

HIE Supportive Care Management Guidelines

<u>Table of Contents</u>	<u>Pages</u>
I. <u>Fluid and Electrolyte Management</u>	3 - 6
I. What intravenous fluids should be initiated upon admission to the NICU?	
II. What should be the initial intravenous fluids rate?	
III. What should be the target glucose value for infants with HIE?	
IV. What should be the target Magnesium level for infants with HIE?	
V. References	
II. <u>Feeding Guidelines</u>	7 - 9
I. What should be used for feeds?	
II. When should feeds be started and at what volume?	
III. How quickly should feeds be advanced?	
IV. References	
III. <u>Respiratory and Ventilator Management</u>	10 - 14
I. What are the goal values for PaCO ₂ and PaO ₂ on Arterial Blood Gases (ABGs)?	
II. What parameters are recommended for FiO ₂ and oxygen saturations?	
III. What defines a patient who may be a candidate for ECMO?	
IV. How should temperature correction factor into interpretation of blood gases?	
V. Should patients be extubated during the cooling or rewarming process?	
VI. References	
IV. <u>Cardiovascular Support</u>	15 - 20
I. What is the goal Mean Arterial Blood Pressure (MAP) for infants with HIE?	
II. What is the optimal method to manage hypotension with HIE?	
III. How does hypothermia affect hemodynamic status post asphyxia?	

- IV. When should an echocardiogram be obtain for infants with HIE?
- V. Should serum markers of cardiac injury be obtained in infants with HIE, what markers, and when should they be obtained?
- VI. How should bradycardia associated with hypothermia be managed?
- VII. References

V. **Neurologic and Seizure Management** **21 - 25**

- I. What Medications Should Be Used for Analgesia Infants Being Cooled for HIE?
- II. When and How Should Infants be Monitored for Seizures?
- III. How Should Seizures be Managed in Neonates with HIE?
- IV. Optimal Time for Brain Imaging in Neonates with HIE?
- V. References

Network Statement

The Florida Neonatal Neurologic Network support the following management guidelines for infants with HIE. We acknowledge a variety of management styles, consensus statements and scientific data exist in this area, however, these

guidelines are based on the best available evidence and pooled expert opinions at the time of this document's creation.

-May 2011

I. Fluid and Electrolyte Management

Section Contents

- I. What intravenous fluids should be initiated upon admission to the NICU?**
- II. What should be the initial intravenous fluids rate?**
- III. What should be the target glucose value for infants with HIE?**
- IV. What should be the target Magnesium level for infants with HIE?**
- V. References**

I. 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.

Recommendations:

1. Use D₁₀W or D₁₀W with protein as the initial intravenous fluid. May consider starting lipids at low concentrations.
2. Add electrolytes as required based on the results of serum electrolytes.
3. May need to increase dextrose concentration to maintain adequate glucose delivery (glucose infusion rate) in light of fluid restriction (see below II).

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

II. 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).

Recommendations:

1. Suggested starting rate of 40-60 ml/kg/day which can be adjusted based on the neonates clinical presentation.
2. Fluid management on subsequent days (past day 1) may be adjusted based on urine output, creatinine levels and electrolytes. Children with oliguria, hyponatremia, 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.

III. 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).

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).

During asphyxia, anaerobic glycolysis accelerates the use of glycogen stores; as a consequence, hepatic glycogen stores are depleted, and hepatic glucose production rapidly becomes insufficient to meet cerebral metabolic demands (2). Perinatal asphyxia also may be associated with hyperinsulinemia, which may impair hepatic glucose production further and contribute to cerebral energy depletion by increasing uptake of glucose by peripheral

tissue (2). When hypoglycemia is coupled with asphyxia, the cerebral metabolic effects of the latter are magnified (3). In addition, hypoglycemia has been associated with impairment in cerebral autoregulation (3).

The use of glucose as a therapy for HIE in animal models have shown conflicting results (2, 3). Human clinical observations have demonstrated a correlation between lower levels of serum glucose concentrations and higher Sarnat scores (4). Further, initial hypoglycemia (≤ 40) is an important risk factor for perinatal brain injury in depressed neonates (3).

For infants with hyperinsulinism such as infant of diabetic mothers, an operational threshold of 60mg/dl is appropriate for defining the lower limit of normal, as these neonates have very low levels of alternative fuels such as ketones and lactate at low blood glucose concentrations (5). Since HIE may be associated with hyperinsulinism, an ideal target of 60-70 mg/dl may be beneficial.

Recommendations:

1. Screen for hypoglycemia as early as possible.
2. 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.
3. Avoid marked hyperglycemia (≥ 150 mg/dl).

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

IV. What should be the target Magnesium level for infants with HIE?

Post asphyxia, during the secondary energy failure phase of HIE, there is an excessive release of glutamate which in turn opens NMDA channels within the brain. These open channels allow for excessive calcium influx into neurons which may result in sustained neuronal injury (6). Magnesium (Mg^{2+}) is a known NMDA receptor antagonist which may block this calcium influx thereby reducing cortical damage (7). The evidence for the use of Mg^{2+} as a neuroprotective agent in both animal models of HIE and human trials are inconclusive (8). However, there are several human study that support the infusion of Mg^{2+}

sulfate post asphyxia to improve short-term neurodevelopmental outcome with no major adverse events associate with the infusion (8-10). In the above referenced studies, mean Mg^{2+} serum concentrations were ≥ 2.15 mg/dL (1.2 mmol/L) for the treatment groups. Of note, normal term neonatal mean reference Mg^{2+} levels over the first five days of life are 1.92 mg/dL +/- 0.27 (11).

Recommendations:

1. Obtain Mg^{2+} level with the first set of electrolytes and then at least every 24 hours until stable.
2. Maintain Mg^{2+} level within the normal range (1.7 to 2.2 mg/dL).
3. If Mg^{2+} level is < 1.7 mg/dL may infuse Mg^{2+} Sulfate (25-50 mg/kg/dose) over 1-2 hours.

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

V. References

1. Kecskes Z, Healy G, Jensen A. Fluid restriction for term infants with hypoxic-ischaemic encephalopathy following perinatal asphyxia. Cochrane Database Syst Rev 2005(3):CD004337.
2. McGowan JE, Perlman JM. Glucose management during and after intensive delivery room resuscitation. Clin Perinatol 2006;33(1):183-96, x.
3. Salhab WA, Wyckoff MH, Laptook AR, Perlman JM. Initial hypoglycemia and neonatal brain injury in term infants with severe fetal acidemia. Pediatrics 2004;114(2):361-6.
4. Basu P, Som S, Choudhuri N, Das H. Contribution of the blood glucose level in perinatal asphyxia. Eur J Pediatr 2009;168(7):833-8.
5. Deshpande S, Ward Platt M. The investigation and management of neonatal hypoglycaemia. Semin Fetal Neonatal Med 2005;10(4):351-61.
6. Choi DW, Hartley DM. Calcium and glutamate-induced cortical neuronal death. Res Publ Assoc Res Nerv Ment Dis 1993;71:23-34.
7. Nowak L, Bregestovski P, Ascher P, Herbet A, Prochiantz A. Magnesium gates glutamate-activated channels in mouse central neurones. Nature 1984;307(5950):462-5.

8. Bhat MA, Charoo BA, Bhat JI, Ahmad SM, Ali SW, Mufti MU. Magnesium sulfate in severe perinatal asphyxia: a randomized, placebo-controlled trial. *Pediatrics* 2009;123(5):e764-9.
9. Ichiba H, Tamai H, Negishi H, Ueda T, Kim TJ, Sumida Y, et al. Randomized controlled trial of magnesium sulfate infusion for severe birth asphyxia. *Pediatr Int* 2002;44(5):505-9.
10. Ichiba H, Yokoi T, Tamai H, Ueda T, Kim TJ, Yamano T. Neurodevelopmental outcome of infants with birth asphyxia treated with magnesium sulfate. *Pediatr Int* 2006;48(1):70-5.
11. Constantine S. Serum Magnesium Levels in the Newborn. *Pediatrics* 1964;33:696-974.

II. Feeding Guidelines for Neonates with HIE

Section Contents

- I. What should be used for feeds?**
- II. When should feeds be started and at what volume?**
- III. How quickly should feeds be advanced?**
- IV. References**

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].

Recommendations:

1. Feed with breast milk if available and no contraindications exist (AAP policy).
2. May use formula if breast milk is not available.

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

II. 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.

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

III. 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 [8]. 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.

IV. References

1. Kramer, M.S., "Breast is best": The evidence. *Early Hum Dev.* **86**(11): p. 729-32.
2. Le Huerou-Luron, I., S. Blat, and G. Boudry, *Breast- v. formula-feeding: impacts on the digestive tract and immediate and long-term health effects.* *Nutr Res Rev.* **23**(1): p. 23-36.
3. Patki, S., et al., *Human breast milk is a rich source of multipotent mesenchymal stem cells.* *Hum Cell.* **23**(2): p. 35-40.
4. Lambert, D.K., et al., *Necrotizing enterocolitis in term neonates: data from a multihospital health-care system.* *J Perinatol*, 2007. **27**(7): p. 437-43.
5. Maayan-Metzger, A., et al., *Necrotizing enterocolitis in full-term infants: case-control study and review of the literature.* *J Perinatol*, 2004. **24**(8): p. 494-9.
6. Berseth, C.L. and H.H. McCoy, *Birth asphyxia alters neonatal intestinal motility in term neonates.* *Pediatrics*, 1992. **90**(5): p. 669-73.
7. Thyagarajan, B., et al., *Minimal enteral nutrition during neonatal hypothermia treatment for perinatal hypoxic-ischaemic encephalopathy is safe and feasible.* *Acta Paediatr*, 2015. **104**(2): p. 146-51.
8. Tyson, J.E., et al., *Dilemmas initiating enteral feedings in high risk infants: how can they be resolved?* *Semin Perinatol*, 2007. **31**(2): p. 61-73.

III. Respiratory and Ventilator Management

Section Contents

- I. What are the goal values for PaCO₂ and PaO₂ on ABGs?**
- II. What parameters are recommended for FiO₂ and oxygen saturations?**
- III. What defines a patient who may be a candidate for ECMO?**
- IV. How should temperature correction factor into the interpretation of blood gases?**
- V. Should patients be extubated during the cooling or rewarming process?**
- VI. What are the recommendations regarding ventilator management?**
- VII. What are the recommendations regarding the use of nitric oxide (iNO)?**
- VIII. References**

I. 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.

Hypocapnia has also been shown to be harmful in this population. Low CO₂ leads to decreased cerebral perfusion and decreased oxygen release from hemoglobin. Current research has also determined it to be associated with death and poor neurodevelopmental outcome in infants with HIE (2).

Hyperoxia has also been shown to have a detrimental effect on these infants. Hyperoxia leads to increased oxidative stress and increased free radical production. It can be especially toxic in the setting of reperfusion and attenuate brain injury (3). Further, hyperoxia has been associated with death and poor long-term outcomes post asphyxia (2). We therefore recommend goal PaO₂ values of 50-100 mmHg.

Infants who suffer from birth depression and resultant HIE often undergo vigorous resuscitation at birth. As a result, they may have hyperoxia and hypocapnia from birth. After initial asphyxia the cardiopulmonary function often improves rapidly necessitating less support. We recommend obtaining a post resuscitation ABG, and using a conservative ventilator strategy.

Recommendations:

1. 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.
2. Keep PaO₂ in the range of 50-80 mmHg to prevent hyperoxic injury.
3. 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.)
4. 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.

II. What parameters are recommended for FiO₂ 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:

1. Initiate resuscitation with room air (follow the Neonatal Resuscitation Program™ guidelines 6th edition for delivery room management)
2. When oxygen is required, use the least amount of FiO₂ needed to maintain saturations > 92%

Level of Evidence: IB- RCT and Expert opinion based on current review of literature.

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

Infants who suffer from severe HIE often meet ECMO support criteria secondary to pulmonary hypertension with or without meconium aspiration and/or hypoxic respiratory failure. Recent literature has examined the practice of continuing hypothermia therapy while undergoing ECMO with good results (5). One practice management that may be initiated as ECMO becomes likely is nitric oxide (NO). The use of NO, even at low dosing (5 ppm), can decrease the use of ECMO by as much as 35% when the oxygen index is > 25 (3). However, despite the use of NO, ECMO is often still the required therapy in this population. A recent survey to the directors of ECMO programs showed that there is significant variability in how neonates are selected for ECMO once severity of illness criteria has been met. In this survey, 48% of the responders stated they would not offer ECMO to infant's with severe HIE (7).

Recommendations:

1. In the experience of the network sites, hypothermia may be continued safely during ECMO.
2. 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).
3. 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.

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

Hypothermia affects blood gas parameters such as pH and CO₂; at lower temperatures pH increases and CO₂ decreases (6). Most blood gas instruments contain a temperature-controlled sample chamber specified to be 37°C, referred to as α-stat method. In the α-stat method, uncorrected values are used to keep the pH and CO₂ close to the 37°C reference value. Alternatively, in the pH-stat method, the measured pH is corrected to the actual body temperature of the patient. For example, during hypothermia (core temperature 33°C), pH will rise to 7.5 and PCO₂ will decrease 34 mm Hg (6). At this point it is unclear whether the α-stat or pH-stat method should be used for the ventilator management of the asphyxiated neonate undergoing hypothermia (6).

Recommendation:

Modification 5

State Meeting August 6, 2016

1. 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.

V. Should patients be extubated during the cooling or rewarming process?

Recommendation:

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.

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).

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

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 FiO₂ 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 FiO₂ and ventilator settings consideration should be given to starting NO therapy (8).

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

VIII. References

1. Pappas A, et al. Hypocarbia and adverse outcome in neonatal hypoxic-ischemic encephalopathy. *J Pediatr* 2010; **158**(5):752-758.
2. Klinger G, Beyene J, Shah P, Perlman M. Do hyperoxaemia and hypocapnia add to the risk of brain injury after intrapartum asphyxia? *Arch Dis Child Fetal Neonatal Ed* 2005;90:49-52.
3. Lapointe A, and Barrington KJ. Pulmonary hypertension and the asphyxiated newborn. *J Pediatr* 2011; **158**(2):e19-e23.
4. Saugstad OD. Resuscitation of newborn infants: from oxygen to room air. *Lancet* 2010; 376:1970-1971.
5. Massaro A, et al. Therapeutic hypothermia for neonatal encephalopathy and extracorporeal membrane oxygenation. *J Pediatr* 2010; **157**(3):499-502.
6. Groenendaal F, De Voogt K, van Bel F. Blood gas values during hypothermia in asphyxiated term neonates. *Pediatrics* 2009; **123**(1):170-171.
7. Chapman R. Patient selection for neonatal extracorporeal membrane oxygenation: beyond severity of illness. *Journal of Perinatology* 2009; 29: 606-611.
8. Wessel et al. Persistent Pulmonary Hypertension of the Newborn Improved Oxygenation in a Randomized Trial of Inhaled Nitric Oxide. *Pediatrics* 1997.

IV. Cardiovascular Support and HIE

Section Contents

- I. What is the goal Mean Arterial Blood Pressure (MAP) for infants with HIE?
- II. What is the optimal method to manage hypotension with HIE?
- III. How does hypothermia affect hemodynamic status post asphyxia?
- IV. When should an echocardiogram be obtain for infants with HIE?
- V. Should serum markers of cardiac injury be obtained in infants with HIE, what markers, and when should they be obtained?
- VI. How should bradycardia associated with hypothermia be managed?
- VII. References

I. 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 associate 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.

Recommendations:

1. Attempt to maintain MAP between 40mmHg and 60mmHg
2. Infants with pulmonary hypertension may require a MAP on the latter 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.

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, Modification 5 State Meeting August 6, 2016

placenta abruption, cord compression) than volume may be indicated. The unwarranted use of fluids may exacerbate cerebral edema (2).

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).

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).

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 or a combination of Milrinone with low dose epinephrine to prevent systemic hypotension with Milrinone infusion or if the patient had hypotension and PPHN (6, 7).

4. In the case of refractory hypotension to pressor support, consideration should be given to the addition of steroids with hydrocortisone the steroid of choice.

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

III. How does hypothermia affect hemodynamic status post asphyxia?

Mild systemic hypothermia in itself appears to have minimal clinical effects on hemodynamic status. The CoolCap Trial which utilized mild systemic hypothermia to a rectal temperature of 34.5°C did not demonstrate affects on arterial blood pressure or initial treatment with inotropes or volume in infants with moderate to severe HIE (8). In the NICHD whole body hypothermia trial, there were no differences in the incidence of pulmonary hypertension or cardiac arrhythmias between the treatment and controlled groups. However, there was a trend towards an increase use of inotropes in the hypothermia group (9). In addition, the TOBY Trial did not find any significant difference in the incidence of hypotension, cardiac arrhythmias or pulmonary hypertension between hypothermic and normothermic infants (10).

Level of Evidence: IA- Based on Randomized Controlled Trials.

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

We recommend an Echocardiogram be performed in any infant with HIE.

Echocardiogram may be repeated and used to guide therapy in 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.

V. Should serum markers of cardiac injury be obtained in infants with HIE, what markers, and when should they be obtained?

Myocardial dysfunction is often the direct cause of perinatal brain injury. Myocardial damage may be clinically occult with mild HIE or manifest as a systemic hypoperfusion state in the cases of moderate to severe HIE. 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).

Cardiac Troponin T (cTnT), is a structural cytoplasmic protein of myosites and the most cardiac specific of the troponins in the neonatal period (13). 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).

Recommendations:

1. If performed at your center and clinically indicated, obtain an ECG and Echocardiogram if cTnT is ≥ 0.1 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.

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.

Recommendations:

1. If heart rate is <70bpm with evidence of reduced cardiac output (worsening metabolic acidosis, ↑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 <70bpm but >60bpm *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 0.5⁰C 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.

VII. References:

1. Volpe J. Neurology of the Newborn. Fifth ed. Philadelphia: Saunders; 2008.
2. Kimelberg HK. Current concepts of brain edema. Review of laboratory investigations. J Neurosurg 1995;83(6):1051-9.
3. Hunt R, Osborn D. Dopamine for prevention of morbidity and mortality in term newborn infants with suspected perinatal asphyxia. Cochrane Database Syst Rev 2002(3):CD003484.
4. Cheung PY, Barrington KJ. The effects of dopamine and epinephrine on hemodynamics and oxygen metabolism in hypoxic anesthetized piglets. Crit Care 2001;5(3):158-66.
5. Cheung PY, Barrington KJ, Bigam D. The hemodynamic effects of dobutamine infusion in the chronically instrumented newborn piglet. Crit Care Med 1999;27(3):558-64.
6. McNamara PJ, Laique F, Muang-In S, Whyte HE. Milrinone improves oxygenation in neonates with severe persistent pulmonary hypertension of the newborn. J Crit Care 2006;21(2):217-22.
7. Bassler D, Choong K, McNamara P, Kirpalani H. Neonatal persistent pulmonary hypertension treated with milrinone: four case reports. Biol Neonate 2006;89(1):1-5.
8. Battin MR, Thoresen M, Robinson E, Polin RA, Edwards AD, Gunn AJ. Does head cooling with mild systemic hypothermia affect requirement for blood pressure support? Pediatrics 2009;123(3):1031-6.

9. Shankaran S, Laptook AR, Ehrenkranz RA, Tyson JE, McDonald SA, Donovan EF, et al. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. *N Engl J Med* 2005;353(15):1574-84.
10. Azzopardi DV, Strohm B, Edwards AD, Dyet L, Halliday HL, Juszczak E, et al. Moderate hypothermia to treat perinatal asphyxial encephalopathy. *N Engl J Med* 2009;361(14):1349-58.
11. Gunes T, Ozturk MA, Koklu SM, Narin N, Koklu E. Troponin-T levels in perinatally asphyxiated infants during the first 15 days of life. *Acta Paediatr* 2005;94(11):1638-43.
12. Boo NY, Hafidz H, Nawawi HM, Cheah FC, Fadzil YJ, Abdul-Aziz BB, et al. Comparison of serum cardiac troponin T and creatine kinase MB isoenzyme mass concentrations in asphyxiated term infants during the first 48 h of life. *J Paediatr Child Health* 2005;41(7):331-7.
13. El-Khuffash AF, Molloy EJ. Serum troponin in neonatal intensive care. *Neonatology* 2008;94(1):1-7.
14. Matter M, Abdel-Hady H, Attia G, Hafez M, Seliem W, Al-Arman M. Myocardial performance in asphyxiated full-term infants assessed by Doppler tissue imaging. *Pediatr Cardiol*;31(5):634-42.

V. Neurologic and Seizure Management

Section Contents

- I. What medications should be used for analgesia during hypothermia?
- II. When and how should infants be monitored for seizures?
- III. How should seizures be managed in neonates with HIE?
- IV. What is the optimal time for neuroimaging in neonates with HIE?
- V. References

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

Though optimal therapy for sedation in neonates is a highly debated topic, neonates being cooled do demonstrate agitation and irritability in response to cooling. Studies of animal models of global hypoxic insults demonstrate that unsedated piglets subjected to hypothermia post hypoxic injury do not benefit from total body cooling and have grossly elevated cortisol levels, shivering, and generally increased motor activity that is postulated to diminish and even counteract the neuroprotective benefits of total body hypothermia (12). Due to known suppression of the cytochrome P450 pathway due to cooling as well as the risk for polypharmacy and drug interactions in acutely ill neonates, care must be taken in choosing a medication for analgesia (13).

Recommendations:

1. Begin an opiate upon initiation of cooling.
2. Stop unnecessary analgesia and sedation after warming has occurred.
3. 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.
4. 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.

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.

Recommendations:

1. Upon admission to the NICU, neonates suspected of having HIE should have an aEEG placed (see #3).
2. Monitoring duration via aEEG should optimally occur during the entire systemic hypothermia process, including warming.
3. 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.
4. 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

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. 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).

Recommendations:

1. 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.
2. Initial treatment may be with either an intravenous benzodiazepine or IV Phenobarbital at 20 mg/kg.
3. 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).

VI. What is the optimal time for neuroimaging in neonates with HIE?

Appropriate neuroimaging is an important part of evaluating the etiology of HIE and predicting long term neurodevelopmental outcomes. Magnetic Resonance Imaging with diffusion weighted images and spectroscopy of the basal ganglia is the imaging study of choice (10). Elevated lactate peaks and low N-acetylaspartate levels in the basal ganglia are associated with poor neurodevelopmental outcomes (10, 11). Deep gray matter injuries including basal ganglia injuries and thalamic injury can indicate acute injury while injuries in the watershed areas can indicate prolonged partial hypoxia (5).

Recommendations:

1. Head ultrasound should be acquired on admission.

2. MRI with diffusion weighted images and spectroscopy of the basal ganglia is the preferred study.
3. 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.

Level of Evidence: IA randomized control trials.

V. References

1. Pressler RM, Boylan GB, Morton M, et al.: **Early serial EEG in hypoxic ischaemic encephalopathy.** *Clinical Neurophysiology* 2001; 112:31–37.
2. de Vries LS, Toet MC: **Amplitude integrated electroencephalography in the full-term newborn.** *Clinical Perinatology* 2006; 33:619–632.
3. van Rooij L, Toet MC, et al.: **Effect of Treatment of Subclinical Neonatal Seizures Detected With aEEG: Randomized, Controlled Trial** *Pediatrics* 2010; 125:358-366.
4. Evans DJ, Levene MI.: **Anticonvulsants for preventing mortality and morbidity in full term newborns with perinatal asphyxia.** *Cochrane Database*; 2007; Jul 18;(3):CD001240.
5. Glass HC, Ferriero DM: **Treatment of Hypoxic-Ischemic Encephalopathy in Newborns.** *Current Treatment Options in Neurology* 2007;9 :414–423.
6. Abend, et al. **Levetiracetam for Treatment of Neonatal Seizures.** *Journal of Child Neurology* 2011; 26:465-470.
7. Khan, et al.: **Use of Intravenous Levetiracetam for Management of Acute Seizures in Neonates.** *Pediatric Neurology* 2011;44:265-269.
8. Ramantani, et al.: **Levetiracetam: Safety and Efficacy in Neonatal Seizures.** *European Journal of Paediatric Neurology* 2011;15: 1-7.
9. Cilio, Ferriero.: **Synergistic Neuroprotective Therapies with Hypothermia.** *Seminars in Fetal & Neonatal Medicine* 2010;15: 293-298.
10. Boichot, Walker, Durand, et al.: **Term neonate prognoses after perinatal asphyxia: contributions of MR imaging, MR spectroscopy, relaxation times, and apparent diffusion coefficients.** *Radiology* 2006; 239:839–848.
11. Barkovich, Miller, Bartha, et al.: **MR imaging,MR spectroscopy, and diffusion tensor imaging of sequential studies in neonates with encephalopathy.** *American Journal of Neuroradiology* 2006; 27:533–547.
12. Thoresen, Satas, Loberg, et al.: **Twenty-four hours of mild hypothermia in unsedated newborn pigs starting after a severe global hypoxic-ischemic insult is not neuroprotective.** *Pediatric Research.* 2001;50 (3):405– 411.

13. Tortorici, Kochanek, Polovac: **Effects of hypothermia on drug disposition, metabolism, and response: A focus of hypothermia-mediated alterations on the cytochrome P450 enzyme system.** *Critical Care Medicine* 2007; Sep; 35(9):2196-204.