


*State of Florida Systemic Supportive
Care Guidelines*



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I. FEN

- **1. What intravenous fluids should be initiated upon admission to the NICU?**

Although no exact literature exists, the most common practice is to start intravenous D₁₀W (10% dextrose solution) upon arrival to the NICU.

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- Recommendations:
- Use D₁₀W or D₁₀W with protein as the initial intravenous fluid. May consider starting lipids at low concentrations. Neonates undergoing hypothermia may have delayed lipid processing. If lipids are used, monitoring of triglycerides should be considered and lipids titrated according to triglyceride results.
- Add electrolytes as required based on the results of serum electrolytes.
- May need to increase dextrose concentration to maintain adequate glucose delivery (glucose infusion rate) in light of fluid restriction (see below II).
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- Level of Evidence: V- Expert opinion based on current review of the literature.

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- **What should be the initial intravenous fluids rate?**
- No randomized trials have been performed to examine the initial rate of fluid therapy and long term outcomes. Current recommendations to limit the consequences of HIE include careful management of fluids, with avoidance of fluid overload and thus avoidance of cerebral edema (1). Recommendations for fluid restriction in neonates are based on the experience of restricting fluid intake in adults or older children (1).

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- Recommendations:
- Suggested starting rate of 40-60 ml/kg/day which can be adjusted based on the neonates clinical presentation.
- Fluid management on subsequent days (past day 1) may be adjusted based on urine output, creatinine levels and electrolytes. Children with oliguria, hyponatraemia, increasing creatinine levels, or severe HIE should continue to be restricted to the lower range of total fluid volume intake. In milder cases of HIE, with limited multi-organ system involvement, fluid volumes may be liberalized in an attempt to improve nutrition.
- Level of Evidence: IIIA- Systematic review and Expert opinion based on current review of the literature.

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- **What should be the target glucose value for infants with HIE?**
 - Under normal conditions, the human brain relies almost entirely on glucose to provide substrate for metabolism (2). In newborn infants, cerebral glucose use may account for 70% of total glucose consumption (2). Although, the newborn brain can use other substrates, such as lactate or ketones, as an energy source, the supply of these alternate substrates are usually unpredictable and may not compensate entirely for a decrease in glucose availability (2).

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- Hypoglycemia is the blood glucose concentration at which the glucose supply to the brain is less than the demand for substrate created by the rate of brain energy metabolism. Because this balance cannot easily be measured, the definition of hypoglycemia is based on statistical analysis of blood glucose concentrations measured over the first few days of life in specific neonates (2).

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Recommendations:

- Screen for hypoglycemia as early as possible.
- The target glucose range should be at least above 40mg/dl **in the first 24 hours of life** with an ideal target of 60-70mg/dl or higher.
- Avoid marked hyperglycemia (≥ 150 mg/dl).

Level of Evidence: IV- Case Series and Expert opinion based on current review of the literature.

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- **I. What should be used for feeds?**
- Feeding should be started with breast milk if available. Although there is no evidence to directly support the claim that breast milk is better than formula for improving the outcome of neonates with HIE, evidence has shown that breast milk may improve cognitive abilities in term neonates (1). Although born at or near term, neonates who have suffered from HIE are at higher risk of developing necrotizing enterocolitis (NEC). Studies have demonstrated that breast milk feeding is associated with a lower incidence of NEC (2). In addition, breast milk is a rich source of multipotent mesenchymal stem cells (3).

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- *Recommendations:*
- 1. Feed with breast milk if available and no contraindications exist (AAP policy).
- 2. May use formula if breast milk is not available.
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- *Level of Evidence:* IV- Case Series and Expert opinion based on current review of the literature.

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- **When should feeds be started and at what volume?**
- Recent studies have demonstrated NEC to occur from 9-15 days of age in term neonates with HIE (4, 5). Many of the risk factors present in term neonates for developing NEC, such as hypotension, may be present in neonates with HIE after the initial insult (4). Further, the effect of hypothermia on feeding tolerance in this population is currently unknown. In addition, studies have illustrated that intestinal motility in neonates with HIE is abnormal at 7 days post insult (6). Recently, reports have demonstrated the safety of minimal enteral feeds in neonates undergoing hypothermia [7].
- Recommendations:
- Feeding may be started as early as deemed appropriate by the clinical team. This may be with small amounts during hypothermia in neonates without hypotension or the need for pressor support. The clinician may also examine LFTs and creatinine when making decisions about feeding initiation and volumes since these may represent other end-organ damage which may indirectly suggest gut injury.
- Level of Evidence: IV- Case Series and Expert opinion based on current review of the literature.

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- **How quickly should feeds be advanced?**
- There is no evidence for term neonates who have suffered from HIE to guide the advancement of feeds. Therefore, one may extrapolate the experience and rationale used for preterm neonates (7). Route of feeding and type of feed may also be considered in the advancement of feeds.
- Recommendations:
- Feeds may be advanced as rapidly as appropriate based on clinical condition and route of feeding.
- Level of Evidence: V- Expert opinion based on current review of the literature.

Respiratory

- **What are the goal values for PaCO₂ and PaO₂ on ABGs?**
- With regard to CO₂, the goal may be values within the normal range (40-55 mmHg Note: although higher PaCO₂ may be appropriate for certain infants with significant ventilator requirements).
- Infants who have suffered a hypoxic-ischemic insult will have resultant changes in metabolism that lead to less CO₂ production.
- Also, CO₂ may be low secondary to respiratory compensation for the initial metabolic acidosis.
- Hypothermia may reduce CO₂ production as well (1). These factors combined lead to less ventilator support needed to obtain a desirable CO₂.

Respiratory

Recommendations:

- Keep PaCO₂ in the range of 40-55 mmHg (Note: these are suggested ranges and may need to be modified for individual patient care based on the bedside clinicians exam and the patient's underlying pathophysiology). If the neonate is self hyperventilating to a lower level, assure that mechanical ventilation is not contributing to further decreases in CO₂ by lowering support as much as clinically indicated.
- Keep PaO₂ in the range of 50-80 mmHg to prevent hyperoxic injury.
- Avoid over ventilation by starting with a conservative initial ventilator rate (For example 30 breaths per minute. This suggestion should be modified based on the clinical presentation.)
- ABG post resuscitation, manage ventilator to obtain goal PaO₂ and PaCO₂
- *Level of Evidence: IV- Case Series and Expert opinion based on current review of the literature.*

Respiratory

- **What parameters are recommended for FiO_2 and oxygen saturations?**
- As outlined above, hyperoxia is particularly harmful in this population. Current guidelines recommend the use of room air for the initial resuscitation of term infants. Infants resuscitated with room air have higher Apgar scores at 5 minutes, higher heart rates at 90 seconds of age, and took their first breath 30 seconds earlier than those who received 100% oxygen (4).
- Recommendations:
- Initiate resuscitation with room air (follow the Neonatal Resuscitation ProgramTM guidelines 6th edition for delivery room management)
- When oxygen is required, use the least amount of FiO_2 needed to maintain saturations > 92%
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- *Level of Evidence:* IB- RCT and Expert opinion based on current review of literature.

Respiratory

• **What defines a patient who may be a candidate for ECMO?**

- Recommendations:
- In the experience of the network sites, hypothermia may be continued safely during ECMO.
- Early discussion of the ECMO criteria for infants with severe HIE should be established. The discussion should include multiple disciplines (neonatology, pediatric surgery, ethics committee).
- May consider rewarming slowly by 0.2°C to see if the pulmonary vascular resistance relaxes with mild increases in the temperature. The clinician may consider proceeding straight to ECMO if the baby is very early in the hypothermia course or rewarming to a target range which is still considered neuroprotective, 35°C. Conversely, the clinician may consider rewarming fully if the neonate is close to the end of the 72 hour cooling period in an attempt to avoid ECMO.
- *Level of Evidence:* IV- Case Series and Expert opinion based on current review of the literature.

Respiratory

IV. How should temperature correction factor into the interpretation of blood gases?

Recommendation:

- Recognition that blood gas values will vary depending on the method used in calibration; the clinician may consider alternative ventilator strategies to obtain goal blood gas values.
- *Level of Evidence:* V- Expert opinion based on current review of literature.

Respiratory

- **V. Should patients be extubated during the cooling or rewarming process?**
- Based on case reports it appears to be a safe practice if the infant meets all the parameters needed for safe extubation. These infants represent a unique population and awareness of their high-risk status must be considered: airway protection (if diminished gag reflex), seizure activity, and apnea associated with the cooling and/or rewarming process
- *Level of Evidence: V-* Expert opinion based on current review of literature.

Respiratory

VI. What are the recommendations regarding ventilator management?

- As discussed previously, initial ventilator settings should be conservative, with moderate pressures and respiratory rate. Initial PEEP should also be conservative. Overdistension of the lung may increase PVR and reduce venous return, therefore impairing peripheral and cerebral perfusion. Finding the optimal balance between sufficient MAP to allow lung recruitment and its potential negative effects on circulation may often require multiple chest radiographs and echocardiography (3).
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- *Level of Evidence: V-* Expert opinion based on current review of literature.

Respiratory

VII. What are the recommendations regarding the use of nitric oxide (iNO)?

- As discussed in the section on ECMO, iNO can effectively improve oxygenation in the asphyxiated newborn, with or without evidence of PPHN.
- It may also be used, even at smaller doses, to aid in the weaning of FiO_2 if the patient is on high settings.
- In previous studies, oxygen used has diminished after the initiation of iNO therapy.
- If infants are on high FiO_2 and ventilator settings consideration should be given to starting NO therapy (8).
- *Level of Evidence: V*- Expert opinion based on current review of literature.

Cardiovascular

What is the goal Mean Arterial Blood Pressure (MAP) for infants with HIE?

- Blood pressure must remain in a safe range post HIE with the goals of avoiding hypotensive associated cerebral ischemia while ensuring the infant is not hypertensive with subsequent intra-cerebral hemorrhage.
- The ideal MAP for *term* infants with HIE has not been established.
- Since infants operate over a narrow blood pressure range, and hypoxic-ischemia impairs cerebral autoregulation, it is recommended to maintain MAP within the critical margin of **40mmHg to 60mmHg** (1) unless the hemodynamics suggest a more optimal MAP.

Cardiovascular



Recommendations:

1. Attempt to maintain MAP between 40mmHg and 60mmHg
2. Infants with pulmonary hypertension may require a MAP on the higher end of this scale
3. Attempt to avoid acute fluctuations in blood pressure

Level of Evidence: V- Expert opinion based on current review of literature

Cardiovascular

II. What is the optimal method to manage hypotension with HIE?

- There is minimal documentation regarding the ideal method to augment MAP for infants with HIE.
- If there is clinical or historical evidence of hypovolemia (i.e. severe anemia, placenta abruption, cord compression) than volume may be indicated.
- The unwarranted use of fluids may exacerbate cerebral edema (2).

Cardiovascular

- A 2002 Cochrane systemic review evaluating **Dopamine** for the prevention of morbidity and mortality with HIE was found to be inconclusive (3).
- Further, Dopamine may not be the ideal first line agent for infants with evidence of pulmonary hypertension (PPHN) and HIE because it increases both systemic (SVR) and pulmonary vascular resistance (PVR) (4).
- **Dobutamine**, at high doses, can also increase pulmonary artery pressure while reducing afterload and therefore would not be an ideal agent for infants with HIE and PPHN (5).

Cardiovascular

- **Epinephrine**, at low to moderate dosing, will increase SVR with little effect on PVR. In addition, epinephrine can improve myocardial perfusion and dysfunction. Infants with HIE and PPHN, epinephrine may be the optimal choice for blood pressure augmentation (4).
- **Milrinone** increases myocardial contractility and acts as a vasodilator (systemic and pulmonary). Infants with myocardial dysfunction, Milrinone may be a superior agent to improve contractility ensuring MAP is within target range prior to its initiation (6, 7).

Cardiovascular

- Recommendations:

1. If infant is hypotensive, start treatment with a pressor which supports the clinical need of the neonate.
2. Obtain an Echocardiogram to assist in management. If myocardial dysfunction is evident on echocardiogram, consider the addition of Epinephrine.
3. This is the recommended approach for hypotensive, encephalopathic infants *with or without* PPHN. Of note, the addition of Milrinone as a single agent may be beneficial in PPHN when normotensive (6, 7).
4. In the case of refractory hypotension to pressor support, consideration should be given to the addition of steroids.
5. A majority of neonates with HIE do not have acute volume or blood loss. Unless there is a history of volume or blood loss, caution should be used in volume expansion for hypotension given the risk of cerebral edema and renal insufficiency due to hypoxic-ischemic injury.

Level of Evidence: IV- Case Series and Expert opinion based on current review of the literature.

Cardiovascular

VI. When should an echocardiogram be obtain for infants with HIE?

We recommend an Echocardiogram be performed in any infant with HIE and any of the following clinical scenarios:

1. Elevated cardiac enzymes if performed at your center
2. Clinical evidence of cardiac dysfunction
3. Clinical evidence of pulmonary hypertension
4. Hypotension (MAP < 40mmHg)
5. Requiring inotropic support

Level of Evidence: V- Expert opinion based on current review of literature.

Cardiovascular

- **V. Should serum markers of cardiac injury be obtained in infants with HIE, what markers, and when should they be obtained?**
- Serum cardiac markers may assist in injury detection and guide clinical management.
- Recent evidence suggests cardiac Troponins are superior to other markers of myocardial injury (LDH, CK, CK-MB) in detecting earlier, cardiac specific injury (11, 12).
- Further, there is only one commercially available assay for Troponin T making standardization between different studies and reference ranges relatively consistent.
- Although there is not an accepted normal range for cTnT in neonates, a value of ≥ 0.1 **ng/ml** in the setting of HIE has been considered as elevated in several studies and as a potential indicator of mortality in the neonatal period (11-14).

Cardiovascular



Recommendations:

1. If performed at your center and clinically indicated, obtain an ECG and Echocardiogram if cTnT is $\geq 0.1\text{ng/ml}$ to evaluate myocardial ischemia and cardiac function.
2. As stated above, Cardiac Troponin T may also be predictive of outcome and may aid the bedside clinician with additional prognostic information.

Level of Evidence: IIC- based on outcome data and case-controlled studies.

Cardiovascular

VI. How should bradycardia associated with hypothermia be managed?

- Relative bradycardia (**70-100 bpm**) is not an uncommon occurrence in infants undergoing hypothermia.
- However, pathologic bradycardia can be a result of cardiac dysfunction, arrhythmias, deep hypothermia and increased intracranial pressure.
- Clinical intervention should be initiated when bradycardia is associated with evidence of decreased cardiac output, electrolyte abnormalities, elevated cardiac enzymes, and/or ECG abnormalities.

Cardiovascular

Recommendations:

1. If heart rate is <70 bpm with evidence of reduced cardiac output (worsening metabolic acidosis, \uparrow lactic acid, prolonged capillary refill time, diminished pulses, low or borderline low MAP) obtain electrolytes including ionized calcium, ECG, echocardiogram, and ensure core temperature is appropriate.
2. If heart rate is <70 bpm but >60 bpm *without* evidence of reduced cardiac output, normal electrolytes, normal ECG and echocardiogram then close clinical observation is a reasonable approach.
3. The bedside clinician may consider rewarming by 0.5°C to see if the HR increases if below 60 or below 70 with evidence of reduced cardiac output.

Level of Evidence: V- Expert opinion based on current review of literature.

Neurologic and Seizure Management

I. What medications should be used for analgesia during hypothermia?

- Recommendations:
- Begin an opiate upon initiation of cooling.
- Stop unnecessary analgesia and sedation after warming has occurred.
- If opiate at low dosages does not provide adequate analgesia, the dose can be gradually increased as well as having other medications may be added. The goal should be continuous and adequate analgesia and anxiolysis to prevent excessive irritability and agitation and not an attempt to maintain the infant on mechanical ventilation, unless clinically indicated.
- The clinician may consider obtaining a serum cortisol to assess the degree of stress. The cortisol along with the heart rate may aid the clinician with the management of sedation.
- Level of Evidence: V Expert opinion based on current review of the literature and animal models.

Neurologic and Seizure Management

II. When and how should infants be monitored for seizures?

- Multiple studies have shown the benefit of continuous EEG monitoring of neonates with HIE.
- Besides being a very useful early predictor of neurologic outcomes(1,2), studies have shown that aggressive treatment of seizures decreases neurologic sequelae (3).
- Due to the large amount of resources consumed by continuous EEG monitoring, amplitude integrated EEG has been used extensively for neonates with HIE for monitoring.
- The ease of application and interpretation of aEEG makes it especially useful in continuous monitoring.

Neurologic and Seizure Management

- *Recommendations:*

- Upon admission to the NICU, neonates suspected of having HIE should have an aEEG placed (see #3).
- Monitoring duration via aEEG should optimally occur during the entire systemic hypothermia process, including warming.
- If video EEG is used for continuous monitoring instead of aEEG, someone at the bedside of the patient should be trained in interpretation of the EEG or the aEEG feature on the video EEG should be monitored by the bedside personnel.
- If aEEG demonstrates seizure activity and/or an abnormal background pattern, it is recommended to obtain formal EEG evaluation and continuously monitor for electrographic seizures until warming has occurred and seizures are under control (2).
- *Level of Evidence:* IIC based on outcome data and case control studies

Neurologic and Seizure Management

III. How should seizures be managed in neonates with HIE?

- HIE is the number one cause of neonatal seizures.
- Despite the high incidence of seizures in this population of neonates, a Cochrane review did not find benefit in morbidity and mortality with routine use of prophylactic anti-epileptic medications (4).
- Though there is no evidence to support routine prophylaxis, studies have shown a definite benefit to aggressive therapy of seizures: clinical or electrographic.
- FDA approved management for seizures in neonates is limited to Phenobarbital and Fosphenytoin or Phenytoin.

Neurologic and Seizure Management

- Studies have not demonstrated a benefit of Phenobarbital over Phenytoin (5). Recent randomized control studies have demonstrated that Keppra is a safe and effective therapy in neonatal seizures with vastly better pharmacokinetics and side effect profile than Phenobarbital and Phenytoin (6,7,8).
- Some studies have also demonstrated a potential neuroprotective benefit of Keppra and neurotoxic side effects associated with Phenobarbital and Phenytoin (9).

Neurologic and Seizure Management

- Recommendations:
- Any electrographic or clinical evidence of seizures should be aggressively treated with appropriate anti-epileptic therapy and close monitoring for recurrence as over 50% of seizures from HIE will require more than one medication for treatment.
- Initial treatment may be with either an intravenous benzodiazepine or IV Phenobarbital at 20 mg/kg.
- Maintenance treatment should be started in all neonates with seizures and continued until a week after warming.
- A week after warming, the need for continued anti-epileptics should be discussed by the primary care team in conjunction with neurology and guided by each individual situation (5).

Neurologic and Seizure Management

- **VI. What is the optimal time for neuroimaging in neonates with HIE?**
 - Recommendations:
 - Head ultrasound should be acquired on admission.
 - MRI with diffusion weighted images and spectroscopy of the basal ganglia is the preferred study.
 - Suggested MRI imaging can be performed at 4-5 days of life and again at 7-12 days. If only one MRI can be performed, it should occur during the 7-12 day period. These recommendations may need to be adjusted in critically ill neonates who will be compromised in obtaining the MRI.
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 - Level of Evidence: IA randomized control trials.

III. What defines a patient who may be a candidate for ECMO?

- Recommendations:
- In the experience of the network sites, hypothermia may be continued safely during ECMO.
- Early discussion of the ECMO criteria for infants with severe HIE should be established. The discussion should include multiple disciplines (neonatology, pediatric surgery, ethics committee).