerations](#) for metabolic management

CONSENT

Obtain consent from parents for:

- Transfusion consent
- CRRT Consent (on CHCO intranet: English, Spanish) - Nephrology
- Surgical procedure for placement of catheter(s)

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8. Urea Cycle Disorders: Management. Up to Date, accessed February 1, 2025.

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Clinical Pathways and Measures Committee – 2/24/2025
 Pharmacy & Therapeutics Committee – 2/6/2025

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REVIEW | REVISION SCHEDULE

Scheduled for full review on 2/24/2028

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