Cooling is standard of care in perinatal asphyxia for term and late preterms in developed countries. In India therapeutic hypothermia (TH) in perinatal asphyxia with HIE management has started picking up and most of level 3 neonatal units either in private or medical college set up have started practicing it with good results. The National Neonatology Forum in its accreditation programme has made it mandatory for level 3 B accreditation. It is now appropriate time for NNF to bring out a manual on “Therapeutic hypothermia for perinatal asphyxia” so that it can help the new units to start cooling therapy and also provide standardized care. The NNF at its annual convention every year conducts workshops on Therapeutic hypothermia. Hence, it was further necessary to have a manual on the same. The NNF is thankful to Prof. B Vishnu Bhatt and Dr. Adhisivam B and all the other contributors to have accepted the request and complete the project in the record short time of couple of weeks. We are also thankful to the Miracradle® team (Pluss Advanced Technologies Pvt. Ltd.) for sponsoring the printing of this manual to be distributed to all the delegates attending the 37th annual convention of NNF-2017 at Gurgaon.
Miracradle® Neonate Cooler is an affordable passive cooling device which uses the advanced savE® Phase Change Material technology to induce therapeutic hypothermia among newborns suffering from birth asphyxia.

Tried and tested by credible hospitals and doctors, Miracradle® hopes to give every baby in the developing world, a fair chance to survive.

THE MIRACRADLE® ADVANTAGE

**EASY TO USE**
Minimal manual supervision required. PCMs can be charged in a normal refrigerator.

**SAFE**
Passive cooling system; does not have any electrical supply near the baby.

**EFFICIENT**
Gives precise temperature control.

**ECONOMICAL**
Less than 1/5th of the cost of the available electronic devices.

**LONG LASTING**
The PCMs are designed for repetitive use.
There is ample evidence for the benefit of therapeutic hypothermia for term and late preterm neonates with perinatal asphyxia. Though it is the standard of care practiced in most of the developed countries, it is yet to gain momentum in India. We are happy that National Neonatology Forum (NNF), India is bringing out a manual on therapeutic hypothermia for perinatal asphyxia. The chapters in this manual have been contributed by clinicians with expertise in the field. Both theory and practical aspects of therapeutic hypothermia with special relevance to the Indian context have been covered. We are sure that this manual will be of great help to Neonatology fellows and Pediatric postgraduates in understanding the principles of therapeutic hypothermia and the nuances of practical application of this intervention.

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INTRODUCTION

The WHO definition of perinatal asphyxia is “failure to initiate and sustain breathing at birth”. Perinatal asphyxia leads to multi-organ dysfunction in the neonate and the neurological dysfunction inherent to this clinical condition is referred as Hypoxic Ischemic Encephalopathy (HIE). HIE is characterized by clinical and laboratory evidence of acute or sub-acute brain injury secondary to asphyxia. The primary causes of HIE are systemic hypoxemia and/or reduced cerebral blood flow. Every year, around 4 million babies die in the neonatal period (first 28 days of life) globally and asphyxia is one of the major causes accounting for 23% of these neonatal deaths. Among the survivors of asphyxia, cerebral palsy is a dreaded complication associated with loss of potential productive member for the society and direct burden lasting for the entire life on the individual and family and social institutions. Hence every effort should be made to prevent perinatal asphyxia and pediatricians should be well versed with the management of this important clinical condition.

EPIDEMIOLOGY

It is a sad fact that most of the neonatal deaths due to asphyxia (99%) occur in developing countries. HIE occurs in 1.5 per1000 full term births. While 15 - 20% of neonates with HIE die early, 25% will survive with disabilities. Moreover HIE is a major problem at all levels - individual, family and society, contributing to 15-28% of children with cerebral palsy and 25% of all children with developmental delay. Despite significant advances in perinatal care, cerebral palsy among term infants continues to occur. The long term neuro-developmental outcome depends on the severity of the neonatal encephalopathy.
According to NNPD 2003 data, Apgar score <7 at 1 minute (including moderate and severe asphyxia) was noted in 9% of all intramural deliveries while 2.5% babies continued to have Apgar scores <7 at 5 minutes of age. Bag and mask ventilation was required in 4.5% infants while less than 1% infants required cardiac compressions and/ or medications as part of resuscitation at birth. Clinical features of HIE were noted in 1.5% of all babies and it accounted for 20% of neonatal deaths.

**ETIOLOGY**

It is practically impossible to ascertain the exact time of the hypoxic insult sustained by a newborn unless some convincing evidence is available. Some of the common etiology for HIE are listed in Table 1. The clinical presentation of neonatal encephalopathy due to varied etiologies can overlap and hence it is difficult for the clinician to identify the etiology using neurological examination alone. It is always prudent to exclude other causes of neonatal encephalopathy when the perinatal risk factors are not clear.

**PATHOPHYSIOLOGY**

HIE does not refer to a single event but rather refers to a continuing process beginning from the time of hypoxic insult. There are two different episodes of neuronal impairment which are known to occur during HIE. The immediate hypoxic insult is called the primary phase and this is followed by a short period of recovery (latent phase) lasting for approximately six hours. Subsequently there is a longer phase during which there is a release of chemical mediators causing secondary neuronal damage. Neurons may die during the actual ischemic or primary phase itself. Several neurons however recover at least partially in the ‘latent’ phase but die hours or even days later (secondary or delayed cell death) (Fig.1).

Based on the cerebral energy state, HIE involves two phases of energy failure - primary and secondary. The blood flow and oxygen substrates in the brain are decreased in primary energy failure. Reduction in ATP and other phosphorylated compounds like phosphocreatine and significant tissue acidosis are important features during this phase. An “excito toxic - oxidative cascade” characterized by excessive stimulation of neurotransmitter receptors and membrane depolarization causing increased intracellular calcium is also observed. Increased levels of intracellular calcium activate nitric oxide synthase to perpetuate the release of nitric oxide, which in turn affects mitochondrial respiration (Fig.2). Signals from damaged mitochondria lead to apoptosis or programmed cell death till energy stores are available. However cessation of these energy supply results in cell necrosis. Activation of caspase enzyme system can also trigger apoptosis. Resolution of hypoxia can reverse the decrease in ATP and intracellular pH and enhances recycling of
neurotransmitters. In case of prolonged and severe insult, the initial cascade of events will cause a second phase of energy failure in the mitochondria. This secondary energy failure differs from the primary in that the decline in the levels of ATP and other phosphorylated compounds are not associated with brain acidosis. The secondary energy failure is characterized by continuing excite toxic-oxidation cascade, apoptosis, inflammation and altered growth factor levels and protein synthesis (Table 2). The interval between the primary and secondary energy failure is called the latent phase, an important therapeutic window (approximately 6 hours). When neuronal tissue sustains a hypoxic insult, cell death may be either delayed or remain progressive depending on the region and severity of the injury. Gestational age has a role in the susceptibility of the brain to hypoxic damage. In term neonates, the gray matter is primarily affected (selective neuronal necrosis) while in the preterm it is the white matter leading to periventricular leucomalacia. The other factors which contribute to the degree of damage include cellular susceptibility, watershed areas, regional metabolic rates and degree of asphyxia.

**OXIDATIVE STRESS AND DNA DAMAGE IN ASPHYXIA**

There are three important pathways that lead to free radical production. First one is Fenton reaction. During hypoxic ischemia, protein-bound iron is liberated from its binding proteins in the neuronal and microglial cells. Non protein bound iron (NPBI) or free iron usually accumulates during hypoxic ischemia. When the damaged brain is reperfused and re-oxygenated, toxic hydroxyl free radical will be formed as NPBI react with hydrogen peroxide. Thus NPBI is related to excessive neuronal damage immediately following the insult. Second, the activation of neuronal and inducible nitric oxide synthase leads to the generation of the nitric oxide radical (NO), which reacts with superoxide to form the toxic peroxynitrite (ONOO). Peroxynitrite and reactive oxygen species cause DNA damage and cell death. Finally, hypoxanthine, accumulated during the hypoxic-ischemic episode as a degradation product of ATP, is metabolized to uric acid by xanthine oxidase (XO). This reaction gives rise to further formation of superoxide radicals (Fig.3). The toxicity of these free radicals contribute substantially to reperfusion injury of the neuronal tissue after the hypoxic insult. Neonatal brain is more susceptible to oxidative stress because of low concentrations of antioxidants, a high consumption of oxygen and presence of high concentrations of unsaturated fatty acids that break down to form more oxygen free radicals.

**CLINICAL FEATURES**

The important CNS clinical features of HIE include altered level of sensorium, seizures and tone abnormalities. Their appearance is variable depending on the progression of energy failure and severity of insult and the usual time frame of these clinical features is depicted in Fig. 4. For quantifying the severity of HIE, Sarnat and Sarnat classification is commonly used while Levene’s classification is also helpful (Tables 3 and 4). Though the CNS features are sine qua non of HIE all other organ systems including the kidney and heart are also affected in variable proportions depending on the disease severity and quality of care (Table 5). When
the neonate sustains a hypoxic insult, almost all organs are at risk of cell injury and death. However, certain organs are more vulnerable to injury than others despite inbuilt physiological reflexes trying to protect these vital organs.

Acute kidney injury (AKI) is a common occurrence in infants with neonatal encephalopathy (NE), with a reported incidence of 50–72%. Most of these studies are small and employ varying definitions for AKI based on elevation of serum creatinine, oliguria, decreased glomerular filtration rate and presence of haematuria and proteinuria. Nevertheless, these studies emphasize the frequency of AKI complicating NE and underline the uncertainty surrounding the precise and early diagnosis of AKI in critically ill neonates. The majority of AKI following perinatal hypoxia-ischemia is prerenal in origin and often non-oliguric.

Cardiac dysfunction is part of the clinical spectrum of multi-organ dysfunction in term infants with HIE. In children with HIE, the reported incidence of cardiovascular dysfunction ranges from 29 to 78%. Oxygen deprivation secondary to a hypoxic and/or ischaemic insult causes myocardial damage. This eventually leads to decreased cardiac output, impaired myocardial contractility, systemic hypotension and pulmonary hypertension.

**DIFFERENTIAL DIAGNOSES**

History of prolonged and difficult labor coupled with need for significant resuscitation, low Apgar scores, altered sensorium and early onset seizures will usually point towards HIE. However, other differential diagnoses like inborn errors of metabolism, neuromuscular disorders, developmental defects of brain and sepsis should be kept in mind as their clinical features may overlap with HIE. It is not uncommon to find meconium aspiration syndrome and sepsis associated with HIE in term and preterm babies respectively.

**APPROACH TO DIAGNOSIS**

A detailed history including antenatal and delivery details reflecting events leading to compromised blood supply and/or oxygenation of the fetus should be obtained. History of placental abruption, cord around neck, cord prolapse, maternal hemorrhage, trauma, cardiorespiratory arrest, uterine rupture or significant fetal decelerations if present should be recorded. There is increased risk of neonatal encephalopathy if the mother has fever during antepartum or intrapartum period. A careful neurologic examination needs to be performed to diagnose encephalopathy.


**BOX 1: DEFINITIONS**

**Hypoxia or Anoxia:** A partial (hypoxia) or complete (anoxia) lack of oxygen in the brain or blood.

**Asphyxia:** The state in which placental or pulmonary gas exchange is compromised or ceases altogether.

**Ischemia:** The reduction or cessation of blood flow to an organ which compromises both oxygen and substrate delivery to the tissue.

**Hypoxic-Ischemic Encephalopathy:** Abnormal neurologic behavior in the neonatal period arising as a result of a hypoxic-ischemic event.

**Neonatal Encephalopathy:** A clinical syndrome of “disturbed neurological function in the earliest days of life in the term infant, manifested by difficulty with initiating and maintaining respiration, depression of tone and reflexes, subnormal level of consciousness, and often seizures.”

**Definition of Perinatal Asphyxia (PA)**
- World Health Organization: Failure to initiate and sustain breathing.
- NNPD Network:
  - Moderate PA: Slow/gasping breathing or an Apgar score of 4 to 6 at 1 minute.
  - Severe PA: No breathing or an Apgar score of 0-3 at 1 minute of age.
- American Academy of Pediatrics and American College of Obstetrics and Gynecology: Presence of all of following criteria-
  - Profound metabolic or mixed acidemia (pH< 7.00) in umbilical cord blood.
  - Persistence of low Apgar scores less than 3 for more than 5 minutes
  - Signs of neonatal neurologic dysfunction (e.g., seizures, encephalopathy, tone abnormalities).
  - Evidence of multiple organ involvement (such as that of kidneys, lungs, liver, heart and intestine).
**Fig. 1: Pathophysiology of HIE - Overview**

- Hypoxic depolarization
- Cell lysis
- Excitotoxins
- Calcium entry
- Primary energy failure
- Latent phase (6-15 hours)
- Secondary energy failure (6-48 hours)
- Oxidative metabolism recovery
- Apoptosis
- Inflammation
- Reduced mitochondrial activity
- Seizures
- Edema
- Cell death

**Fig. 2: Pathophysiology of HIE - Key Events**

- Cytosolic $Ca^{2+}$ increase
- Chemilox toxins (metals, CCl₄, quinones, peroxides)
- Impaired $Ca^{2+}$ transport
- Perturbation of cytoskeletal organization
- Phospholipase activation
- Protease activation
- Endonuclease activation
- Glucocorticoids
  - Receptor activation
  - Protein synthesis
  - $Ca^{2+}$ influx
- TCDD
  - Receptor activation
  - Impaired mitochondrial function
Fig. 3: Free radicals production in HIE

Fig. 4: HIE - Clinical Features

<table>
<thead>
<tr>
<th>Time</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth -12 hours</td>
<td>Depressed level of alertness, periodic breathing or respiratory failure, intact pupillary and oculomotor responses, hypotonia, seizures</td>
</tr>
<tr>
<td>12 - 24 hours</td>
<td>Change in level of alertness, seizures, apnoeic spells, jitteriness, weakness in proximal limbs, upper &gt; lower (term), lower &gt; upper (preterm)</td>
</tr>
<tr>
<td>24 -72 hours</td>
<td>Stupor or coma, respiratory arrest, brain stem pupillary and oculomotor disturbances, catastrophic deterioration with severe intraventricular hemorrhage and periventricular hemorrhagic infarction (premature)</td>
</tr>
<tr>
<td>&gt; 72 hours</td>
<td>Persistent yet diminishing stupor, disturbed sucking, swallowing, gag and tongue movements, hypotonia / hypertonia, limb weakness</td>
</tr>
</tbody>
</table>
### Table 1: Etiology of HIE

<table>
<thead>
<tr>
<th>Maternal</th>
<th>Uteroplacental</th>
<th>Fetal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac arrest</td>
<td>Placental abruption</td>
<td>Feto maternal hemorrhage</td>
</tr>
<tr>
<td>Asphyxiation</td>
<td>Cord prolapse</td>
<td>Twin to twin transfusion</td>
</tr>
<tr>
<td>Severe anaphylaxis</td>
<td>Uterine rupture</td>
<td>Severe iso immune hemolytic disease</td>
</tr>
<tr>
<td>Status epileptic</td>
<td>Hyper stimulation with</td>
<td>Cardiac arrhythmia</td>
</tr>
<tr>
<td>Hypovolemic shock</td>
<td>oxytocic agents</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2: Characteristics of energy failures related to HIE

<table>
<thead>
<tr>
<th>Primary energy failure</th>
<th>Secondary energy failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease in cerebral blood flow, oxygen substrates and ATP</td>
<td>Continuing of excite toxic-oxidative cascade</td>
</tr>
<tr>
<td>Excito toxic-oxidative cascade</td>
<td>Activation of microglia-inflammatory response</td>
</tr>
<tr>
<td>Loss of ionic homeostasis across membranes</td>
<td>Activation of caspase proteins</td>
</tr>
<tr>
<td>Entry of intracellular calcium</td>
<td>Reduction in levels of growth factors, protein synthesis</td>
</tr>
<tr>
<td>Mitochondrial disruption</td>
<td>Continuing Apoptosis and necrosis</td>
</tr>
<tr>
<td>Brain acidosis</td>
<td></td>
</tr>
</tbody>
</table>

### Table 3: Sarnat and Sarnat classification of HIE

<table>
<thead>
<tr>
<th>STAGE 1</th>
<th>STAGE 2</th>
<th>STAGE 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of consciousness</td>
<td>Hyperalert</td>
<td>Stuporous</td>
</tr>
<tr>
<td>Neuromuscular control</td>
<td>Lethargic or obtunded</td>
<td></td>
</tr>
<tr>
<td>Muscle tone</td>
<td>Normal</td>
<td>Flaccid</td>
</tr>
<tr>
<td>Posture</td>
<td>Mild distal flexion</td>
<td>Intermittent decerebration</td>
</tr>
<tr>
<td>Stretch reflexes</td>
<td>Overactive</td>
<td>Decreased or absent</td>
</tr>
<tr>
<td>Segmental myoclonus</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Complex reflexes</td>
<td>Weak</td>
<td>Absent</td>
</tr>
<tr>
<td></td>
<td>Weak or absent</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Strong; low threshold</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weak; incomplete; high threshold</td>
<td></td>
</tr>
<tr>
<td>Suck</td>
<td>Absent</td>
<td></td>
</tr>
<tr>
<td>Moro</td>
<td>Absent</td>
<td></td>
</tr>
<tr>
<td>Oculovestibular</td>
<td>Normal</td>
<td>Weak or absent</td>
</tr>
<tr>
<td>Tonic neck</td>
<td>Slight</td>
<td>Absent</td>
</tr>
<tr>
<td>Autonomic function</td>
<td>Generalized sympathetic</td>
<td>Both systems decreased</td>
</tr>
<tr>
<td></td>
<td>Generalized parasympathetic</td>
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Table 4: Levene's classification of HIE

<table>
<thead>
<tr>
<th>Feature</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consciousness</td>
<td>Irritable</td>
<td>Lethargy</td>
<td>Comatose</td>
</tr>
<tr>
<td>Tone</td>
<td>Hypotonia</td>
<td>Marked hypotonia</td>
<td>Severe hypotonia</td>
</tr>
<tr>
<td>Seizures</td>
<td>No</td>
<td>Yes</td>
<td>Prolonged</td>
</tr>
<tr>
<td>Sucking/respiration</td>
<td>Poor suck</td>
<td>Unable to suck</td>
<td>Unable to sustain</td>
</tr>
</tbody>
</table>

Table 5: Organ system dysfunction in perinatal asphyxia

<table>
<thead>
<tr>
<th>System</th>
<th>Dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS</td>
<td>Hypoxic ischemic encephalopathy, intracranial hemorrhage, seizures, long-term neurological sequelae</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Myocardial dysfunction, valvular dysfunction, rhythm abnormalities, congestive cardiac failure</td>
</tr>
<tr>
<td>Renal</td>
<td>Hematuria, acute tubular necrosis, renal vein thrombosis</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Delayed adaptation, respiratory failure, meconium aspiration, surfactant depletion, primary pulmonary hypertension</td>
</tr>
<tr>
<td>GI tract</td>
<td>Necrotizing enterocolitis, hepatic dysfunction</td>
</tr>
<tr>
<td>Hematological</td>
<td>Thrombocytopenia, coagulation abnormalities</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Acidosis, hypoglycemia, hypocalcemia, hyponatremia</td>
</tr>
</tbody>
</table>
Therapeutic Hypothermia (TH) has been proven to be effective in reducing morbidity associated with HIE and has become the standard of care for HIE in developed countries. However in underdeveloped and transitional countries where the problem is more common, therapeutic cooling is still in the nascent phase. There are several reasons for this in resource restricted settings. Similarly, despite availability of compelling clinical evidence that TH initiated within a few hours after hypoxic insult can improve neurological outcome in term infants, implementing the same in resource restricted settings of India is not that easy mainly because of the non-availability of expensive devices used for providing TH in developed countries. Recently, two systematic reviews on the efficacy and safety of TH in low and middle income resource settings have been published. The systematic review by Pauliah et al did not find any statistically significant reduction in neonatal mortality in underdeveloped countries although the confidence intervals were wide. Galvao et al observed that there is ample evidence for designating hypothermia as the standard of care for HIE but more evidence from low income countries is required.

TH is neuroprotective by inhibiting several steps in the excito toxic oxidative cascade which include inhibiting the increase in the concentration of lactic acid, glutamate and nitric oxide in the brain (Fig. 1 and Box 1). Moreover, TH inhibits protease activation, mitochondrial failure, free radical damage, lipid peroxidation and inflammation. TH has been shown to decrease brain energy use, prolong the latent phase, reduce infarct size, decrease neuronal cell loss, retain sensory motor function, and preserve hippocampal structures. Early application of TH preferably within 6 hours i.e. before the onset of the secondary phase of energy failure is likely to be effective and improve neurodevelopmental outcome. Usually it is
continued for a period of 72 hours for better neuro protection. Applying TH immediately or within a few hours after reperfusion and continued for 72 hours has been shown to favorably affect outcome in newborn and adult animals.

**Fig. 1: Pathophysiology of HIE - Key Events**

**Box 1: Summary – Mechanisms of action of Therapeutic Hypothermia**

- Reduction of cerebral metabolism and prevention of edema
- Decrease in energy utilization
- Reduction of cytotoxic amino acid accumulation and nitric oxide
- Inhibition of platelet-activating factor and inflammatory cascade
- Suppression of free radical activity
- Attenuation of secondary energy failure
- Inhibition of apoptosis (cell death)
- Reduction of the extent of brain injury
CHAPTER 3

THERAPEUTIC HYPOTHERMIA FOR NEONATAL ENCEPHALOPATHY
EVIDENCE

Dr. Nishad P

SUMMARY OF EVIDENCE OF BENEFIT

There is now unequivocal and high-quality evidence from multiple large RCTs that neonates with moderate to severe hypoxic-ischemic encephalopathy (HIE) following a perinatal event benefit from hypothermia under tightly controlled conditions. The trials used either head cooling devices (with mild systemic hypothermia), or whole-body cooling alone. A recent Cochrane review included 11 RCTs, comprising a total of 1,505 infants, and concluded that TH resulted in a reduction in the combined outcome of death or neurodevelopmental disability (to 18 months of age).

Cooling resulted in an absolute risk reduction (risk difference, RD) of 15% in the composite outcome. Put another way, the number needed to treat for one additional beneficial outcome (NNTB) was 7 (95% CI: 5 to 10). The RD for mortality with cooling was -9% (95% CI: -13% to -4%); NNTB 11 (95% CI: 8 to 25) and for neurodevelopmental disability in survivors was -13% (95% CI: -19% to -7%); NNTB 8 (95% CI: 5 to 14). The most influential RCTs are listed in Table 1.

Cooling appears to reduce DNA damage induced by oxidative stress and improve neurodevelopmental outcome. There is also evidence that therapeutic hypothermia limits myocardial and renal injury in term infants with HIE.

METHOD OF COOLING

A metaanalysis of the trials that used selective head cooling did not show a statistically significant difference in mortality (RR 0.78, 95% CI 0.59 to 1.04) or major neurodevelopmental disability (all participants,
RR 0.72, 95% CI 0.50 to 1.05). But it is worth noting that the trend toward benefit was strong and consistent, the magnitude of benefit was comparable to the trials that used whole body cooling, and the intervention in the head-cooling trials also included mild systemic hypothermia. In addition, there was a statistically significant reduction in the hypothermia groups when neurodevelopmental disability was assessed in survivors as opposed to all participants (RR 0.66, 95% CI 0.47 to 0.94).

Metaanalysis of the trials that used whole body cooling showed a significant reduction in mortality (RR 0.73, 95% CI 0.61 to 0.89) and a trend towards reduction in neurodevelopmental disability (all participants, RR 0.79, 95% CI 0.62 to 1.01). There was also a significant reduction in neurodevelopmental disability among survivors (RR 0.67, 95% CI 0.53 to 0.83). Apart from concerns about selective head cooling being less effective in cooling deeper brain structures, this method offers no advantages in cost or convenience over whole body hypothermia. Whole body hypothermia can also be delivered using inexpensive devices (discussed next) in low and middle income countries, hence should be the preferred method of cooling.

### Cooling Devices

While most western centers currently prefer systemic hypothermia delivered using servo-controlled mattresses, these devices are expensive. Other techniques have been used to cool infants, ranging from passive hypothermia to fans, ice/gel packs and phase-changing materials. Of the large RCTs, the ICE trial notably used gel packs to cool infants. The use of gel packs to cool infants has been studied in more resource-limited settings and appears to reduce the risk of death or developmental delay. In practice, ice packs are associated with wider fluctuations in temperature and are labor intensive, because of the need to rearrange the number and position of the gel packs based on infant temperature.

Passive cooling is a very practical and inexpensive option, especially for transporting outborn infants who may not arrive in an NICU within the 6-hour window for initiating hypothermia. But some infants do not cool enough with passive cooling, while others may overshoot the target temperature. In a retrospective observational study, only 39% of passively cooled transported infants were within the target temperature range upon arrival at the regional unit, compared to 100% of actively cooled infants.

The use of phase changing material for cooling is increasingly popular in India because of the availability of a relatively inexpensive device. This has been studied as an alternative to servo-controlled cooling and appears to perform reasonably well, with one study reporting that the target temperature was maintained during 96.2% of the cooling phase. As the study authors noted, however, careful monitoring is required, especially during the
induction phase and the rewarming phase. This has also been our experience, and overcooling appears to be a more common problem than failure to induce hypothermia.

**DURATION OF COOLING**

The duration of hypothermia in most trials was 72 hours. One trial cooled infants for 48 hours and another for 48 to 72 hours depending on the neurological status of the infant. In the ICE study, infants were re-warmed by 0.5°C every 2 hours and in two other studies, infants were allowed to re-warm spontaneously at room temperature. All the other studies rewarmed infants by 0.5°C per hour.

In 2014, NICHD investigators reported the initial results of a 2X2 factorial RCT which aimed to determine if cooling infants for a longer duration (for 120 hours), or to a lower temperature (to 32°C), or both are better than cooling at 33.5°C for 72 hours in term infants with moderate to severe HIE. They reported an adjusted risk ratio for NICU deaths of 1.37 (95% CI: 0.92 to 2.04) for the 120 hours group Vs. the 72 hours group. Safety outcomes were similar. The trial was stopped early for safety and futility after enrolling 364 instead of the planned 726 infants. Follow up data were available for 95% (n=347) of these infants at 18-22 months, and showed that death or moderate to severe disability occurred in 56 of 176 infants (31.8%) cooled for 72 hours and in 54 of 171 infants (31.6%) cooled for 120 hours (adjusted RR 0.92, 95% CI 0.68 to 1.25). The adjusted RD was -1.0% (95% CI -10.2% to 8.1%), indicating an NNTB of around 100. It is interesting to note that infants who were cooled for 120 hours at 32°C had the lowest disability rates but the highest mortality rates. Although the authors noted an interaction between longer and deeper cooling, the study was not powered to examine this interaction. Current evidence therefore suggests that cooling for a duration longer than 72 hours is not beneficial.

**DEPTH OF COOLING**

In the NICHD trial discussed above, death or disability occurred in 59 of 185 infants (31.9%) cooled to 33.5°C and in 51 of 162 infants (31.5%) cooled to 32.0°C (adjusted RR 0.92, 95%CI 0.68 to 1.26); adjusted RD was -3.1% (95%CI, -12.3% to 6.1%). Deeper cooling did not appear to be beneficial. The authors observed a significant interaction between longer and deeper cooling (P = .048); the primary outcome rates were 34.5% at 32.0°C for 72 hours, 29.3% at 33.5°C for 72 hours, 28.2% at 32.0°C for 120 hours, and 34.4% at 33.5°C for 120 hours. There is currently no evidence to cool below the commonly used target temperature of 33.5°C (range of 33°C-34°C).
REWARMING

There is concern about decrease in systemic blood pressure during rewarming.23 Rebound seizures can occur during rewarming,24, 25 and in at least one case, the infant had to be recooled for another 24 hours to control the seizures.25 Rewarming has also been reported to affect the EEG background.24 However, it is not clear if another regime for rewarming will be better than the ones used in the RCTs. With current evidence, it appears prudent to rewarm slowly, at a rate of no more than 0.5°C per hour.

COOLING PRETERM INFANTS

As can be seen from Table 1, most RCTs have been done in term and late preterm infants, with a gestational age of 35 weeks or higher. The vast majority of enrolled infants in these trials were born at term. Preterm animal models of asphyxia indicate that hypothermia may offer short-term neuroprotection.27 This would appear to support the idea of offering therapeutic hypothermia to preterm neonates with HIE, but there are serious obstacles to overcome.

In term infants, encephalopathy is more easily attributable to an acute peripartum event, and hence indicates a clinically significant hypoxic-ischemic event. In preterm infants, attributing an abnormal neurologic status to an intrapartum event is harder, because acute pulmonary and cardiac problems are common after birth, as is sepsis. EEG or aEEG, used in some RCTs of hypothermia, is harder to interpret in preterm infants, owing to maturational changes.28, 29

Initial reports of cooling preterm infants indicate that caution is warranted.30, 31 An RCT of whole body hypothermia in preterm infants between 33 and 35 weeks gestational age and weighing ≥ 1500g, with neonatal encephalopathy within 6 hours of birth, is currently recruiting infants (Clinicaltrials.gov identifier: NCT01793129). This is a multicentric trial conducted by the NICHD Neonatal Research Network, and the primary outcome is death or moderate or severe disability assessed at 18 to 22 months corrected age. Until more evidence is generated by this and other trials, hypothermia should not be offered to infants below 35 weeks of gestation.
### Table 1: Etiology of HIE

<table>
<thead>
<tr>
<th>NAME OF TRIAL</th>
<th>COOLING METHOD</th>
<th>PARTICIPANTS</th>
<th>TARGET TEMP. AND DURATION</th>
<th>INCLUSION CRITERIA</th>
<th>PRIMARY OUTCOME</th>
<th>PRIMARY OUTCOME INCIDENCE</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gunn et al, 2001 (18-month outcomes published later: Battin 2001)</td>
<td>Head cooling</td>
<td>22 term infants. Battin 2001: data on more infants (n= 40)</td>
<td>Minimal (rectal 36.3 ± 0.2°C) or mild (35.7 ± 0.2°C)</td>
<td>Encephalopathy</td>
<td>Mortality or major disability at 18 months</td>
<td>44% in normothermic, 26% in combined cooled groups</td>
<td>First RCT (safety study). 15 normothermic controls, 6 minimal cooling, 19 mild cooling.</td>
</tr>
<tr>
<td>Gluckman et al, 2005. CoolCap trial</td>
<td>Head cooling</td>
<td>235 term infants</td>
<td>34°C-35°C rectal for 72 hours</td>
<td>Moderate to severe encephalopathy + abnormal EEG</td>
<td>Death or severe disability at 18 months</td>
<td>66% in conventional, 55% in cooled, aOR 0.61 (0.34-1.09), p=0.10</td>
<td>Selective head cooling.</td>
</tr>
<tr>
<td>Zhou et al, 2010. Chinese RCT</td>
<td>Head cooling</td>
<td>256 infants</td>
<td>34°C nasopharyngeal and 34.5°C -35°C rectal for 72 hours</td>
<td>Encephalopathy</td>
<td>Death or severe disability at 18 months</td>
<td>49% in controls, 31% in cooled. OR 0.47 (0.26-0.84), p=0.01</td>
<td>21 post-randomization exclusions; ~20% had mild encephalopathy. Data unavailable for 41 infants.</td>
</tr>
<tr>
<td>Shankaran et al, 2005. NICHD trial</td>
<td>Whole body cooling</td>
<td>208 term infants</td>
<td>33.5°C esophageal for 72 hours</td>
<td>Moderate or severe encephalopathy</td>
<td>Death or moderate/severe disability at 18 months</td>
<td>62% in usual care, 44% in cooled. RR 0.72 (0.54-0.95), p=0.01</td>
<td>Data unavailable for 3 infants.</td>
</tr>
<tr>
<td>Azzopardi et al, 2009. Total Body Hypothermia for Neonatal Encephalopathy (TOBY) trial</td>
<td>Whole body cooling</td>
<td>325 infants ≥36 weeks</td>
<td>33°C to 34°C rectal for 72 hours</td>
<td>Moderate or severe encephalopathy and abnormal EEG</td>
<td>Death or severe neurodevelopmental disability at 18 months</td>
<td>53% in usual care, 45% in cooled. RR 0.86 (0.68-1.07), p=0.17</td>
<td>Data unavailable for 2 infants. Survival without disabilities higher and rate of CP lower in cooled group.</td>
</tr>
<tr>
<td>Simbruner et al, 2010. neo.nEURO network RCT</td>
<td>Whole body cooling</td>
<td>129 infants</td>
<td>33°C to 34°C rectal for 72 hours</td>
<td>Moderate or severe encephalopathy and abnormal EEG</td>
<td>Death or disability at 18 months</td>
<td>83% in usual care, 51% in cooled. RR 0.21 (0.09-0.54), p=0.001</td>
<td>Data on 18 infants not available. All infants received morphine infusions.</td>
</tr>
<tr>
<td>Jacobs et al, 2011. Infant cooling evaluation trial (ICE trial)</td>
<td>Whole body cooling</td>
<td>221 infants ≥35 weeks</td>
<td>33°C to 34°C rectal for 72 hours</td>
<td>Moderate or severe encephalopathy and abnormal EEG</td>
<td>Death or major disability at 24 months</td>
<td>66% in controls, 51% in cooled. RR 0.77 (0.62-0.98), p=0.001</td>
<td>Data on 13 infants not available. Cooling initiated at referral hospital. Mild encephalopathy in 15% of hypothermia group and 23% of controls.</td>
</tr>
</tbody>
</table>


According to the Lancet Global Series on Neonatal survival, an estimated 4 million babies die every year in the neonatal period. Ninety nine percentage of these deaths are in low to middle income countries. India contributes to one-fifth of global live births and more than a quarter of neonatal deaths. The neonatal mortality rate (NMR) as of 2013 is 28 per 1000 live births, of which the NMR for rural and urban is 31 and 15 per 100 live births respectively. Intrapartum complications and birth asphyxia account for 23% of neonatal deaths globally and 19.2% of neonatal deaths in India, of which 97.8% of deaths due to asphyxia occur in the first week of life and 70% within the first 24 hours. The reported incidence of deaths due to hypoxia varies from 2 to 16.2% in community-based studies, with case fatality rates ranging from 38.5 to 74%. Survivors of Hypoxic ischemia encephalopathy carry an additional burden of long term morbidity, neurological disability and functional impairment. As of today, the only modality for treatment and a means to decrease long term morbidity in babies with perinatal asphyxia is the initiation of therapeutic hypothermia within the first 6 hours of life.

COOLING IN LOW AND MIDDLE INCOME COUNTRIES

There has been considerable debate regarding the use of cooling in low and middle income countries. Increased rates of maternal malnutrition, inadequate maternal pelvis size, poor antenatal
obstetric care, late referral of complicated pregnancies, lack of trained birth attendants for
and basic equipment for neonatal resuscitation, lack of referral centers that can manage
neonates that require ventilation, increased rates of HIV, malaria and puerperal sepsis are
factors that increase the risk of perinatal asphyxia. 6

While the perinatal services offered in high income-low neonatal mortality countries are
either institutional deliveries or home deliveries with rapid transport to a tertiary level
neonatal unit, 25% of deliveries in India are home deliveries with minimal care thereafter. 3
Lack of access to transport, large distances and costs that are required to be borne for
transport, coupled with weak communication systems and deliveries in resource poor
settings can lead to delay in care that can be offered to a sick neonate. Even in cases of
institutional delivery, delay in transport and referral can lead to loss of the window for
initiation of therapeutic hypothermia.

An increased rate of perinatal infections has also raised concern when cooling in India.
Data from animal studies suggest that hypothermia may not be neuroprotective after
bacterial lipopolysaccharide-sensitized brain injury as compared to hypothermia without
bacterial lipopolysaccharide. 7 There has also been concern that hypothermia can lead to
decreased neutrophil function and chemotaxis and increased or worsening sepsis.
However, reported rates of culture proven sepsis in a trial of cooling with gel packs done in
India was 6.5%, with similar rates reported from the National Institute of Child Health and
Human Development (NICHD) trial. 8 In a case series of 40 babies from a tertiary level NICU, of
40 babies who received therapeutic hypothermia, only one had a positive blood culture
result and 11 had results that were positive for C-reactive protein. 9

Other concerns that have been expressed are that the population has increased rates of
intrauterine growth retarded babies, and an increased incidence of meconium aspiration
syndrome. Temperature fluctuations and shivering have been pointed out as drawbacks to
cooling with low-tech methods. However, when done under close monitoring, the
fluctuations seen with manual cooling devices are no different from those seen in the NICHD
and Total Body Hypothermia for Neonatal Encephalopathy (TOBY) trials.

A constant criticism of therapeutic hypothermia by hypothermia-sceptics is that
hypothermia decreases mortality but leads to an increase in survival of neonates with
neuro-developmental morbidities. In India, there is a lack of institutionalized developmental
follow up and support for children with developmental delay and disability is limited from
governmental organizations and the society at large. This situation, however, has the
potential to change and improve. While the economics of cooling in low to middle income
countries has not yet been worked out, data from the TOBY trials show a clear benefit to
cooling.
EQUIPMENT USED AND TRIALS FROM INDIA

Cooling equipment used in the high-income countries is expensive and unsuitable for wider use in low and middle-income countries. Studies have looked at passive cooling (keeping the baby without clothes, and without the use of a radiant warmer) during transport and the induction phase of therapeutic hypothermia. This was found to lead to over cooling, with temperatures < 32°C noted. It was also thought to be unlikely to be able to sustain temperatures within the target range for the 72 hour duration of cooling that is required.\(^{11}\)

Whole body cooling has been described from other countries using water bottles, gloves filled with water, a laminar flow device and a servo controlled fan. The first trial of whole body cooling in India was reported from the Christian Medical College, Vellore, and was a study done to determine the feasibility and safety of whole body cooling in newborn infants with perinatal encephalopathy in a low resource setting. This described hypothermia using ice gel packs. This study involved neonates >35 weeks gestation who were cooled to a rectal temperature of 33±0.5°C for 72 hours. Twenty infants were included in this study that used reusable ice gel packs obtained from the immunization clinic at no added expense. While this low cost alternative required frequent changes of packs, more nursing input and constant monitoring, the target temperature was achieved and maintained with ease. The study concluded that whole body cooling in term infants with perinatal asphyxia was achievable, safe and inexpensive in a low-resource setting. However, the swings of temperature, and shivering of the cooled infant lead to the beginning of a search for a better low cost solution.\(^{12}\)

The second published trial in India came from the Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Pondicherry, a year later, which cooled babies with cloth covered gel packs and followed them up to an age of 6 months. These infants were assessed at 6 months using Baroda Developmental Screening Test, and the group that received therapeutic hypothermia showed a significant reduction in the combined rate of death or developmental delay at 6 months of age by 21% (8.1% in the TH group vs. 29% in the control, RR 0.28, 95% CI: 0.11-0.70; p = 0.003).\(^{13}\) The same researchers from JIPMER also showed that therapeutic hypothermia reduced oxidative stress as measured by total antioxidant status and malondialdehyde, and reduced oxidative stress-induced DNA damage.\(^{14}\)

In 2009, Iwata et al published their report of the successful use of phase changing material (PCM) for cooling newborn piglets that had been exposed to hypoxia. The use of the PCM mattress was found to give more stable cooling, and a longer period within the target range of temperature.\(^{15}\) The first randomized controlled trial of whole body cooling using phase changing material was conducted in Calicut in south India in 2013. Thirty three infants with Thompsons encephalopathy score >5 were cooled. However, the study found that cooling with PCM was effective only when the ambient temperature was <28°C, and required close temperature monitoring by the nursing staff.\(^{16}\)
In 2014, a study was conducted on 28 newborns in the neonatal unit of the Madras Medical College, Tamil Nadu, which assessed the feasibility of the use of the Tecotherm-HELIX cooling mattress. This was a servo-controlled cooling device developed for low to middle income countries, with an estimated cost of US$1000. It worked on the basis of recirculating water mixed with alcohol through a re-usable cooling mattress to achieve a set temperature of 33.5°C. The advantage of the Tecotherm-HELIX cooling mattress was that refilling the machine with water every 6 – 8 hours was the only additional nursing input required. However, the cooling mattress required replacement once in the 6 month study period.

During the years from 2011 to 2014, a wholly indigenous passive cooling mattress that was based on phase changing material was in development at the Christian Medical College, Vellore. Multiple attempts were made to find the ideal PCM that was easy to use, safe, lightweight, portable and gave precise temperature control of 33-34°C for 72 hours with minimal manual supervision and no requirement of constant electricity. The feasibility of the technology was reported in 2015, on a retrospective series of 41 babies with HIE who had been cooled with PCM (OM 32™ or HS 29™) to a target rectal temperature of 33-34°C. This was successful in maintaining the target temperature range 96.2% of the time in the cooling phase.

The final product was the CMC PCM Mattress- Patent-3184/DEL/2013. This used a cascaded system of PCMs that were incorporated in a polymer matrix that provided form stability and ensured that the PCM retained its shape and form, preventing leakage. The melting points, thicknesses, conductivities and placement of the involved layers were such that a “quasi-automated” cooling system was created, which functioned similar to a servo controlled system. Pluss Advanced Technologies, who supplied the phase change material worked closely with the research team from Christian Medical College Vellore, and later marketed it as the MiraCradle®. Over the years, from 2011, more than 200 babies have been cooled successfully, with minimal complications and successful maintenance of temperature within the target ranges. More than 150 commercial PCM mattresses are currently in use in India and data of 103 babies cooled in 10 different hospitals in India with good results has been sent for publication. They are also used across the world, in South Africa, Turkey and in Kenya.

**SYSTEMATIC REVIEW AND META-ANALYSIS**

A systematic review by Pauliah et al. did not show any significant improvement in mortality and concluded that cooling cannot be recommended in both low and middle income countries until further data suggest benefit. However, the confidence intervals in this review were wide, and it was speculated by the authors that the reasons for the lack of treatment effect observed were poor quality of the included studies; lack of efficiency of low technology cooling devices; lack of optimal neonatal intensive care, sedation and ventilation support; intrauterine growth restriction; and maternal malnutrition.
The review concluded that therapeutic hypothermia using low technology methods was achievable, safe and inexpensive. When combined with intensive care, this is proven to significantly reduce the mortality and neurological morbidity in survivors at discharge. The Meta-Analysis by Rossouw et al shows that low technology cooling devices are effective, and make a difference in the mortality and morbidity of the babies when used in an intensive care setting where mechanical ventilation is available, and when it is possible to provide more intensive nursing. The initial feasibility study from India had shown that cooling with manual application of cloth-covered gel packs was feasible with a nurse-to-infant ratio of 1:3.\textsuperscript{12}

A meta-analysis by Galvao et al.\textsuperscript{23} of 16 studies and a total of 1889 neonates (of which 8 of the studies included were conducted in lower income countries) showed that hypothermia significantly reduced mortality (RR = 0.77; 95% CI: 0.65-0.92). Meta-regression analysis also revealed that hypothermia efficacy does not increase as the gross domestic product per capita of the country in which it is done rises, and they concluded that there is enough evidence to support therapeutic hypothermia as the standard of care for hypoxic-ischemic encephalopathy.

**CONCLUSION**

India, with diverse patient profiles, has centers that have facilities that equal those in high income countries. A trial of cooling can no longer be done in a high income country due to the loss of equipoise. To do so in our country – to offer cooling versus normothermia in babies with perinatal asphyxia should raise ethical questions. In areas that lack basic facilities, the focus should remain on improving antenatal and neonatal care to prevent asphyxia. Training of personnel, following standard protocols for cooling, setting up and maintaining a national registry to monitor neurodevelopmental outcome (similar to the TOBY registry) is what we should achieve. While the equipment used in high income countries cannot be sustainably used in low and middle income countries, therapeutic hypothermia using low cost technology can provide sustainable, efficient and effective treatment with minimal costs and maximal benefits, and should be implemented as a standard of care for infants with moderate or severe HIE and refusal cannot be justified where facilities exist.
BIBLIOGRAPHY


Many tertiary level hospitals in India have started providing therapeutic hypothermia as standard of care to newborn with moderate to severe degree of hypoxic ischemic encephalopathy. One of the limiting factors to provide therapeutic hypothermia in India is availability of cooling device. Therapeutic hypothermia can be provided as selective head cooling or whole body cooling. In this article, we will discuss what would constitute an ideal cooling device, what are the devices available and a description on how they function.

**THE CHARACTERISTICS OF AN IDEAL COOLING DEVICE**

- It should induce cooling rapidly to the desired core temperature
- It should maintain the core temperature tightly within the target range
- It should allow re-warming in a slow and controlled manner
- It should be easy to use
- It should require minimal nursing input
- It should not interfere with access to the baby
- Environmental temperature should not affect cooling efficacy
- Safety systems in case of accidental probe displacement
Since the early 2000’s, therapeutic hypothermia has been tried either as selective head cooling or as whole body cooling. Many of these devices are cost-prohibitive. Hence alternate low cost cooling systems have been developed for use in resource limited settings. The various high technology devices with their cooling methods are summarized in Table 1.

**Cooling Equipment- High technology devices**

1. **BLANKETROL 2** (Cincinnati subzero products Inc, USA) was used in the NICHD trial. It is a microprocessor controlled device based on conductive water therapy. Target temperature is achieved by heating and cooling water circulated through mattress and wraps. Due to fluctuations in temperature, additional blankets were used around the baby. The rewarming process is manually done in the device.

   **BLANKETROL 3** used gradient programme technology to minimize fluctuations in water temperature. It did not require use of additional blankets. It involved precooling to 5°C 15 minutes prior to starting. Oesophageal probes were used for temperature recording. Data export software was incorporated.

2. **Criticool from MTRE**, Charter Kontron, Milton Keynes, UK, is a microprocessor controlled servo device. It has a large basal unit and disposable cure wraps through which water is circulated. Access to baby is restricted due to wraps covering the baby. The rewarming phase can be set in manual or controlled mode. Controlled rewarming is set at 0.2°C per 30 minutes. It takes 7.5 hours to rewarm.
3. **Tecotherm TS med 200** from Tec-com, Halle Germany: Is a manual cooling device which was used in the TOBY trial.

4. **Tecotherm Servo** from Tec-com, Halle Germany: This consists of a mattress that is wrapped around baby’s trunk and legs. The device is fully automated and requires no further input after initiation. The baby’s temperature is cooled to 33.5°C within 30 minutes. This temperature is maintained for 72 hours and a fully automated rewarming process starts. The rewarming occurs to 37°C at 0.2-0.5°C/hour (requiring around 7 hours for rewarming). The monitor displays rectal and skin temperature. Data can be transported out of the machine and analyzed. Default temperature settings on the machine can be altered according to individual needs.

5. **Cool cap** (Olympic Medical Cool Care System, Olympic Medical, Seattle, WA, USA): This was used for selective head cooling. Olympic cool cap system maintains the water in the fitted cap at an operator specified temperature. The rest of the body is exposed to radiant warmer. It requires lot of nursing input. Rectal temperature is used to guide the set temperature. Target temperature is 34-35°C. Rewarming is manual in cool cap.

There is a statistically significant reduction in the composite outcome of death or major neurodevelopmental disability in both selective head cooling and whole body cooling as per Cochrane meta-analysis. During selective head cooling there is a temperature gradient between the surface and deeper structures of the brain. Even when we effectively cool the surface of brain to desired temperature, the deep brain structures may not be adequately cooled. This is a significant concern as profound hypoxic injury particularly affects the deep brain structures. In a comparative study there were lesser lesions on MRI after whole body cooling in comparison to selective head cooling.
<table>
<thead>
<tr>
<th>NAME OF DEVICE</th>
<th>DESIGN</th>
<th>FEATURES</th>
<th>ISSUES</th>
<th>RECURRENT EXPENSES</th>
</tr>
</thead>
</table>
| Blanketrol 2   | Mattress Wraps | Coolant–water Wraps                        | 1. Temperature fluctuation  
2. Rewarming –manual  
3. Not portable | Cooling wraps      |
| Blanketrol 3   | Mattress Wraps | Coolant–water Wraps                        | 1. Pre-cooling required.                                 | Cooling wraps      |
2. Not portable   | Cooling wraps      |
| Tecotherm Servo| Mattress | 1. Fully automated Rewarming –automated    |                                                          | Coolant top ups and mattress |
|                |          | 2. Portable                               |                                                          |                     |
|                |          | 3. Alcohol based coolant                  |                                                          |                     |
| Cool cap       | Cap      | 1. Selective head cooling                  | Manual rewarming  
More nursing input | Cooling cap        |
COOLING EQUIPMENT-LOW COST DEVICES

Various low technologies methods like passive cooling, ice gel pack, cooling fan, etc., have been tried to achieve therapeutic hypothermia because of the high cost and unavailability of servo controlled equipment. There have been concerns of overcooling, fluctuations in temperature, cold injury like subcutaneous fat necrosis, increased shivering and need of more nursing input. Increase in awareness, intensive monitoring, refinement of technology (e.g., use of phase changing material) and appropriate intervention (e.g., use of analgesia, frequent change in position) have helped to achieve therapeutic hypothermia without overcooling and minimal fluctuations of temperature. We have shown the efficacy and safety of low technologies devices like frozen gel pack and phase changing materials which is comparable to standard servo-controlled cooling equipment. A recent systematic analysis has shown that low technology device in tertiary level settings has improved survival and neurological outcome in HIE babies with moderate to severe encephalopathy.

PASSIVE COOLING

Babies are kept naked with radiant warmer switched off. This has been mainly tried during transportation for induction phase of cooling. It is feasible to achieve cooling passively but there has been concern of overcooling. Several studies have reported significant overcooling (<32°C) in approximately one third of the babies. There is no published data regarding use of passive cooling for maintenance and rewarming phase.

FROZEN/ICE GEL PACK

ICE trial, a multi-center randomized controlled trial, showed improved disability free survival in babies with moderate to severe HIE after achieving therapeutic hypothermia with frozen gel pack. In India, the feasibility trial from Christian Medical College, Vellore showed safety and effectiveness of frozen gel pack (FGP) for therapeutic hypothermia.

Method: Insert rectal probe 5 cm inside and fix to thigh. Switch off the radiant warmer. For induction phase, distribute 4-5 packs over the head, both axillae, back and abdomen. Once the temperature reaches 34°C, remove packs one by one, targeting the temperature of 33.5 ± 0.3°C. The packs on the head and back are to be removed last.

Gel packs should be stored in deep freezer. Wrap the FGP with cloth and avoid direct skin contact for longer duration. This minimizes cold injury to skin. Always have rectal probes for temperature monitoring. Skin probes are NOT an acceptable alternative. Leave only one FGP at the temperature of 33.5°C. Set the alarm limit at 33.2°C and 33.8°C on monitor during maintenance phase. At the end of 72 hours of induced hypothermia, remove cool packs and turn on the radiant warmer to raise the body temperature by 0.3°C/hour to reach a target temperature of 36.5°C. (This should take 12-15 hours). The temperature probe should
be removed after monitoring the temperature for a further 12 hours (72 + 12 hours after initiation of cooling).

If the infant’s rectal temperature increases to 33.8°C, more cloth covered cooling-gel packs should be placed and then subsequently removed when the rectal temperature reaches 33.5°C.

If the temperature decreases to 33°C, remove cooling gel packs/turn warmer on till temperature reaches 33.5°C

**PHASE CHANGING MATERIALS**

Phase changing materials (PCM) are made of salt hydrate, fatty acid and esters or paraffin, melting at a set point. PCMs absorb and release heat at a nearly constant temperature and can store 5–14 times more heat per unit volume compared to material like water or masonry. When a baby is placed on a bed made of PCM, heat from the baby is transferred to the PCM which absorbs the heat till it melts. Hence, PCM has the potential to provide a mechanism of heat removal which will be easier and safer to use than ice packs. Keeping the melting point of the PCM at the target temperature will ensure that the baby’s temperature will not fall below this temperature. The device designed by our unit has used PCM with 2 different melting point: PCM 21 with melting point at 21°C for induction phase and PCM 29 with the melting point at 29°C for maintenance phase. The theory and methodology has been described in detail.¹¹ PCM should not be frozen. It should be stored in the lower compartment of refrigerator.

In our study with PCM, induction time was 45 minutes, only 3.8% of temperature readings were outside the target range and fluctuation of core body temperature was 0.28°C.⁵

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**Equipment description**

1. Outer covering layer - good conductor (only lines)
2. Foam layer (orange-yellow)
3. Insulating layer (green)
4. PCM layer (red)
5. Water pack layer (blue)

Top view of mattress with PCM and water packs

Cross-section with outer covering
**METHODS**

Switch off radiant warmer. Fix the rectal probe.

Remove the PCM from refrigerator and keep it in room temperature for 30 minutes before commencing cooling. Use PCM 21 for induction and PCM 29 for maintenance phase if nursery temperature is 27°C or above. If nursery temperature is 26°C or less, use 29 PCM for both the phases.

If you are using 21 PCM for induction, remove it once rectal temperature is 34°C.

If the infant’s rectal temperature increases to 33.8°C, change 29 PCM if it is melted. If 29 PCM is good, add a 21 PCM and then subsequently remove when the rectal temperature reaches 33.5°C.

If the temperature decreases to 33.2°C, introduce a bed sheet between baby and PCM. If temperature remains low, turn warmer on till temperature reaches 33.5°C.

PCM based devices have been successfully used in CMCH, JIPMER and various other hospitals in India over the past few years with documented evidence of safety and efficacy.

**OTHERS**

Laminar flow device, cooling fans, clay pots have been used for therapeutic hypothermia in various studies.

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**Table 2: Comparison of different cooling device**

<table>
<thead>
<tr>
<th></th>
<th>Frozen gel pack</th>
<th>Phase changing material</th>
<th>Servo controlled device</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time taken to reach target temperature, minutes; median (IQR)</td>
<td>45 (10, 100)</td>
<td>90 (25, 150)</td>
<td>90 minutes (NICHD) 30 minutes (TOBY)</td>
</tr>
<tr>
<td>Temperature fluctuation during cooling phase, °C; mean (SD)</td>
<td>0.4</td>
<td>0.28</td>
<td>0.4 (TOBY) 0.5 (NICHD) (semi-automated)</td>
</tr>
<tr>
<td>Temperature readings outside the target range</td>
<td>9.8 %</td>
<td>3.8 %</td>
<td></td>
</tr>
<tr>
<td>Subcutaneous Fat Necrosis</td>
<td>13 %</td>
<td>2.2 %</td>
<td>2.8 %</td>
</tr>
<tr>
<td>Laborious nursing input</td>
<td>More</td>
<td>Less</td>
<td>Least</td>
</tr>
</tbody>
</table>
Fully automated servo controlled Cooling devices are ideal for providing therapeutic hypothermia to newborn with asphyxia. Affordability is the main issue. Low technology cooling devices like frozen gel packs and Phase change materials are effective, safe and an affordable alternative in intensive care settings.

**BIBLIOGRAPHY**


WHICH NEONATES TO COOL?

Neonates can be considered for cooling if the following criteria are met (NICHD criteria):

1. Gestational age $\geq$ 36 weeks
2. Less than 6 hours old
3. A pH of 7.0 or less or a base deficit of 16 mmol per liter or more in a sample of umbilical cord blood or any blood during the first hour after birth. If the pH is between 7.01 and 7.15, a base deficit is between 10 and 15.9 mmol per liter, or a blood gas is not available, additional criteria are required. These include an acute perinatal event (e.g., late or variable decelerations, cord prolapse, cord rupture, uterine rupture, maternal trauma, hemorrhage, or cardiorespiratory arrest) and either a 10-minute Apgar score of 5 or less or assisted ventilation initiated at birth and continued for at least 10 minutes.
4. Moderate to severe encephalopathy on clinical examination.

TYPES OF COOLING

Two different types of hypothermia were practiced:

a) Selective head cooling
b) Whole body cooling

Though selective head cooling appears to be attractive, it does not correlate well with core body temperature. There is also differential cooling between the superficial and deeper parts of the brain causing differential perfusion. In contrast, whole body cooling correlates well with core body temperature but associated with more adverse effects.
PREREQUISITES TO PRACTICE THERAPEUTIC HYPOTHERMIA

The minimum prerequisites to start the practice of therapeutic hypothermia have been depicted in Table.1:

Table 1: Minimum requirements to practice therapeutic hypothermia.

<table>
<thead>
<tr>
<th>Place</th>
<th>Personnel</th>
<th>Paraphernalia</th>
<th>Protocols</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well established</td>
<td>Trained doctors &amp;</td>
<td>Radiant warmer, Cooling device, ABG machine, Multi-</td>
<td>Evidence based standard protocol. Neuro-</td>
</tr>
<tr>
<td>level-3 NICU care.</td>
<td>Staff nurse</td>
<td>parametric parameters, Ventilators</td>
<td>development follow up.</td>
</tr>
</tbody>
</table>

DIFFERENT PHASES OF COOLING THERAPY

The different phases of therapeutic hypothermia are depicted in the Table 2.

Table 2: Phases of therapeutic hypothermia.

<table>
<thead>
<tr>
<th>Hypothermia phases</th>
<th>Strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>INDUCTION</td>
<td>Rapid cooling to 33-34°C. Duration: 45 minutes-1 hour. Monitor temperature and vitals. Treatment of shock and seizures. Avoid shivering and overcooling. Rectal probe inserted 5 cm into the rectum and skin probe over the abdomen are connected to the monitor for continuous monitoring. The radiant warmer is switched off.</td>
</tr>
<tr>
<td>MAINTENANCE</td>
<td>The target temperature is monitored every 15 minutes for the first four hours and later hourly for 72 hours. Vital parameters like heart rate, capillary filling time and blood pressure are recorded hourly. Close monitoring of temperature and vitals. Maintain temperature: 33-34°C. Total Duration: 72 hours. Monitor urine output and adjust total fluid intake. Monitor for multi-organ damage. Adjust drug dosages. Look for bed sores and skin damage.</td>
</tr>
<tr>
<td>REWARMING PHASE</td>
<td>Slow rewarming initiated. Duration: 6-10 hours. Temperature raise: 0.5°C/hour. Look for seizures. Avoid fluid shifts. Careful vitals monitoring. After rewarming feeding is started gradually.</td>
</tr>
</tbody>
</table>
As cooling is used more widely and has been newly introduced in neonatal units, continued surveillance of its use in clinical practice is mandatory. The initial management of infants with HIE following admission to the neonatal unit consists of standard neonatal intensive care measures, continuous core temperature monitoring using a rectal probe and initiation of therapeutic hypothermia. Monitoring of such infants is critical to the neurological outcome. We describe here the systematic approach to monitor these infants.

**TEMPERATURE MONITORING**

Both the core temperature and skin temperature are monitored continuously. The core temperature is usually monitored by rectal or oesophageal probe. The rectal probe should be inserted 3-6 cm and secured to the thigh. The oesophageal probe is inserted to a length of measured distance (Angle of mouth to tragus and up to a point 2 cm above Xiphisternum). The temperature is recorded every 15 minutes till a core temperature of 33.5°C is achieved and thereafter every hour till rewarming is completed. The core temperature should be maintained between 33.5°C to 34°C. The fluctuation of temperature during the maintenance phase should be very minimal as it can adversely affect the neurological outcome.

**CARDIORESPIRATORY CARE**

Hypothermia is consistently associated with sinus bradycardia as it slows the atrial pacemaker and intracardiac conduction. The QT
interval also can be prolonged. The heart rate can be even lower than 100. Heart rate drops by nearly 14 beats per one degree drop in temperature. HR up to 70 can be tolerated as long as it is normal sinus rhythm and normal SPO2 and BP are observed. Therefore, it is vital to observe these neonates with continuous cardiac monitoring preferably with multi-channel monitoring. Sinus bradycardia usually does not need intervention. Close monitoring of blood pressure is very essential to identify shock since CRT will be not a reliable indicator of hypo perfusion in babies receiving cooling therapy. All infants should be monitored closely with invasive blood pressure monitoring (if possible) and treated with inotropes accordingly.

**MECHANICAL VENTILATION**

Ventilation may not be needed for all neonates during cooling, however, it is important to maintain normal pCO2, pO2, pH and respiratory effort. Decreasing body temperature lowers metabolic rate by about 5-8% per °C. Furthermore, partial pressure of blood gases and pH are also affected because of altered gas solubility during hypothermia. With each degree Celsius decrease in core temperature, pH increases by 0.015, pCO2 and pO2 decrease by 4% and 7% respectively. Excessively low pCO2 during therapeutic hypothermia may result in altered cerebral blood flow auto regulation, and reduced cerebral perfusion, and may lower the seizure threshold. Hence, blood gas values should be corrected for core body temperature. The corrected blood gas values should be maintained within the normal range by appropriate ventilator adjustments.

**CARDIO-RESPIRATORY MANAGEMENT**

- Correct respiratory acidosis by manipulating ventilator support
- Start mechanical ventilation if repeated desaturations associated with seizures or incipient respiratory failure with rising oxygen requirements and increasing respiratory acidosis are observed.
- Avoid hypocapnia. Aim for pCO2 around 45 - 50 mm during cooling
- Maintain SaO2 > 92% to lessen risk of pulmonary hypertension
- Obtain arterial access to monitor blood pressure if mechanical ventilation is required
- Monitor regional perfusion using capillary refill scores and core-peripheral temperature gap as guides to peripheral blood distribution
- Aim for mean blood pressure (BP) > 40 mm Hg. A low BP requires assessment. Perform echocardiographic assessment (if available) of cardiac contractility and stroke volume to guide fluid/inotrope administration
**SKIN MONITORING**

Poor skin perfusion occurs during cooling. The skin has to be inspected periodically and the back to be inspected at least 12 hourly. The position has to be changed 6 to 12 hourly from flat to slightly tilted in the supine position. Cyanosis of the hands and feet is common and usually transient.

**FLUID BALANCE**

Disturbances in electrolytes and glucose homeostasis are common in infants with HIE, including those receiving therapeutic hypothermia. Fluid balance is essential in cooling neonates as the metabolic rate is low, and they may not need large volume of fluids. It is challenging to restrict fluids and supplement adequately. Fluid boluses should be avoided as it can lead to exacerbation of oedema which is due to capillary leak. The cooled babies may need more volume during rewarming phase due to redistribution of fluid into the tissues and increased diuresis.

It is recommended that serum electrolytes and plasma glucose should be kept within the normal range during hypothermia treatment. Hypocalcemia, hypomagnesemia, and hypoglycemia are common in asphyxiated newborn infants. Hence close monitoring of electrolytes and blood gas should be performed as per needs of the baby.

**FLUID BALANCE**

- Hypoglycemia can be a serious complicating factor in HIE. Monitor plasma glucose closely (4 hourly) and adjust glucose intake accordingly.

- Oliguria/anuria is common following HIE; Monitor urinary output and aim for urine output ≥ 1ml/kg/hour. Observe for bladder retention. Urinary catheterization may be useful.

- Daily weight monitoring should be carried out.

- Initial intravenous fluid requirements are approximately 40 ml/kg/day 10% Dextrose solution. Monitor blood electrolyte levels 8 hourly for first 24–48 hours.

- Grade up fluid depending on the weight gain and presence of oedema, as these babies tend to retain lot of fluid.

- Consider electrolyte additives or parenteral nutrition after 24 - 48 hours when electrolytes/renal function stable.

- Give maintenance potassium supplementation if renal function is adequate (2 mmol/kg/day). Avoid potassium supplementation during cooling, as hyperkalemia may occur on rewarming.
HEMATOLOGICAL MONITORING

It is preferable to monitor lab parameters during cooling as mentioned below.

<table>
<thead>
<tr>
<th>INVESTIGATIONS</th>
<th>TIMINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC</td>
<td>0, 24, 48, 72 hours</td>
</tr>
<tr>
<td>Electrolytes /RFT</td>
<td>12, 24, 48, 72 hours</td>
</tr>
<tr>
<td>Coagulation profile</td>
<td>0, 24, 72 hours</td>
</tr>
<tr>
<td>LFT</td>
<td>0, 24, 72 hours</td>
</tr>
<tr>
<td>ABG</td>
<td>0, 12, 24, 48, 72 hours</td>
</tr>
</tbody>
</table>

NEUROLOGICAL MONITORING

Details are elaborated in chapters 10, 11 and 12.

CONCLUSION

Meticulous neonatal care provided by multi disciplinary team is critical for ensuring better outcomes for infants with HIE on therapeutic hypothermia.

BIBLIOGRAPHY

Inadvertent excessive cooling (cold-injury syndrome) may occur during therapeutic hypothermia and may be due to inadequate monitoring, inexperienced staff or non-servocontrolled cooling systems. Asphyxiated newborns with HIE per se are known to have impaired thermo-regulation. The effects of excessive cooling, especially pulmonary and cardiac dysfunction, are expected to be more serious in asphyxiated infants who already have multiorgan dysfunction, or the multi-organ dysfunction initially triggered by the HIE may be exaggerated by superimposed cold-injury syndrome.

Excessive cooling can cause cardiovascular instability and re-emergence of seizures. Some of the problems associated with cold-injury syndrome include increased mortality; development of sclerema, skin erythema, and acrocyanosis; pulmonary hemorrhage; renal failure; increased blood viscosity and disseminated intravascular coagulation; hypoglycemia; acid base and electrolyte disturbances; increased risk of infections (secondary to decreased leukocytomobility and phagocytosis); significant cardiovascular disturbances including sudden cardiac arrest and ventricular tachyarrhythmia. Sinus bradycardia and thrombocytopenia have been reported to be the only significant adverse effects of hypothermia in all of the current meta-analysis of the cooling trials. Advances in intensive care including continuous cardio-respiratory monitoring, mechanical ventilation, and better understanding of pathophysiology of hypothermia have reduced many of the adverse effects previously reported with therapeutic hypothermia.
**CARDIOVASCULAR**

Therapeutic hypothermia is consistently associated with sinus bradycardia as it slows the atrial pacemaker and intra-cardiac conduction. The QT interval can also be prolonged, and hypotension can occur.

**HEMATOLOGICAL**

Hypothermia-induced coagulation abnormalities include platelet dysfunction, increased fibrinolytic activity and prolongation of prothrombin time and partial thromboplastin time. However, no increase in bleeding complications is reported in any of the three large randomized cooling trials.

**RENAL**

Therapeutic hypothermia can suppress antidiuretic hormone, and in experimental animal models cooling was associated with decrease in renal perfusion and glomerular filtration rate. However, according to a recent meta-analysis, there was no statistically significant difference in the rate of oliguria in cooled infants.

**DRUG METABOLISM**

Drugs including anti convulsants, sedatives, neuromuscular paralyzing agents, antibiotics, and inotropic agents are commonly used in asphyxiated infants while receiving therapeutic hypothermia. Metabolism and excretion of these drugs and their metabolites may be modified by cooling, as well as by the frequent presence of hypoxic ischemic hepatocellular and renal injury complicating HIE. Close monitoring of anti convulsant levels and clinical level of sedation and paralysis while morphine and paralyzing agents are used, is warranted during treatment with hypothermia. Typical adjustment of gentamicin dosing for impaired renal function based on trough serum concentrations is recommended when treating actual or suspected infection during therapeutic hypothermia.

The common complications noted with therapeutic hypothermia from JIPMER, Pondicherry are listed in Table 1.
Table 1: Complications of Therapeutic hypothermia

- Bradycardia (25%) and other cardiac arrhythmia (1%)
- Thrombocytopenia (13% - 25%)
- Hypoglycemia (10%)
- Hypocalcemia (6%)
- Shock (8%)
- Sclerema and Subcutaneous fat necrosis (6%)
- Acid-base and electrolyte disturbances
- DIC (5%)
- Pulmonary hemorrhage
- Increased blood viscosity- hemoconcentration

Though therapeutic hypothermia is generally safe, it is important to cool neonates using strict protocols and often at centers with considerable experience with cooling.

BIBLIOGRAPHY

For every infant with HIE that benefits from hypothermia, many more do not. Hence, there is an urgent need to focus on adjuvant therapies that may be neuro protective in this condition. Enhancing the endogenous neuro protective responses of the body using melatonin, endogenous endocannabinoids, or erythropoietin may also be more physiologic, and less likely to cause adverse effects. 

**XENON**

Xenon is one of the leading adjuvant therapies being investigated in neonatal HIE. Xenon is a potent NMDA receptor antagonist and can decrease neuronal apoptosis, and also inhibits AMPA and kainate receptors. 

The multicenter Total Body hypothermia plus Xenon trial (TOBY-Xe) enrolled 92 infants (36–43 weeks, 46 randomly assigned to hypothermia alone and 46 to xenon plus hypothermia). The primary outcomes were reduced thalamic lactate to N-acetyl aspartate (NAA) ratios (on magnetic resonance spectroscopy) and preserved fractional anisotropy (FA) in the posterior limb of the internal capsule on MRI within 15 days of birth. Lactate to NAA ratios can predict neurodevelopmental outcomes. Changes in FA also correlate well with outcomes in infants with HIE. No significant differences on MRI were detected between the groups. Based on these results, the authors concluded that combined treatment with hypothermia and 30% xenon for 24 hours may not improve clinical outcomes compared to hypothermia alone. The CoolXenon3 trial (ClinicalTrials.gov Identifier: NCT02071394) is currently underway, and is likely to be
completed by August 2019. Xenon is, however, very expensive. The need for special ventilation circuits that can reuse the gas implies that even if it is shown to be effective, xenon is unlikely to be a favored adjuvant therapy in more resource-limited countries including India.

**ERYTHROPOIETIN/DARBEPOIETIN**

Although originally identified as an erythropoietic factor, Erythropoietin (Epo) plays many roles in the human body. It has myriad effects on immunomodulation, inflammation, angiogenesis, and neurodevelopment. Many cell types in the central nervous system express EPO receptors during different stages of development, suggesting a role for Epo. It has been shown to be neuroprotective in a variety of experimental settings in animal models, using a wide range of doses (1000 to 30,000 U/kg). Recombinant human Epo has also been shown to improve neurological outcomes in preterm infants. The use of Epo in term infants with hypoxic-ischemic encephalopathy is relatively more recent. When compared to hypothermia, a potential advantage is that Epo may be effective even when started more than 6 hours (but <48 hours) after birth. In a randomized trial of Epo (without hypothermia) involving 167 infants in China, those receiving Epo had significantly lower Thompson scores by day 7. The composite outcome of death or moderate-severe disability at 18 months was lower (24.6%) in the Epo group compared to controls (43.8%). On subgroup analysis, benefits were limited to infants with moderate hypothermia. In this study, the Epo dose used was 300 (52 infants) or 500 U/kg (31 infants) on alternate days for 2 weeks. There was no obvious toxicity or hematopoietic effect in the Epo group.

A small, prospective non-randomized study of Epo in infants with HIE found fewer neurologic and developmental abnormalities at 6 months in infants administered a 5-day course of Epo at a dose of 2500 IU/kg, when compared to control groups. Another phase II placebo-controlled trial of Epo used an Epo dose of 1000 U/kg (n = 24) or placebo (n = 26) at 1, 2, 3, 5, and 7 days and found improved motor function at 1 year and less MRI brain injury in the Epo group. This group had earlier conducted a phase I trial of Epo with hypothermia and shown that Epo at 1000 U/kg given intravenously resulted in plasma Epo levels similar to animal studies of neuro protection. Some adult studies have reported an increased risk of adverse outcomes with the use of Epo. In addition, questions about dose and duration of therapy remain. A recent pharmacokinetic analysis of 47 infants who previously received Epo in 2 trials suggested that in infants receiving hypothermia, a dose of 1000 U/kg every 24 hours for the first 2 days resulted in achievement of target levels.

**MELATONIN**

Melatonin, like erythropoietin, is endogenously produced and serves normal functions in the human body, but is also available in a synthetic form. The pineal gland synthesizes melatonin from tryptophan, with secretion peaking at around 3-4 am in normal adults. In
adults, melatonin secretion follows a circadian rhythm (one cycle per 24 hours). In neonates, the rhythm is ultradian (many cycles per 24 hours). Melatonin has antioxidant and anti-inflammatory properties and can reduce apoptosis. In mouse models of excitotoxic brain injury, melatonin has a dose-dependant neuroprotective effect. It also has no known adverse effects, making it an attractive candidate for adjuvant therapy.

In a small study, 10 asphyxiated infants were given oral melatonin (8 doses of 10 mg each at 2-hour intervals) and were noted to have reductions in the levels of malondialdehyde and nitrite/nitrate at 12 and 24 hours. The study used 10 asphyxiated infants and 10 healthy infants as controls. There were no deaths in the melatonin group, and 3 deaths among the asphyxiated controls. A randomized controlled trial of melatonin in infants with HIE reported that infants who received melatonin in addition to hypothermia had fewer seizures and less white matter abnormalities on MRI. Controls included a group of infants who received hypothermia alone, and a group of healthy infants. Survival without neurological abnormalities to 6 months of age was higher in the melatonin/hypothermia group.

An advantage of melatonin is that it crosses the placenta and the blood-brain barrier and appears to be safe, and can potentially serve as a neuro protectant when administered antenatally.

**MAGNESIUM**

The role of magnesium sulfate in neuro protection in the preterm fetus at risk of imminent delivery is now well established. Magnesium salts modulate NMDA-mediated neuronal injury and may be neuro protective in infants being cooled for HIE. An RCT of magnesium sulfate infusion involving 50 neonates in Bangladesh reported better neurologic status at discharge in the experimental group. While others have also reported better outcomes with the use of magnesium sulfate, these studies did not include infants undergoing hypothermia. A multicenter RCT of hypothermia plus magnesium sulfate versus hypothermia plus placebo in 60 term and near-term infants with moderate to severe HIE reported no differences in neonatal death, seizures, hypotension or other adverse outcomes but long-term outcomes are not reported.

**ANTIEPILEPTIC DRUGS**

Antiepileptic drugs are commonly used in neonates with HIE to control seizures. In theory, control of seizures itself may protect neurons from the effects of repetitive firing and energy depletion. However, some of the newer anticonvulsants have been proposed to have other neuroprotective effects that may be beneficial in HIE.

Topiramate (TPM) is a well-known anticonvulsant that modulates AMPA and kainite receptors and other ion channels. In neonatal rats, topiramate helps to limit damage from oxygen-glucose deprivation. Topiramate may reduce excitotoxic injury and limit neuronal
cell loss in neonatal HIE, and this effect is probably independent of its anticonvulsant effect. However, hypothermia has been shown to prolong the half-life of TPM, hence more pharmacokinetic data may be required. The NeoNATI trial was a pilot randomized multicentric trial designed to assess the safety and efficacy of TPM in neonates undergoing hypothermia for HIE.\textsuperscript{23} The trial involved 44 term infants, 23 in the hypothermia group and 21 in the hypothermia + TPM group. There were no significant differences in mortality, severe neurological disability, MRI changes or safety outcomes between the groups, but the combined treatment group had a lower prevalence of epilepsy.

Levetiracetam is increasingly used for neonatal seizure control. Besides its anticonvulsant effect, levetiracetam regulates AMPA and NMDA receptor mediated transmission, and reduces reducing glutamate release.\textsuperscript{24} Since levetiracetam also has reasonable efficacy in controlling neonatal seizures and a low toxicity, it is an attractive candidate for adjuvant treatment. However, evidence from RCTs is yet to be generated.

2-IMINOBIO Tin

2-Iminobiotin (2-IB) is a biotin analogue which inhibits inducible nitric oxide synthase, and may prevent NO-mediated mitochondrial injury. 2-IB was shown to hypoxia-mediated neurotoxicity in an in-vitro human neuronal cell model.\textsuperscript{25}

N-ACETYL CYSTEINE

N-Acetylcysteine (NAC) scavenges oxygen radicals and decreases inflammation and nitric oxide (NO) production in experimental stroke models.\textsuperscript{24} In rat models of stroke, NAC reduces infarct volume and improves neurologic scores. In newborn piglets with hypoxic brain injury, NAC helps maintain normal cerebral amino acid chemistry.\textsuperscript{27} A large RCT of NAC to evaluate its effect on broncho pulmonary dysplasia (BPD) in extremely low birth infants found no reduction in BPD, but there was less periventricular leukomalacia in the NAC group.\textsuperscript{28} Studies of NAC in term infants with asphyxia are yet to be done.

CANNABINOIDS

Cannabinoids may be neuro protective by inducing hypothermia or through other specific mechanisms. However, since the only reported benefit of cannabinoids is in animal models and cannabis use during pregnancy has been linked to cognitive defects in infants, it is likely that more experimental data will be required before human trials can be conducted.\textsuperscript{2}
**HUMAN CORD BLOOD**

Stem cell therapy appears to be neuro protective in animal models of hypoxic-ischemic injury. Since umbilical cord blood (UCB) is an easily accessible and ethically acceptable source of stem cells, this therapy would be attractive, if proven to be effective in human infants with HIE. In an open-label feasibility trial in 23 infants cooled for HIE, non-cryopreserved autologous UCB cells were administered. 74% of cell recipients survived to 1 year with BSID scores >85, compared to 41% of concurrent cooled infants.

**REMOTE ISCHEMIC POST CONDITIONING**

In clinical studies of transient ischemic attack and angina, brief non-lethal episodes of ischemia have been shown to be protective. This is called ischemic preconditioning. When this technique is used after the major ischemic episode, we call it ischemic post conditioning. In remote ischemic post conditioning (RIPC), the brief ischemic stimulus is applied to a non-vital organ (e.g. a limb) away from the affected organ (e.g. the brain). While the exact mechanisms by which RIPC confers protection are yet to be described, a neuronal pathway (involving the autonomic nervous system), a humoral pathway (involving, as the name suggests, mediators transported through the bloodstream) and a systemic response (including reduced neutrophil activation and decreased expression of genes involved in inflammation and apoptosis) are believed to be involved. Studies in animal models of HIE indicate that RIPC may be beneficial. Clinical trials in neonates with HIE are yet to be conducted.

**CONCLUSION**

While a number of adjunct therapies are being studied, many are currently not ready for wide spread adoption due to reasons of limited evidence, cost, or convenience. However, it appears likely that this situation will change very soon, given the number of trials that are in progress.
BIBLIOGRAPHY


In the 1960s, Dr. Maynard and Prior introduced aEEG as an adjunct to continuous EEG (cEEG) to monitor cerebral function during surgical anaesthesia. Full array electro-encephalography uses about 16 electrodes and requires the expertise of a neurophysicist who is trained to interpret EEG. The advantage of aEEG over continuous EEG include limited number of electrodes, ease of operation with shorter training of personnel to interpret, immediate interpretation at the bedside itself and condensed output. The equipment is more cost effective than cEEG. With advent of therapeutic hypothermia in asphyxiated babies, aEEG is increasingly being used as eligibility to start cooling, to detect subclinical seizure activity and to assess as a long term prognosticator.

All aEEG machines will give a trace of raw EEG as well as either bilateral or cross-cerebral aEEG traces. In aEEG, the signals from continuous EEG are amplified, filtered, rectified and compressed using a piecewise semi-logarithmic transformation and is portrayed as a slow trend display. It is useful for continuous monitoring of brain function.
PLACEMENT OF ELECTRODES

The recording measures differences in electrical potential and displays the changes in electrical activity over time. Unlike cEEG, a minimum of 3 electrodes are required in aEEG (single channel monitoring). Of these two are biparietal (P3 and P4) and the third is the ground electrode. It can use two channel monitoring (Brainz Monitor and Olympic Brainz Monitor) where two additional electrodes are used in the central (C3 and C4) or frontal (F3 and F4) regions which improves the sensitivity of detecting seizures and also detecting laterality of lesions. The number of electrodes can be increased on witnessing seizures. The logic behind parietal placement of electrodes is that this overlies the cerebral cortex at the junction of the anterior, middle and posterior cerebral circulations and thus might be most affected in ischaemia. The electrode placement is shown in Fig. 1.

Fig. 1: Electrode placement

WHAT TO LOOK FOR IN AN αEEG TRACE?

While analyzing an αEEG trace, it is necessary to comment on the following:

A. Background activity
B. Seizure activity
C. Sleep wake cycle
A. BACKGROUND ACTIVITY

This is a representation of the background electro-cortical activity of the underlying brain. The monitor displays both the EEG and aEEG traces. X-axis represents time and Y-axis represents EEG amplitude on a semi-logarithmic scale. Background pattern refers to the dominant pattern of electrical activity. This varies depending on gestational age, medications and state of arousal. There are different patterns of background activity which are classified as either normal or abnormal.

Normal patterns include
- Continuous Normal Voltage (CNV) or background
- Discontinuous background (normal in preterm or moderately abnormal in term babies) (DC)

Abnormal patterns include
- Burst Suppression pattern (BS)
- Continuous Low Voltage (CLV)
- Iso-electric or Flat Trace (FT)

CONTINUOUS BACKGROUND

Here, the lower margin of the aEEG trace is above 5 µV and the upper margin is above 10 µV. This pattern is commonly seen in full term infants. (Fig. 2.)

Fig. 2:
DISCONTINUOUS PATTERN

EEG: In discontinuous pattern, there are periods of lower amplitude interspersed with periods of higher amplitude.

aEEG: There is a wide depressed trace with a lower voltage of <5µV and upper voltage of >10µV. (Fig. 3.)

Fig. 3:

INTERPRETATION: Discontinuous pattern may be normally seen in prematurity. However, it is sometimes encountered after cerebral injury in term babies and after anti-convulsant therapy. In very preterm babies, the discontinuous pattern mimics burst suppression and is called “tracédiscontinu”. As the premature infant approaches term, the pattern changes to a continuous pattern.

BURST SUPPRESSION PATTERN

EEG: There are periods of abnormally high amplitude activity (bursts) interspersed with periods of markedly suppressed amplitude (suppression).

aEEG: There are burst spikes (with amplitudes of >25µV) interspersed with iso electric suppression where there is no or minimal electrical activity with flat lower margins having voltage 0-1µV. (Fig.4.)

Fig. 4:
**INTERPRETATION:** Prolonged burst suppression pattern is highly suggestive of severe brain injury and is often seen in asphyxiated babies with severe encephalopathy. Since EEG inactivity is associated with damage to non-specific but widespread regions of the brain, the time of interburst interval (IBI) (the period of suppressed activity between bursts) may correlate with long term outcome. It is thought that there is high probability of adverse neurological outcome if IBI exceeds 30 seconds.

**CONTINUOUS LOW VOLTAGE PATTERN**

**EEG:** There is continuous low amplitude

**aEEG:** There is narrowing of EEG trace with both the upper and lower margins having and amplitude of <5µV. (Fig. 5.)

![Fig. 5](image)

**INTERPRETATION:** A prolonged continuous low voltage pattern is highly suggestive of severe brain injury. This is often seen in asphyxiated babies with severe encephalopathy.

**FLAT TRACE**

**EEG:** In this pattern, the amplitude is very low (close to zero)

**aEEG:** aEEG shows low amplitude with a narrow trace, upper and lower margins are <5µV and almost close to zero µV (Fig. 6.)

![Fig. 6](image)
INTERPRETATION: Prolonged flat trace is an ominous sign indicative of severe brain injury. This pattern is often associated with poor neuro developmental outcome as well as death.

B. SEIZURES
HOW TO DETECT SEIZURES ON aEEG?

Seizures may be appreciated as solitary or repetitive seizures (Fig. 7.) or status epilepticus (Fig. 8.). Solitary seizure refers to a single episode where there is a spike or sharp wave with elevation of the lower margin. It is seen as an abrupt rise in the minimum amplitude and simultaneous rise in maximum amplitude. This is often followed by a short period of decreased amplitude. On continuous EEG, seizure activity is seen as repetitive sharp waves or spikes. The duration is at least 5 to 10 seconds.

Fig. 7:

Fig. 8:
C. SLEEP WAKE CYCLE (SWC)

Normal sleep wake cycle is seen as smooth sinusoidal variations, mostly in the minimum amplitude. Continuous pattern with good variability and no repetitive waveform (like spike or sharp waves) is witnessed while the newborn is awake or in active sleep. This is seen as narrowing of the wave on aEEG. This alternates with widening that represents discontinuous pattern seen when a baby is in quiet sleep. A mature or developed cycle lasts about 20 minutes. Therefore, sleep wake cycles are seen as alternating widening and narrowing of the aEEG trace. (Fig. 9.)

Fig. 9:

[Graph of aEEG trace]

ASPHYXIA AND aEEG

Hypoxia or ischemia is associated with suppression of the EEG waveform. The duration and amplitude of suppression can correlate with the severity of the hypoxic event. Thus, early aEEG background pattern may be used as an adjunct in selecting newborn who may benefit by therapeutic hypothermia. Various researchers have also tried to use the aEEG trace either with or without hypothermia as a prognosticator.

aEEG AS CRITERIA TO INITIATE HYPOTHERMIA

The TOBY trial in the UK used three criteria to cool newborn:

1. Evidence of asphyxia
2. Evidence of moderate or severe encephalopathy
3. aEEG evidence of hypoxic injury. This included a 30 minute aEEG with any of the following:
   a. normal background with some seizure activity
   b. moderately abnormal activity
   c. suppressed activity
   d. continuous seizure activity

Similarly, the Cool cap trial and the European trials on hypothermia used aEEG as a criteria for recruitment. However, the NICHD trial and the ICE trial did not have aEEG as entry criteria to initiate cooling. Though we have been using aEEG in asphyxiated newborn since 2009 and have practised therapeutic hypothermia since 2007, we do not use aEEG abnormality as essential criteria for cooling newborn.
A study by Skranes et al from Norway assessed if aEEG as an entry criteria improved selection of infants for cooling. They compared the trace at 6 hours of life with MRI lesion load and 24 months outcome. They found that babies most babies with continuous normal background at entry were normal at 24 months. Babies with severe EEG voltage criteria (BS, CNV or FT) were more likely to have adverse outcome with time to normal trace in these babies being the best predictor of outcome. Hence they suggested that recruitment for cooling should be only in babies who had abnormal aEEG background.

**aEEG AS A PROGNOSTICATOR**

Researchers have looked at the prognostic value of early aEEG (at <6 hours or prior to initiation of cooling) as well as changes in aEEG over time to assess if it would prognosticate on long term neurological outcome. The results when comparing early aEEG to outcome have been variable.

In a follow up analysis of the TOBY trial data, the value of early aEEG to accurately predict death or disability at 18 months was studied. In a cohort of 315 babies, it was seen that the positive predictive value (PPV) of a severely abnormal aEEG by voltage and pattern was 0.63 and 0.59 respectively in non-cooled infants and 0.55 and 0.51 in cooled infants (p>0.05). The authors attributed the lower PPV in cooled babies to the neuro protective effect of cooling.

Similarly, Marianne Thoresen et al studied the value of early as well as changes in pattern and voltage over 72 hours in cooled and non-cooled babies. They recruited seventy-four infants whose outcome was assessed at 18 months. The positive predictive value of an abnormal aEEG pattern at <6 hours was 84% in non-cooled babies vs 59% for cooled infants. The recovery time to normal background pattern was the best predictor of poor outcome in both cooled and non-cooled babies (96.2% and 90.9% respectively). Never developing sleep wake cycling over 72-96 hours always predicted poor outcome. Infants treated with hypothermia had good outcome if the background became continuous by 48 hours.

Thus, early aEEG abnormalities are more likely to predict adverse outcome in babies who do not receive hypothermia. Both these studies show that early aEEG may not accurately predict outcome in cooled infants. Change in pattern from abnormal (BS, CNV or FT) to continuous normal voltage by 48 hours predicted good outcome and never achieving sleep wake cycle by 96 hours uniformly predicted poor outcome.

Chandrasekharan et al published a meta-anlysis of all studies using aEEG for prognostication. This looked at aEEG criteria at various time periods (6, 24, 48 and 72 hours). They considered only continuous background as normal pattern and all other patterns (DC, BS, CLV and FT) as abnormal and used death or disability at 1 year as adverse outcome measure. Nine studies involving 520 infants were used in the meta-analysis. The pooled sensitivity and specificity for an abnormal trace at 6 hours of age in predicting adverse were 96% and 39%. The diagnostic odds ratio of an abnormal trace was highest (66.9%). They also showed that a normal background at 6 hours predicted good outcome.
Similarly, a systematic review of prognostic tests in term infants with HIE showed that aEEG had the highest sensitivity and specificity in predicting outcome (0.93 and 0.9 respectively) followed by EEG, visual evoked potential. Diffusion weighted MRI had higher specificity whereas T1, T2 weighted MRI had better sensitivity.

**WHAT IS THE EFFECT OF COOLING ON aEEG?**

In most infants with asphyxia, the aEEG background will eventually become normal over few days. As seen in the few studies quoted, aEEG may normalize earlier in cooled infants because of the neuro protective role of hypothermia. A study was done to see if the amplitude of the aEEG trace would change with cooling but no change was found. However, it is possible that the amplitude of seizures can decrease with cooling and hence it may be more difficult to diagnose electrical seizures in cooled infants. An EEG is always necessary to diagnose seizures in hypothermic infants. Studies also show that the frequency and duration of seizures is less in hypothermic infants. Hence aEEG may be a poor to diagnose electrical seizures in cooled babies.

Therefore, aEEG may be used as an adjunct to clinical criteria to select babies for cooling. Babies with continuous normal background at 6 hours may not benefit much with cooling. Babies with persistently abnormal trace are most likely to have death or adverse long term neurological outcome. Seizures may not be adequately detected by aEEG especially in cooled babies and hence it may useful to study the raw EEG to identify seizures. Hence aEEG may be a useful adjunct in babies who are offered therapeutic hypothermia.

**TAKE HOME POINTS**

- Though not essential, amplitude integrated EEG may be a useful tool to identify babies who would most benefit by hypothermia.
- Continuous normal background at initiation of hypothermia is a good prognosticator.
- Persistence of abnormal trace at 48 or 72 hours may indicate poor prognosis.
- Never achieving sleep wake cycle by 96 hours always denotes poor long term prognosis.
- Seizures cannot be adequately diagnosed by aEEG especially in babies undergoing therapeutic hypothermia.


Cranial ultrasonography (CUG) is the first choice for initial radiological evaluation as it is very convenient, portable and non-invasive.

**Technique:** Brain is usually visualized through anterior fontanelle in two planes namely the coronal and sagittal. The angle of the transducer may be changed to evaluate the periphery of the brain with special attention to the subcortical white matter and the grey-white matter differentiation. The visualization of the cerebellar hemispheres is enhanced by obtaining images through the right and left mastoid fontanels. This technique has also been shown to improve the detection of posterior fossa hemorrhages. The modern cranial US requires switching from the curved - to a linear - array transducer, which allows high-resolution imaging of the brain with the detailed interrogation of the subarachnoid space and superficial cortex as well as deeper brain structures. Important factors influencing USG findings are brain maturity, the duration and severity of insult, and timing of imaging studies.

**Fig. 1:** Brain structures as seen in CUG

**Acute changes in grey-scale sonography**

The brain sites that are more vulnerable to hypoxic injury are determined largely by maturity of the brain. Less intense insults cause intraventricular hemorrhages and periventricular white matter injury in preterm neonates and parasagittal watershed territory infarcts in term neonates. Severe hypoxia-ischemia in both preterm and term
neonates preferentially damages the deep grey matter like Basal ganglion (BG) and thalamus. The neurons of the cerebral cortex are the most vulnerable, most often hippocampus. Regional vascular factors play a certain role because of neuronal injury is more marked in vascular water-shed zones during ischemia, in parasagittal cerebral cortex. The brainstem, cerebellum, and the deep grey matter are generally spared from injury in mild to moderate hypoxic-ischemic insults due to auto regulatory mechanisms. However, more prolonged insults may cause injury to the watershed zones, which are relatively hypoperfused as a result of shunting during a pressure passive state of cerebral circulation.

**USG changes in HIE can be classified as:**

- Peripheral - mild to moderate Hypoxic ischemic insult
- Central - severe Hypoxic ischemic insult

Peripheral brain abnormalities include changes in the grey-white matter differentiation and changes in the echogenicity of the cortex and subcortical white matter (Fig. 2&3). Early US findings include a global increase in cerebral echogenicity and the obliteration of the CSF spaces, suggesting diffuse cerebral oedema (Fig. 2,3,4). However, the small size of liquor spaces alone is not specific for brain oedema and slit like ventricles can be seen in healthy newborns during the first 3 days of life.

An increase of parenchymal echogenicity with partial or total obliteration of normally visible structures is correlated with severity of HIE. Although the phenomenon of increased echogenicity (the so-called “bright brain”) is fully developed by the second–third day of life, the moderate to severe increase of parenchymal echogenicity as early as at the age of 12 ± 2 h has a high sensitivity (88%) for death or severe disability and can be an early predictor of permanent brain damage in asphyxiated infants. By the second-third day of life, the predictive value of the “bright brain” phenomenon can be as high as 90-100%. Long-lasting increase in parenchymal echogenicity (5-7 days and more) is a predictor of poor outcome at 18 months of age.

**Fig. 2:** Asymmetrical hyperechoic appearance of the brain in perinatal asphyxia
Central brain abnormalities in infants with severe global asphyxia include changes in echogenicity of the deep grey matter (basal ganglia and thalami), brainstem and the periventricular white matter\(^4\) (Fig. 5, 6). The presence of thalamic echogenicity (so-called “bright thalamus”) generally suggests a more severe injury and correlates with a poorer outcome\(^8,9\). Increased echogenicity in the basal ganglia, thalami, and brainstem is readily apparent after 7 days of severe HIE\(^5,10\).
**Fig. 5:** a) Coronal US image obtained with a vector transducer shows ill-defined increased echogenicity in the left basal ganglia region with a more focal hyperechoic area (arrow) in the left putamen. b) Magnified coronal US view using a linear transducer shows diffuse increased echogenicity, with more focal areas of abnormally increased echogenicity in the left caudate head (arrowhead) and left putamen (arrow). c) Axial MR image shows restricted diffusion on DWI in the thalami and there are other findings in addition.

**Fig. 6:** Thalamic hemorrhage as seen on CUG (left) and MRI (right)

**ACUTE CHANGES IN THE DOPPLER SONOGRAPHY:** Cerebral vascular resistance index (RI) is used for predicting clinical outcome from 24 hours of age in the infants with moderate or severe HIE (Fig. 7). In severe HIE, RI below 0.55 had a positive predictive value (PPV) for death or disability of 75% and a negative predictive value (NPV) of 100%. High RI was found in most infants who subsequently had a poor outcome. It is possible that hypothermia will affect the cardiovascular system in the ways that might change RI. Outcomes of babies with HIE vary according to the severity of the injury. Low RI is not predictive of poor outcome during HT, but regains the predictive power after rewarming.

**Fig. 7:** Color Doppler indices of anterior cerebral artery in severe asphyxia
EVOLUTION OF SONOGRAPHIC CHANGES: The best way to visualize white matter is at 7.5 MHz or higher frequencies. Sonographic changes in the earlier phase are uncertain as cell reaction and microvascular changes develop after 48 hours. Under normal conditions a difference in echogenicity can be observed between relatively hypoechoic cortex and mildly hyperechoic white matter. Gyral white matter core echogenicity can be compared in patients in a sagittal or coronal section through the gyrus cinguli. Early indicators hinting at the need for further imaging are 1) fuzzy, swollen brain, 2) relative hypoechoic aspect of caudate, 3) appearance on day 2 or day 3 of four hyperechoic columns in coronal section through deep grey matter, 4) luxury perfusion or reversed diastolic flow in large arteries, 5) early hyperechoic haemorrhage in ischemic areas and 6) gyral core hyperechogenicity.

MRI and CUS: in the recently published data shows that modern CUS can pick up abnormalities including parenchymal almost similar to MRI except focal lesions near the cortex.6,17

IN SUMMARY

1. CUG is an excellent tool in screening and monitoring of asphyxiated infants with HIE and evaluating the prognosis of asphyxiated infants.

2. CUS may miss some lesions as compared to MRI but still very useful especially in babies who are critical.

3. In the infants with HIE treated with therapeutic hypothermia, the low resistance index is probably not as good a predictor of a poor outcome as in normothermia and further studies are needed in this area.

4. Repeat CUG at regular intervals may improve identification of brain abnormalities especially in centers where MRI facility is not available.
BIBLIOGRAPHY


Hypoxic Ischemic Injury in term neonates causes global Hypoxic Ischemic Injury (HII) in MRI. HII occurs due to interruption of placental flow (antepartum), or events during delivery (intrapartum) or hypoxic damage after delivery (postnatal). MRI imaging is the most sensitive imaging technique to detect early hypoxic injury secondary to perinatal asphyxia. MRI injury is also considerably less in infants who have undergone TH. MRI helps in both diagnosis and prognosis of HIE. This chapter has been written with objective of highlighting the various hypoxic injuries occurring in term neonates.

ROLE OF NEUROIMAGING IN THERAPEUTIC HYPOTHERMIA (TH) INCLUDE

- Diagnosis
- Assess the pattern and severity of injury
- Prediction of clinical outcome based on pathologic lesions observed on imaging
- Information about long term prognosis

MR IMAGING- PRACTICAL TIPS

Transporting MR imaging in any sick neonate could be complex. The following should be done:

- Proper Communication - ICU and MRI
- Replace standard length tubes with extension tubes
- Transport in incubator to maintain temperature
- Monitoring of vital signs during transport and scan
- Time taken to complete all sequences: 30 to 45 minutes
- Use MR compatible equipment: Pulse oximeter, ECG system, Infusion pump, Ventilator, Resuscitation equipment. MR compatible incubator if available
- Temperature maintenance during the imaging
- Preventing Movement and Noise: Swaddling, Ear plugs/Muffs
- As far as possible avoid oral sedation, swaddling and timing after feeding if permitted
- If HIE stage III, baby may be already drowsy especially with the use of anti-convulsants
- If needed Oral sedation (Chloral hydrate) 25-50mg/kg could be used. Or Intranasal sedation with Midazolam (100 microgram) could be used

**PROTOCOL**

- MRI-preferably 3 Tesla; if unavailable 1.5 Tesla could be used
- Sequences to be included: Axial and sagittal T1 Weighted Images (T1WI) and T2WI, coronal T2 FLAIR(fluid attenuated inversion recovery), axial DWI(Diffusion weighted Images) and GRE (Gradient recalled echo) images, MRA (MR angiogram), MRV (MR venogram) and 1 or 2 MR spectroscopy sequences in ventro-lateral thalamus and lentiform nucleus and centrum semi-ovale (Calculate lactate/NAA ratio)
- MRI usually done between 5 and 14 days in infants who have undergone TH

**PATTERN OF INJURY IN HIE IN TERM BABIES**

Pattern of injury depends on the brain maturity, duration and severity of insult and type of MRI sequencing and timing of imaging

<table>
<thead>
<tr>
<th>Event</th>
<th>Profound hypoxic injury</th>
<th>Partial hypoxic injury</th>
</tr>
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<tbody>
<tr>
<td>Event</td>
<td>Acute severe event like cord prolapse, abruption, uterine rupture</td>
<td>Prolonged partial hypoxia-ischemia like difficult delivery, maternal fever</td>
</tr>
<tr>
<td>Pathology</td>
<td>Energy failure leading to cell necrosis followed by secondary energy failure and programmed cell death</td>
<td>Cortical necrosis; laminar necrosis and selective neuronal necrosis</td>
</tr>
<tr>
<td>Pattern of Injury</td>
<td>Basal ganglia and thalamus (BGT) pattern and posterior limb of internal capsule (PLIC) pattern. If severe entire cerebrum affected</td>
<td>Cortical/subcortical pattern</td>
</tr>
<tr>
<td>Sarnat Staging</td>
<td>HIE Stage II and III</td>
<td>Clinical manifestation may be subtle</td>
</tr>
</tbody>
</table>
Myelination of posterior limb of internal capsule (PLIC) appearing as hyperechoic in T1W and hypoechoic in T2W images (Fig. 3 and 4.). Under normal circumstances, PLIC is myelinated in term neonates. In HIE, myelination could be affected.

DW imaging detects the alteration in diffusion of free water. With acute injury, the intracellular water content increases and there is restriction in the movement of water in and out of the cell. Areas of diffusion restriction would be shown as increased signal. DW imaging signal intensity starts appearing within 1 to 2 days of injury, peak by 4 to 5 days and pseudo-normalizes by day 7 of injury. T1 and T2 W imaging changes starts by 3 days of injury and scan on day 7 continue to show more obvious changes. Interpretation of MRI should take into account the time of MRI imaging and the type of imaging.
Conventional T1 and T2WI are most useful at end of 1st week. BGT pattern indicates acute hypoxic ischemic injury.

**Fig. 6: DW changes (Diffusion weighted images in a term neonate with acute ischemic insult)**

Fig. 6 is showing diffusion restriction in basal ganglia region. DW changes occur within 24 hours of injury, peaks at 5 days of life and pseudo-normalizes by end of 1st week.
CORTICAL AND SUB-CORTICAL WHITE MATTER PATTERN

Fig. 7: Partial hypoxic injury results in DW changes in water-shed area in cortical/sub-cortical region

Fig. 8: Typical diffusion restriction in cortical and sub-cortical region including corpus callosum

Fig. 7 is showing diffusion restriction in inter-vascular watershed zones involving both the cortex and subcortical white matter. This pattern is indicative of sub-acute/ prolonged partial hypoxia. DW image signal should be compared to that of cerebellar signal. That would indicate the degree of diffusion restriction in cortical and subcortical area.

Fig. 9: Grades of white matter injury

Severe WM injury involves loss of grey- WM differentiation as shown in Fig. 9

Fig. 10: Parasagittal injury in term Vs. periventricular injury in preterm hypoxia

In preterm injury, the lesion is near the ventricles and in term it is near parasagittal region as depicted in Fig. 10.
In preterm, periorolanic cortex spared, basal ganglia involvement is less severe as depicted in Fig. 11 and 12.

**LONG TERM NEURODEVELOPMENTAL CORRELATION OF DIFFERENT PATTERNS OF MRI INJURY**

**a. MILD BGT (Basal Ganglia Thalamus)**

![Diagram of Mild BGT outcomes](image)

- **Mild BGT**
  - Normal PLIC
    - Walking at 2 years
  - Equivocal PLIC
    - 2/3 walking at years, some may start late

**Feeding**
- 10% may have some mild feeding problems, no need for a gastrostomy

**Speech & language**
- 25% may have some speech problems; in most cases mild-moderate

**Vision**
- The probability of visual impairment very low, unless there is extensive white matter injury

**DQ**
- >84 in 80% and >70 in 90% especially if PLIC normal

**Seizures**
- >84 in 80% and >70 in 90% especially if PLIC normal

**Cerebral palsy** 10-15% (only-moderate impairment)
- Normal or mild: 3-6%
- Moderate: 11%
- Severe: 19%

Look at the cortex
b. Moderate BGT pattern

Moderate BGT

Equivocal PLIC
- Cerebral palsy 60%
  Mostly mild (75%)
  2/3 will be walking, may start late

Abnormal PLIC
- Cerebral palsy 75%
  Moderate (50%) or severe (40%)
  70-80% will not walk at 2 years

Feeding
- 40-50% may have some feeding problems, but fewer than 10% will need a gastrostomy

Speech & language
- Most children will have some speech problems; severe in 25%

Vision
- 20-55% will have some visual impairment depending on the severity of white matter and brainstem injury

DQ
- 50-75% of children are assessable, up to 35% of them will have a DQ <70

Seizures
- Look at the cortex
  - Normal or mild: 3-6%
  - Moderate: 11%
  - Severe: 19%

Look at the cortex

Cerebral palsy 60%
- Mostly mild (75%)
- 2/3 will be walking, may start late

Cerebral palsy 75%
- Moderate (50%) or severe (40%)
- 70-80% will not walk at 2 years

c. Severe BGT pattern

Severe BGT

Cerebral palsy 98%
- Mostly severe (95%)

Feeding
- 90% will have some feeding problems
- Gastrostomy
  - Look at the pons
    - Normal: 35%
    - Moderate: 50%
    - Severe: 90%

Speech & language
- 95% will have some speech problems, severe in most

Vision
- 50-75% will have some grade of visual impairment, especially with moderate-severe white matter and brainstem injury

DQ
- Children are in general difficult to assess because of their motor impairment at this age
  - Look at the cortex
    - Normal: 25-30%
    - Mild: 45-50%
    - Moderate: 60%
    - Severe: 75%

Relatively better outcome have been seen with watershed predominant pattern of injury. There have been reports of suboptimal head growth, behavioral problems and delay in language.
MRS in TH

Concepts of MRS

MRS acquires signals from metabolites in predefined regions of brain. Regions to be included are deep grey matter and cortical region. The signals are acquired from choline (Cho), creatine (Cr), N-acetylaspartate (NAA) in normal status. Lactate peaks in Hypoxic damage due to alteration in oxidative metabolism.

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Marker</th>
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<tbody>
<tr>
<td>N-acetylaspartate (NAA)</td>
<td>Neuron and their processes; Indicative of intact central nervous tissue</td>
</tr>
<tr>
<td>Choline (Cho)</td>
<td>Membrane turnover &amp; myelination</td>
</tr>
<tr>
<td>Creatine (Cr)</td>
<td>Brain metabolism</td>
</tr>
<tr>
<td>Lactate</td>
<td>Anaerobic metabolism</td>
</tr>
<tr>
<td>NAA/Cho</td>
<td>Value of 0.62 indicative of poor neurodevelopmental outcome (De Vries 2001)</td>
</tr>
<tr>
<td>NAA/Cr ratio</td>
<td>Value &gt;0.67 predictive of death or severe CP at 2 years (Ancora 2013)</td>
</tr>
<tr>
<td>Lac/NAA ratio</td>
<td>Value of &gt; 0.29 in deep grey matter is indicative of poor neurodevelopmental outcome (Thayill 2010); Good marker for severity in sub-acute to chronic phase</td>
</tr>
<tr>
<td>Lac/Cho &amp; Lac/Cr ratio</td>
<td>Value of &gt; 1 indicative of poor neurodevelopmental outcome</td>
</tr>
</tbody>
</table>

Fig. 13: MRS in occipital region shows lactate peak (superimposed with lipid peak). Choline levels are low indicating disrupted myelin

Fig. 14: MRS line diagram showing different peaks. NAA - N acetylaspartate; Cr - Creatine; Lac - Lactate; Cho - Choline
In babies undergoing Therapeutic Hypothermia, there are certain questions which need to be answered:

- Q1. When do we obtain MRI?
- Q2. Is there any specific MRI pattern in these babies?
- Q3. Does TH reduce the MRI abnormalities in babies with asphyxia?
- Q4. Does TH alter the predictive value of MRI in HIE?

**Q1. When do we obtain MRI?**

**Ans.** Mean 8 days for T1, T2 changes - Obtain in 1-2 weeks, DW changes 3-5 days - Within 1 week; Interpretation of MRI should take into account the type and timing of MRI.

**Q2. Is there any specific MRI pattern in these babies?**

**Ans.** No; Same BGT pattern with or without PLIC changes and cortical and sub-cortical pattern occurs in infants undergoing TH. Smaller studies have shown that pseudo-normalization of diffusion restriction changes occurred later.

**Q3. Does TH reduce the MRI abnormalities in babies with asphyxia?**

**Ans.** Yes; In TOBY trial, they found that among 131 infants treated with TH, less BGT injury and fewer abnormalities of PLIC were identified.

**Q4. Does TH alter the predictive value of MRI in HIE?**

**Ans.** No; MRI retains the predictive value and abnormal MRI predicts adverse neuro-developmental outcome. The pooled sensitivity and specificity for DW imaging is 58% and 89%, respectively. Sensitivity and specificity for T1/T2 changes done ≤ 1 week is 84% and 90%, respectively. If done ≤ 2 wk, the sensitivity and specificity is 98% and 76%, respectively.

**CONCLUSION**

- MRI imaging is the most sensitive imaging technique to detect early hypoxic injury secondary to perinatal asphyxia.
- MRI is done between 5 and 14 days of life. Interpretation should take into consideration the type of imaging and the timing. DW changes occurs within 24, peaks in 3-4 days and pseudo-normalizes in 7 days, T1 and T2 changes are evident in 3 days and scan by 7 days continues to show new changes.
- MRI injury is less with TH. Both BGT and cortical/sub-cortical injury were observed less in those undergoing cooling.
- MRI remains as a good predicting tool for the outcome in infants undergoing TH.
- MRS in deep grey matter region measuring the ratios of Lac/NAA, Lac/Cho & Lac/Cr and NAA/Cr & NAA/Cho helps in predicting long term adverse outcome.


With improved survival of high risk neonates, follow-up programs are becoming as important as the initial intensive care itself. In India owing to the high incidence of perinatal asphyxia, survivors of neonatal encephalopathy (NE) form a significant proportion of all patients enrolled in any follow-up program. It has long being recognized that infants suffering from HIE deserve long term follow-up. With the advent of therapeutic hypothermia (TH), it has become even more important to follow-up these infants, in order to know the long term effects of TH.

**NEED FOR FOLLOW-UP**

Neonates suffering from perinatal asphyxia and neonatal encephalopathy are at an increased risk of neuro motor/sensory impairments. The Cochrane meta-nalysis of 11 RCTs on TH has shown significant reduction in the composite outcome of mortality or major neurodevelopmental disability at 18 months of age. It also showed a significant reduction in neurodevelopmental disability in survivors (RR 0.77 (95% CI 0.63 to 0.94). Though TH significantly reduces neuromorbidity as compared to controls, yet among the surviving infants a sizeable number suffer from varying degrees of neurodisability, which emphasizes the need for rigorous long term follow-up of these children. Shankaran et al have published outcomes following TH at 6-7 years of age, in which though TH did not result in significant reduction in the combined outcome of death or an IQ score below 70 at 6 to 7 years of age, it was still shown to reduce the rate of death with no increase in the rates of a low IQ score or severe disability among survivors. Since TH is now standard practice in NICUs, it is essential that long term neurodevelopmental outcome data become available soon, to determine if the benefit of TH at 1.5-2 years is indeed sustained beyond early childhood.
Survivors of TH need to be followed-up in the same manner as any other high-risk neonate, till long term data revealing any specific pattern of neurodevelopmental sequelae is available.

**DURATION OF FOLLOW-UP**

By 18-24 months of age motor impairments can be confirmed and formal assessment of cognitive and language function can be performed with good prediction to early school age performance. Major neuroimpairment usually becomes overt in early childhood itself. However survivors of NE though apparently normal in early childhood may develop subtle cognitive and behavioural abnormalities later on.

Like other high risk infants, it is necessary to follow up cases of TH till 8-10 years of age, if possible throughout their school years, even if they appear to be normal in early childhood. At the least, they should be followed up till 18-24 months of corrected age (CA).

**FREQUENCY OF FOLLOW-UP**

The first visit may be planned at 2 weeks post discharge. Thereafter at 3, 6, 9, 12, 18 and 24 months or 2, 4, 8, 12, 18 and 24 months corrected age. As the child needs to come at 6, 10 and 14 weeks for immunization, the initial few visits may be combined with these. Then on, every 6 monthly or yearly till follow-up lasts. The 18-24 months visit is mandatory for formal development assessment. In case the child develops any medical or neurodevelopmental concerns, more frequent visits will be required.

**AGE CORRECTION**

Corrected age is used for growth and development assessment of preterm (<37 weeks) till 24 months. Currently TH is offered only to neonates 36 weeks and above.
Table 1: Roles of each member of the follow-up team

<table>
<thead>
<tr>
<th>Personnel</th>
<th>Responsibility</th>
</tr>
</thead>
</table>
| Pediatricians / neonatologists    | Coordinator  
Assessment of growth and screening for developmental delay  
Management of inter-current illnesses  
Immunization  |
| Pediatric neurologist             | Management of neuro-disabilities, seizures |
| Child psychologist                | Formal development/IQ assessment  
Screening and management of behavioral disorders |
| Ophthalmologist                   | Assessment of visual acuity  
Screening and management of strabismus and refractive errors |
| Otorhinolaryngologist             | Hearing assessment  
Management of hearing impairment |
| Dietician                         | Management of infants with failure to thrive |
| Speech therapist                  | Language assessment  
Management of oromotor dysfunction |
| Medical social worker/counsellor  | Counselling parents  
Arranging disability certification, free bus pass etc. |
| Physiotherapist/Occupational therapist | Physiotherapy and rehabilitation |
| Special educator                  | Special education |

Those administering tests of neurodevelopmental assessment, depending upon the test used might require formal training and certification.

**FOLLOW-UP DURING NICU STAY**

Findings of a structured neuro exam needs to be documented daily during and at least until 1 week after TH, though it is often not possible to perform a complete examination due to the infant's sickness, intubation and effect of sedatives and anti-seizure medications. Sarnat staging and Thompson scoring are two such examination methods. Levene's classification is a simplified system, shorter and easy to perform.

Though significant correlation exists between developmental status at 2 years and the Sarnat grade and persistently abnormal neuro exam on day 3, the best predictability of the outcome at 2 years is seen with the neurological examination at discharge (positive and
negative predictive values of 86% and 72% respectively). In infants with moderate Sarnat scores, abnormal outcome occurred in 25% if the discharge examination was normal and in 70% if it was abnormal. The time taken to establish oral feeding also correlated significantly with neurological outcome \( r=0.40, p=0.008 \).\(^{13}\)

The role of cranial sonography, MRI and EEG have been described in other chapters in this manual.

**POST DISCHARGE FOLLOW-UP**

**FEEDING HISTORY**

Infants with severe NE may suffer from significant oromotor disturbances leading to difficulties in feeding. Neonates suffering from perinatal asphyxia may be born with low birth weight or intrauterine growth restriction (IUGR), in which case adequate post natal feeding has to be ensured. A detailed history of the child's feeding pattern must be elicited inclusive of history of difficulty in sucking/chewing/swallowing, choking episodes, drooling, repeated lower respiratory infections and failure to thrive. Those with oromotor dysfunction need prompt referral to an occupational therapist or a speech and language pathologist.

**MEDICAL PROBLEMS**

Epilepsy has been reported to develop in 9-33% of HIE.\(^{14}\) Though every attempt must be made to wean off all anti-convulsants by discharge, some infants may have to be discharged on anti-convulsant medication. Details of any episode of seizure post discharge must be obtained.

Apart from seizure disorder, cases of cerebral palsy suffer from a host of other medical problems as well like hypertonia, drooling, recurrent respiratory infections, skeletal deformities and contractures etc. Relevant history must be elicited and examination performed. As parents are often uneducated, instructions regarding medications are poorly understood. They must be requested to bring with them all the medications that the child is on at every visit, in order to explain prescriptions clearly. Also this way the physician knows for certain all the medications that the child is on, as drug interactions have to be borne in mind when prescribing new drugs.

**IMMUNIZATION**

Immunization must proceed in survivors of HIE in the same manner as that of normal children, including those with seizure disorder.

**GROWTH**

Weight, length/height and head circumference must be accurately checked at each visit. Weight should be checked on an electronic weighing scale, length up to 2 years must be checked with an infantometer and head circumference with a non-stretchable tape.
Growth must be plotted in the WHO child growth standards. For preterms Fenton growth charts (http://www.ucalgary.ca/fenton/2013chart) may be used till 40 weeks CGA.

**NEUROLOGICAL ASSESSMENT**

Neurological examination must be done at every visit with special attention to muscle tone. The NNF recommends neuro-motor assessment of high risk infants at least once during the first 6 months, once during the second six months and once yearly. \(^{11}\)

Skull shape must be noted, fontanelles and sutures must be palpated.

**Amiel-Tison neurological assessment at term (ATNAT)** is a systematic way of performing the neurological examination. If the full exam is not possible, then a general neuro-exam with measurement of AT angles for assessment of muscle tone may be done.

**Table 2. Amiel–Tison angles**

<table>
<thead>
<tr>
<th>Age (months)</th>
<th>Adductor angle</th>
<th>Popliteal angle</th>
<th>Dorsiflexion angle</th>
<th>Scarf sign</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3</td>
<td>40°-80°</td>
<td>80°-100°</td>
<td>60°-70°</td>
<td>Elbow does not cross midline</td>
</tr>
<tr>
<td>4-6</td>
<td>70°-110°</td>
<td>90°-20°</td>
<td>60°-70°</td>
<td>Elbow crosses midline</td>
</tr>
<tr>
<td>7-9</td>
<td>110°-140°</td>
<td>110°-160°</td>
<td>60°-70°</td>
<td>Elbow goes beyond axillary line</td>
</tr>
<tr>
<td>10-12</td>
<td>140°-160°</td>
<td>150°-170°</td>
<td>60°-70°</td>
<td></td>
</tr>
</tbody>
</table>

ATNAT at term age has been shown to have good agreement with neurological examination (k=0.83) and BSID scores (MDI, k=0.64; PDI, κ=0.74) at 12-15 months of age. \(^{15}\)

**Measuring the AT angles**

Check the angles when the infant is in a quiet alert state. Maintain the head in midline.

**Adductor angle**- With the infant in supine position, hold both lower limbs extended and pull them apart gently as far as possible. Measure the angle formed between the two legs. Look for asymmetry between the two sides.

**Popliteal angle**- Bring the thighs by the side of the abdomen and extend the knee. Measure the angle formed between the leg and the thigh. Check both sides simultaneously.

**Ankle dorsiflexion**- Check each side separately. Extend the knee with one hand and with the other apply slow pressure on the sole to flex the foot. Measure the angle formed between the dorsum of the foot and the anterior aspect of the leg. This is the ‘slow angle’. Repeat the manoeuver with rapid flexion of the foot, this gives the ‘rapid angle’. Normally both angles are equal. A difference of more than 10° is abnormal.

**Scarf sign**- Lift the infant’s head to 45°, hold the wrist and try to pull the hand towards the opposite shoulder.

Angles smaller and larger than the normal indicate hypertonia and hypotonia respectively.
MOTOR SKILLS

Observation of spontaneous movements of the infant (Prechtl’s assessment of general movements) has been found to be predictive of future motor development. The first stage is that of writhing general movements (GMs) which are present inutero to 6 to 9 postterm weeks and are characterized by small to moderate amplitude and slow to moderate speed movements. From 9 to 20 postterm weeks, writhing movements are replaced by fidgety movements involving the neck, trunk and limbs. These are small-amplitude movements of moderate speed and variable acceleration in all directions.

Abnormal GM has been found to correlate with lesions in MRI in term infants with HIE. Cramped-synchronized GM, a type of abnormal rigid movements, lacking fluency with the limbs and trunk contracting and relaxing almost simultaneously have been found to correlate with central gray matter lesions in the MRI. They have been reported to be 100% specific and 68.7% sensitive for prediction of cerebral palsy. Abnormal GM has been found to correlate with lesions in MRI in term infants with HIE. Cramped-synchronized GM, a type of abnormal rigid movements, lacking fluency with the limbs and trunk contracting and relaxing almost simultaneously have been found to correlate with central gray matter lesions in the MRI. They have been reported to be 100% specific and 68.7% sensitive for prediction of cerebral palsy. Abnormal GM has been found to correlate with lesions in MRI in term infants with HIE. Cramped-synchronized GM, a type of abnormal rigid movements, lacking fluency with the limbs and trunk contracting and relaxing almost simultaneously have been found to correlate with central gray matter lesions in the MRI. They have been reported to be 100% specific and 68.7% sensitive for prediction of cerebral palsy.

Assessment of GMs may be done during an outpatient visit by video recording the infant’s spontaneous movements during wakeful state for 10-15 minutes at 1 month and 3 months.

Other methods of motor examination are the Alberta Infant Motor Scale (AIMS), Test of Infant Motor Performance (TIMP) and Peabody Developmental Motor Scales (PDMS). In a case of cerebral palsy, assessment of severity of disability is to be done using the GMFCS (The Gross Motor Function Classification System). It classifies the functional status of the child into 5 levels.

1. Walks without restrictions; limitations in more advanced gross motor skills
2. Walks without assistive devices; limitations walking outdoors and in the community
3. Walks with assistive mobility devices; limitations walking outdoors and in the community
4. Self-mobility with limitations; children are transported or use power mobility outdoors and in the community
5. Self-mobility is severely limited even with the use of assistive technology

DEVELOPMENT ASSESSMENT

DEVELOPMENT SCREENING TEST

A developmental screening test has to be done once within the first 6 months, once within the next 6 months and yearly thereafter.

DIAGNOSTIC DEVELOPMENT TEST

A formal assessment of development is to be done at corrected age of 12 months and again between 18-24 months. If an assessment has to be done before 12 months, it is best
done only by 6-8 months.\(^8\) If at any point the screening test has abnormal results or there is any caregiver concern regarding development then a formal assessment must be completed within 2 months.\(^{11}\)

**Table 3: Commonly used tests for developmental assessment**

<table>
<thead>
<tr>
<th>Responsibility</th>
<th>Age range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct assessment</td>
<td></td>
</tr>
<tr>
<td>Denver Development Screening Test (DDSTII)</td>
<td>0-6 years</td>
</tr>
<tr>
<td>Bayley Infant Neurodevelopment Screener (BINS)</td>
<td>3 months-2 years</td>
</tr>
<tr>
<td>Parent-completed tool</td>
<td></td>
</tr>
<tr>
<td>Ages and Stages Questionnaire (ASQ) III</td>
<td>1 month-5.5 years</td>
</tr>
<tr>
<td>Parents Evaluation of Developmental Status(PEDS)</td>
<td>0-8 years</td>
</tr>
<tr>
<td>Diagnostic test</td>
<td></td>
</tr>
<tr>
<td>Griffiths III III Mental Development Scales</td>
<td>1 month-5 years</td>
</tr>
<tr>
<td>Bayley Scales of Infant and Toddler Development III</td>
<td>1 month-3.5 years</td>
</tr>
<tr>
<td>Developmental Assessment Scales for Indian Infants (DASII)</td>
<td>0-2.5 years</td>
</tr>
</tbody>
</table>

Mukherjee et al in a comparison of various screening tests recommend BINS and the ASQ for screening of high risk children.\(^{17}\)

**ASSESSMENT IN THE PRESENCE OF DISABILITIES**

The usual tests of development cannot be administered to those with visual and hearing impairment. In those with hearing impairment the Leiter International Performance Scale-Revised can be used to assess nonverbal cognitive function. For children with visual impairment without significant motor impairment the Verbal Comprehension Index of the Wechsler scales can be used.\(^{18}\)

In the protocol of the TRUFFLE study if BSID could not be administered due to impairments, an estimate of cognitive delay was made as no delay, 3-6 months delay or more than 6 months delay.\(^{19}\)

**OPHTHALMOLOGICAL EVALUATION**

Mercuri et al reported abnormalities of visual function in 41% of cases of NE secondary to HIE, at school age.\(^{20}\) The Cochrane meta-analysis showed a non-significant decrease in blindness among survivors of TH.\(^3\)
Prior to discharge, red reflex must be checked in every neonate. At each visit visual milestones must be elicited from the mother. In infants, clinical assessment of visual function is mainly by fixation and following. One should also look for squint, roving eye movements and nystagmus. With the infant lying down or seated on the mother's lap, a red wool, target or any attractive toy can be used to check for fixation and following. The assessment must be done binocularly and then monocularly. Care should be taken that the objects do not make noise as the child may respond to the auditory rather than the visual signals. Visual acuity can be formally assessed in young children using Cardiff cards or Teller Acuity Card.

Formal assessment by an ophthalmologist for refraction, strabismus and any other visual problems should be done at 1 year and annually thereafter till 5 years of age. Robertson et al recommend early referral to a pediatric ophthalmologist in case of: HIE III, HIE II with abnormal neurological examination or reduced visual awareness at hospital discharge and stroke associated with HIE.

HEARING EVALUATION

Of HIE survivors, up to 17% of those with and 6.3% of those without residual neurological deficits, have been found to have hearing loss. Incidence of permanent hearing loss has been reported to be 6% to 10% in follow-up cases of TH. The Cochrane meta-analysis of seven studies failed to show any significant reduction in the incidence of sensorineural hearing loss requiring aid in neonates subjected to TH.

Hearing screening is to be done via Brainstem Auditory Evoked Responses (BAER/BERA), as OAE misses auditory neuropathy. However if unavailable, then at least a screening OAE must be done. Hearing screening is usually prior to discharge, in any case it must be completed before 1 month of age. Mietzsch et al in a pilot study in moderate to severe HIE reported transient suppression of DPOAEs and prolongation of ABR waveforms in the first week which normalized by the third week. They suggested that cooling might hasten recovery of this transient auditory dysfunction. However this was only a pilot study with a small sample size of 9 (4 cases and 5 controls). Further research will provide directions as to whether screening in these infants should be delayed beyond the first week.

If the neonate fails the screening test, a diagnostic BERA has to be done before 3 months of age and appropriate intervention initiated before 6 months of age.

For those at high risk for hearing loss even if the initial screening test is passed, the NNF recommends a behavioral audiometry at 1 year of age. The American Academy of Paediatrics recommends diagnostic audiologic testing between 24 and 30 months in the presence of risk factors. Perhaps it would be prudent to say that in follow-up cases of TH, irrespective of the initial screen result, auditory milestones must be elicited at every visit along with a clinical assessment of hearing and a repeat diagnostic test must be performed between 1 to 2 years of age.
**TFT SCREENING**

Thyroid screening must be offered universally to all infants.

**LANGUAGE ASSESSMENT**

The NNF recommends a language assessment between 1 and 2 years of age. Robertson et al recommend one between 3 and 5 years. Language assessment must include testing of skills of expressive and receptive language, organization and grammar. Few of the tests used are Receptive-Expressive Emergent Language Test, Peabody Picture Vocabulary Test (PPVT), Linguistic Profile Test and Three Dimensional Language Acquisition Test (3D-LAT).

**COGNITIVE ASSESSMENT**

Shankaran et al reported an IQ <70 in 27% of survivors of TH at 6-7 years of age. Survivors of moderate encephalopathy have been found to have lower scores on school readiness test conducted at 5.5 years. Performance in intellectual, scholastic and neuropsychological tests are uniformly poor in survivors of severe NE. Those with moderate NE show more varied results with intelligence scores below those of children with mild NE and age-matched peers, but within the normal range. They perform poorly in reading, spelling and mathematical skills. Cognitive dysfunction of low severity may not become apparent till the child faces complex tasks, which will happen only at later school age. Due to these reasons, cognitive assessment needs to be done during the child’s schooling years.

Cognitive assessment should include assessment of intelligence, executive function, sensorimotor functions (visual-motor precision, fine motor speed), visual spatial processes (design-copying, visual closure) and memory and learning. IQ can be assessed from 3 years of age. A battery of tests have to administered to the child at different ages (3-4 years, 6-7 years and 8-10 years of age ) in order to complete a comprehensive assessment of cognitive functions.

In the Indian setting, extensive testing over several years would not be practicable. In our country a practical approach might be to conduct an IQ test between 3-4 years and repeat it at 8-10 years. IQ determined at 8 years predicts IQ at older age better than if determined earlier. Like development assessment tests, there are a host of tests for assessing intelligence. Worldwide the most commonly used tests are the Wechsler’s tests. Wechsler’s Preschool and Primary Scale of Intelligence for young children (WPPSI, IVth edition is applicable from 2:6 – 7:7 years of age) and the Wechsler Intelligence Scale for Children (WISC, Vth edition is for children aged 6:0-16:11 years) for older ones. Stanford-Binet Intelligence Scales and Seguin Form Board (SFB) are other commonly used tests. Specific neuropsychological tests like NEPSY II (A developmental neuropsychological assessment) are required in order to diagnose attention, memory, executive function and information processing deficits.
BEHAVIOURAL ASSESSMENT

Children suffering from moderate to severe NE are 5.9 times more likely to be diagnosed with an autism spectrum disorder as compared to controls at 5 years. Autism screening should be conducted universally in all children between 18-24 months. Modified Checklist for Autism in Toddlers (M-CHAT), Social Communication Questionnaire, Trivandrum Autism Behavior Checklist are few of the tools available. Diagnosis can be established using Childhood Autism Rating Scale (CARS), INCLLEN diagnostic tool for ASD (INDT-ASD) or Indian Scale for Assessment of Autism (ISAA).

The Achenbach Child Behavior Check List (CBCL) is a good tool to identify behavioural abnormalities based on parental perception of child’s behaviour.

Assessment of functional status which would also reflect the quality of life can be measured using the Vineland Adaptive Behavior Scales (VABS). Robertson et al recommends evaluation of adaptive behaviour at 3-5 years and the 8-10 years.

There is no consensus regarding the timing, frequency and tests for developmental assessment in the follow-up of TH. If further research reveals a specific profile of neurodevelopmental sequelae in this group of infants, that would guide the choice of tests to be used. Till then each centre may design its protocol depending on the manpower, patient load and funds available. The tests for development/behaviour assessment must have a sensitivity and specificity of > / = 70%. Some of the development assessment tools are freely available, whereas others have to be purchased and are expensive. A reasonable protocol is suggested in Table 3.
<table>
<thead>
<tr>
<th>Age Range</th>
<th>Examination Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 weeks post discharge</td>
<td>Med &amp; Neuro exam</td>
</tr>
<tr>
<td>1.5 months (immunization visit)</td>
<td>Screening BERA, thyroid screening if not done earlier</td>
</tr>
<tr>
<td>3 months</td>
<td>Med &amp; Neuro exam, Clinical assessment of vision and hearing, Prechtl’s assessment of general movements, Complete audiological evaluation if failed BERA</td>
</tr>
<tr>
<td></td>
<td>DDST II/BINS</td>
</tr>
<tr>
<td>6 months</td>
<td>Med &amp; Neuro exam, DDST II/BINS</td>
</tr>
<tr>
<td>9 months</td>
<td>Med &amp; Neuro exam, DDST II/BINS</td>
</tr>
<tr>
<td>12 months</td>
<td>Med &amp; Neuro exam, BSID III/DASII, Ophthalmological exam</td>
</tr>
<tr>
<td>18-24 months</td>
<td>Med &amp; Neuro exam, BSID III/DASII, MCHAT, Behavioural audiometry, Ophthalmological exam, REELS III</td>
</tr>
<tr>
<td>Every year, after 2 years</td>
<td>Med &amp; Neuro exam, DDST II/ASQ III, Ophthalmological exam (till 5 years)</td>
</tr>
<tr>
<td>3-4 years</td>
<td>WPPSI-IV, CBCL, VABS</td>
</tr>
<tr>
<td>8-10 years</td>
<td>WISC -V, CBCL, CBCL</td>
</tr>
</tbody>
</table>

The RBSK guidelines on examination and follow up of a child with suspected developmental delay are easy to understand and implement. The website provides freely downloadable material (http://nhm.gov.in/nhm-components/rmnch-a/child-health-immunization/rashtriya-bal-swasthya-karyakram-rbsk/2013-12-19-08-13-49.html)
HOW TO MAINTAIN GOOD FOLLOW-UP

Follow-up rates must be at least 80% at the 18-24 months visit. In India most follow-up programs face huge lost to-follow-up. Few measures that can help improve follow-up rates.

Enrol patients into the follow-up program before discharge itself. Prior to discharge counsel the parents regarding the need for follow-up and inform them about the date, time and venue of the first post-discharge visit.

Maintain a database of patient address and contact details. Collect back-up contact numbers.

Make phone call or SMS reminders of the appointments. If patients miss an appointment, call up and find out why and fix another date of visit.

Provide parents with the number of a contact person.

**According to the NICHD network, if a single assessment alone is possible it should be performed at 18-22 months corrected age. Therefore if the patient is unable to come for regular visit, request them to come for a single visit at 18-22 months corrected age.**

Screening tools like Ages and Stages (ASQ) and Cognitive Adaptive Test/Clinical Linguistic and Auditory Milestone Scale (CAT/CLAMS) may be administered over the phone.

All the above measures will be possible only if there exists adequate manpower and funds dedicated to running the follow-up program.

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**KEY MESSAGE**

- Detailed neurological examination must be performed and documented at discharge.
- Follow-up of cases of post-TH should be done in a structured manner.
- Separate assessment of vision and hearing are mandatory.
- Long term follow till at least till 8-10 years of age is needed.


There is sufficient evidence in support of therapeutic hypothermia in term and late preterm newborns with hypoxic ischemic encephalopathy and it reduces mortality without increasing major disability in survivors. We have been practising therapeutic hypothermia for hypoxic neonates since 2009 in our level III NICU. We have used cooling gel packs, phase change material and servo controlled equipment both for service and research purposes. Phase change material - MiraCradle® will be a good investment for the Neonatologists and Pediatricians dealing with cases of perinatal asphyxia. It is easy to use and an affordable equipment in resource limited settings. However, the cooling procedure should be undertaken with close monitoring of the neonate.

DR. B. VISHNU BHAT
Professor and Head, Department of Pediatrics, Division of Neonatology, JIPMER, Pondicherry

Birth asphyxia is one of the largest contributors to neonatal mortality in the developing countries and only approved and proven therapy which has been shown to decreased mortality and morbidity in this condition is therapeutic hypothermia or cooling the brain to reduce further damage. Unfortunately, like most technologies, the servo controlled hypothermia machines are outside the budget of most government and even private hospitals in India and other developing parts of the world. We have had MiraCradle® since 2014 and have cooled more than 70 babies till now. I feel this is one innovation which is totally "Made in India" and holds promise as a low-cost device to help babies with perinatal asphyxia.

DR. SANJAY WAZIR
Consultant Neonatologist, Cloudine Hospital, Gurgaon