



Alake, O., Hardman, S., & Chakkarapani, E. (2018). Managing hypoxic ischaemic encephalopathy in term newborn infant. *Paediatrics and Child Health*, 28(9), 399-404.  
<https://doi.org/10.1016/j.paed.2018.07.002>

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[10.1016/j.paed.2018.07.002](https://doi.org/10.1016/j.paed.2018.07.002)

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## **Managing Hypoxic ischaemic encephalopathy in term newborn infant**

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## **Abstract**

Hypoxic–ischaemic encephalopathy (HIE) is a brain dysfunction resulting from inadequate blood flow and oxygenation to the whole body during the perinatal period. It is a major cause of brain injury and is associated with mortality and significant disabilities in later life. Following HIE acute, secondary and tertiary phases of brain injury lasting from hours to years occurs.

Therapeutic hypothermia reduces death and improves the neurodevelopment in infants with moderate to severe HIE. Passive cooling can be initiated soon after birth in infants that fulfil criteria for the treatment.

Active cooling with appropriate intensive and supportive care including respiratory and cardiovascular support, maintaining normoglycaemia, sedation, and seizure management is essential for minimising the brain injury. In cooled infants likely to have a worse prognosis re-orientation of care is often considered in the infant's best interests.

This paper aims to explain the underlying pathophysiological effects of HIE and its management.

Keywords: Hypoxia-Ischaemia, neonatal encephalopathy, Hypothermia, Aetiology/Therapeutic

## **INTRODUCTION**

### **Definition**

Neonatal encephalopathy (NE) refers to the disturbance of neurological function characterised by difficulty in initiating and maintaining respiration, depression of tone or reflexes, abnormal level of consciousness and often seizures.

Nearly 50-80% of cases of NE are due to acute hypoxic ischaemia secondary to perinatal asphyxia. Perinatal asphyxia is characterised by impairment of gas exchange between the placenta and the foetus resulting in hypoxaemia, hypercapnia accompanied by metabolic acidosis and clinically defined as “failing to initiate or maintain regular breathing at birth”. NE secondary to confirmed intrapartum hypoxia-ischaemia with umbilical cord blood acidosis, clinical encephalopathy, electroencephalographic (EEG) abnormalities and characteristic patterns of injury on brain MRI is termed as hypoxic-ischaemic encephalopathy (HIE); it is often associated with multi-organ impairment.

Other possible causes of NE include neurometabolic disease, genetic conditions, infection (meningitis, TORCH etc), drug exposure, neonatal epilepsy syndromes, nervous system malformation and neonatal stroke. The requirement for investigation to exclude these other causes will depend on the presentation, history and clinical features of the individual case.

### **Prevalence**

Perinatal asphyxia occurs in 2-11/1000 live births in the UK and 80/1000 live births globally. However, only 2-3/1000 babies in the UK and 10 /1000 babies globally develop encephalopathy. Reasons for the reduction in the number of babies developing encephalopathy secondary to perinatal asphyxia includes successful perinatal resuscitation preventing the development of encephalopathy and babies dying before the onset of encephalopathy.

## **PATHOGENESIS AND COURSE OF THE DISEASE**

Pathogenesis of HIE is mainly understood from elegant animal experiments and is mainly triggered by impairment in cerebral blood flow (and hence oxygen delivery to the brain) which could be secondary to prenatal or perinatal factors such as cord prolapse, uterine rupture, abruptio placenta, placenta previa, maternal hypotension, breech presentation, or shoulder dystonia. This then triggers a cascade of events at both the cellular and systemic level (Fig 1).

Following hypoxia-ischaemia induced by reduction in the concentration of inhaled oxygen along with occlusion of the umbilical arteries or carotid arteries or hypotension, 3 phases of brain damage are identified namely acute (primary), secondary and tertiary phases.

In the acute phase, reduction in cerebral blood flow results in impaired oxygenation and reduced glucose thus depleting high energy metabolites such as adenosine tri-phosphate (ATP) as well as reduced oxidative metabolism. The low ATP levels result in failure of the sodium/potassium (Na/K) pumps and calcium channels leading to excessive influx of the positively charged sodium ions. This causes massive neuronal depolarization with cerebral oedema leading to hypoxic depolarization of neuronal cells and hence cytotoxic oedema. There is also accumulation of excitatory amino acids

such as glutamate due to failure of re-uptake and excessive release which increase intracellular calcium resulting in worsening oedema, micro-vascular damage and necrosis/apoptosis.

Following resuscitation and restoration of cerebral blood flow and / or oxygenation, cytotoxic oedema and accumulation of excitatory amino acids resolve with partial recovery of cerebral oxidative metabolism in the latent phase. This is thought to be the optimal timing for therapeutic interventions. However, the cerebral oxidative metabolism may deteriorate in approximately 6 to 15 hours and enter the secondary phase of brain damage.

The secondary phase is characterised by damage to neuronal tissue by increased free radical generation from break down of unsaturated fatty acids (which is present in high concentrations in the neonatal period) and from uncoupling of iron-protein complex which produces free iron that reacts with peroxides. There is also increased levels of extracellular neurotransmitters, especially glutamate (which is present in neuronal pathways such as hearing, vision, somatosensory function, learning and memory) and it over stimulates excitatory receptors thus allowing additional influx of sodium and calcium into the cells in these neuronal pathways.

The excitotoxicity, free radicals generation and resulting cytotoxic edema secondary to cytokine induced inflammation with accompanying cell death mediates the disruptive effect of HIE in this secondary phase which occurs within 6-48hrs after the initial injury. The more severe the hypoxia-ischaemia, the less the duration of latent phase and the more severe the secondary phase of brain damage. This secondary phase of brain damage is marked by the onset of seizures.

The tertiary phase of brain damage includes altered epigenome and ongoing inflammation. These processes may worsen the outcome, predispose a patient to further injury and prevent repair or regeneration after an initial insult to the brain.

All phases of brain injury involves cell death. Cell death processes involve an apoptosis-necrosis continuum. Various hybrid forms of cell death including excitotoxic cell death, programmed necrosis and autophagy are involved in between the classical apoptosis and necrosis.

## **DIAGNOSIS**

### **Evidence of perinatal asphyxia (criteria A)**

Term newborn infants (>36 weeks gestational age) are at risk of developing encephalopathy following perinatal asphyxia. Evidence of perinatal asphyxia is characterised by:

1. History of an acute perinatal event (abruptio placenta, cord prolapse, severe foetal heart rate abnormality, e.g., variable or late decelerations).
2. An Apgar score of <5 at 10 minutes
3. Continued need for assisted endotracheal or mask ventilation initiated at birth and continued for at least 10 minutes.
4. Cord pH or first postnatal blood gas pH at  $\leq 1$  hour  $< 7.0$
5. Base deficit on cord gas or first postnatal blood gas at  $\leq 1$  hour  $> 16$  mEq/L.

If blood gas is not available or if the pH is between 7.01 and 7.15 and base deficit between 10 and 15.9mEq/L, then babies satisfying criteria 1 and 2 or 3 will need a neurological examination.

### **Evaluation for encephalopathy (Criteria B)**

Encephalopathy is typically diagnosed clinically by conducting a neonatal neurological examination (see Table 1) and further confirmed by using bedside electroencephalography such as amplitude-integrated electroencephalography (aEEG).

It was defined as the presence of one or more signs in at least three of the six categories of the modified Sarnat scale (Table 1). The number of moderate or severe signs determined the extent of encephalopathy. If the signs were equally distributed between the moderate and severe categories, the level of consciousness determined the severity of encephalopathy. If the level of consciousness is similar, then the designation of NE is based on the tone. Clinical seizures on the back ground of mild or moderate NE indicates that the infant has moderate grade of NE.

### **Amplitude integrated electroencephalography (aEEG)**

Cross cerebral single channel aEEG is sufficient to assess the global patterns of brain activity. Infants with moderately abnormal or severely abnormal pattern (Fig 2) or electrical seizures on normal background pattern or continuous electrical seizures on aEEG indicate that their brain activity is significantly suppressed following asphyxia. Furthermore aEEG patterns of discontinuous normal voltage, burst suppression, low voltage and flat trace before commencing neuroprotective treatments are robust in predicting death or disability by 18- 24 months of age.

### **MANAGEMENT**

The management of asphyxia starts with a correct perinatal management of high-risk pregnancies and early recognition of perinatal sentinel events indicative of foetal distress such as:

- Decreased foetal movements
- Fetal heart rate abnormalities such as late decelerations, severe variable decelerations, decrease or loss of variability or terminal bradycardia.
- Evidence of placental bleeding and/or fetal blood loss.
- Cord occlusion or prolapse.

### **Resuscitation and post resuscitation care**

The delivery room care is the second fundamental step in management. Resuscitate and support as per neonatal resuscitation guidelines. Obtain cord blood gas analysis in the delivery room and assess for evidence of perinatal asphyxia as listed above. If the infants fulfils any of these criteria:

- After ensuring return of spontaneous circulation with adequate resuscitation turn off the radiant warmer as soon as possible to commence passive cooling
- Exposure of infants to higher oxygen concentration during and post resuscitation is associated with death or disability by 18-20 months of age. Avoid hyperoxia during the resuscitation and the post resuscitation period. Wean oxygen maintaining the transcutaneous oxygen saturation between 90-95% and / or PaO<sub>2</sub> <80mmHg.
- Neurological examination for features of encephalopathy

### **Neuroprotection**

Treatment options in HIE are targeted at ameliorating effects of secondary phase of injury by decreasing energy depletion, reducing metabolic demand, inhibiting the release of excitatory amino acids including glutamate, improving the impairment in glutamate uptake, blocking glutamate receptors, inhibiting inflammation, and blocking the downstream cascade of intracellular events leading to apoptosis and cell death. Current standard treatment is therapeutic hypothermia.

Other treatments that are shown in preclinical studies to reduce brain injury following hypoxic-ischaemia are currently investigated in clinical trials. These treatments include erythropoietin, xenon, N-acetyl cysteine, melatonin, umbilical cord mesenchymal stem cells and cannabinoid

agonists. Some of these therapies are being explored in isolation, while others are combined with moderate hypothermia or other treatments to provide additive or synergistic neuroprotection.

### **Therapeutic hypothermia (TH)**

Therapeutic hypothermia involves reducing the baby's core temperature to 33.5°C for 72hrs period within 6hours of life, and then rewarming at a rate of 0.2-0.6°C/hour over 6-15 hours until core temperature reaches 36.5° C. It prevents the progression of brain injury by reducing the metabolic demand, free radicals generation, secondary energy failure and apoptosis. Cooling is usually administered using a servo-controlled whole-body cooling device.

Multicentre randomised clinical trials have shown that TH reduced the risk of death and disability by 18 months. It also reduced the risk and the severity of cerebral palsy, severe neurodevelopmental delay and results in increased survival with an IQ > 85 at 6-8 years of age. However, nearly 30% of cooled infants had IQ scores between 70 and 84; 96% of cooled children with cerebral palsy had IQ <70 and 9% of cooled children without cerebral palsy had IQ<70. Nearly 20% of children with normal IQ and 28% of those children with IQ between 70 and 84 had special educational needs.

### **Cooling beyond 6hours of life**

Although cooling may be safe beyond 6hours of life, death or disability was comparable between the cooled and non-cooled group (24.4% versus 27.9%, p=0.25) in the late hypothermia trial. Preclinical studies demonstrate that the therapeutic effect of cooling linearly declines upto 9 hours of age and is negligible beyond 9 hours.

### **Mild hypoxic ischaemic encephalopathy**

Nearly 50% of infants with HIE present with mild encephalopathy. Nearly 25% of infants with mild HIE experience an abnormal outcome of death, cerebral palsy or neurodevelopmental test score more than 1 standard deviation below the mean. Currently there is no evidence to support the use of therapeutic hypothermia for infants with mild HIE.

### **Intensive care and supportive treatment**

Early supportive intensive care has been shown to be essential to avoid or to reduce the on-going brain injury in asphyxiated infants. This includes:

#### **a) Respiratory support:**

Infants with severe HIE may have respiratory depression and may require anti-epileptics for seizure control which could cause respiratory depression. Hence, they often require respiratory support during TH.

If babies are ventilated, use volume targeted ventilation to avoid hypocapnia. Target PCO<sub>2</sub> should be between 45-50mmHg and PO<sub>2</sub> < 100mmHg. Hyperoxia increases oxidative stress and free radical production while hypocapnia leads to cerebral hypo-perfusion and cellular alkalosis all of which could worsen neurodevelopmental outcome as well as increase the risk of mortality. Currently there is no evidence for adopting alpha stat (blood gas measurement at 37°C) or pH stat (correction of blood gases to core temperature) during ventilation. While alpha stat based ventilation may preserve cerebral autoregulation, pH stat based ventilation increases cerebral blood flow and oxygenation. Therefore, the optimal blood gas strategy may have to differ between moderate (intact cerebral autoregulation) and severe (impaired autoregulation) encephalopathy.

Most babies with HIE have no underlying lung diseases and as TH decreases the metabolic rate and CO<sub>2</sub> production, they often only require minimal ventilatory support. However, babies with meconium aspiration and or persistent pulmonary hypertension may require higher ventilatory support with or without inhaled nitric oxide or pulmonary vasodilator.

**b) Cardiovascular support:**

Cooled babies have lower heart rate (usually <110bpm) when temperature < 34°C. Heart rate drops by 14-45 beats per minute (10-12 beats per degree fall in core temperature). Nearly 5% of cooled infants have heart rate <80 beats per minute. Cooling does not increase the risk of cardiac arrhythmia. In the electrocardiogram, corrected QT interval increases by 3.12 milliseconds for each degree fall in the core temperature.

During induction of hypothermia, systemic vascular resistance increases followed by a fall in cardiac output during maintenance phase of cooling (6-7% fall in cardiac output for every 1°C fall in core temperature). It is recommended to maintain a mean blood pressure above 45 mmHg during cooling and around 50mmHg during rewarming to maintain adequate cerebral perfusion in the event of compromised cerebral autoregulation. Continuous invasive blood pressure monitoring using arterial line is preferred prior to instituting inotropic support. Care should be taken during the rewarming as the temperature rise could cause peripheral vasodilatation and secondary hypotension.

Dopamine or dobutamine up to 15 micrograms/kg/hour may be required to maintain a mean blood pressure above 45 mmHg.

**c) Analgesia:**

Avoid cold stress as there is evidence from pre-clinical and adult hypothermia studies that being stressed during cooling may disrupt the neuroprotective effect of cooling. Monitor pain and sedation scores (eg: NPASS) and use morphine infusion to avoid distress. Morphine clearance is delayed with cooling and higher serum morphine concentrations might be achieved beyond 10micrograms/kg/hour. Commence morphine at an adequate dosage to keep the babies comfortable and start weaning once steady comfort levels are achieved clinically.

**d) Fluid and Electrolytes:**

During TH, infants are either fed with minimal enteral nutrition or not fed due to concerns of developing ischemic gut disease like necrotising enterocolitis. There is no consensus for providing total parenteral nutrition or dextrose water for nutrition. However, in babies with liver impairment, providing parenteral nutrition can lead to protein and lipid intolerance with higher ammonia and triglyceride levels.

Babies receiving TH are usually fluid restricted due to renal impairment and typically started at 40 mls/kg/day. Depending on the renal function and fluid balance, total fluid requirement will need to be gradually increased up to 90 mls/kg/day by the end of rewarming. Monitor blood glucose as hypoglycaemia contributes to poor outcomes and adjust glucose infusion rates as necessary. Maintain electrolytes with magnesium at high normal levels (>1.0 mmol/L) and avoid base replacement therapy if possible as acidosis improves with re-establishment of circulation.



**e) Developmental care:**

This involves neuro-protective nursing care to minimise over-stimulation and keep infants calm thus minimising metabolic demands on the brain and avoiding increases in intra-cranial pressure. Measures taken include:

- protective sleep by low level lighting, minimising handling and noise
- skin care and comfort positioning (they are at risk of reduced skin perfusion owing to the hypothermia which could result in pressure sores or subcutaneous fat necrosis from reduced movement).

**f) Antibiotics:**

Empiric antibiotics may be indicated for sepsis. Gentamicin dosing interval of 36hrs with serum level monitoring is recommended. Renal impairment in these infants can lead to higher trough gentamicin levels and is associated with high risk of developing hearing impairment. Commonly used infection markers such as c-reactive protein expression is delayed by cooling and is not sensitive to monitor or diagnose infection.

**g) Seizure management:**

Nearly 50% of cooled infants develop clinical or electrical (seen on electroencephalogram (EEG)) seizures. They increase cerebral metabolic demand, trigger release of excitatory neurotransmitter and cause cardiorespiratory instability, all of which exacerbate neuronal injury. All cooled infants will need continuous amplitude integrated electroencephalography monitoring to identify seizures. While repetitive seizures and status epilepticus worsen the neurodevelopment, the lowest critical duration of seizures that need treatment is still not known.

Phenobarbital pharmacokinetics is not affected by cooling and remains the first line of treatment for seizures. Second line agents include phenytoin for infants who do not have haemodynamic instability and levetiracetam for infants with haemodynamic instability. Third line agent includes benzodiazepines or lidocaine. Anticonvulsants are rarely required beyond the first week and studies have not shown any evidence to support prophylactic or long-term use.

**h) Other supportive care**

Aggressively manage coagulopathy. Cooling decreases plasma clearance of neuromuscular blocking agents. Therefore, drug holidays are essential to prevent critical care neuropathy. Remain vigilant to parental concerns, stressors and provide parents with frequent understandable accurate information. Parents' usual concerns include whether their child is in pain, whether their child will be normal and what their future will be like.

## INVESTIGATIONS

- Baseline laboratory work up to include blood gas, blood sugar, lactate, full blood count, clotting profile with fibrinogen, blood culture, liver and renal function tests, electrolytes with calcium and magnesium. These should be monitored at 12-24hrly intervals until the end of

treatment. Frequency of blood gases, lactate and blood glucose will be determined by the results.

- EEG and aEEG: useful to assess severity of HIE and monitoring improvement during treatment. The amplitude EEG (aEEG) can detect a third of single seizures and two-thirds of repetitive seizures, but may miss short lived seizures (<30 s) or those arising from a focus distant from the electrodes which can be detected on the multi-channel electroencephalography (EEG).
- Cranial ultrasound: changes that may suggest severe HIE include cerebral edema (obscured sulcal markings, and closed fissures), increased echogenicity in the basal ganglia and thalamus with reduction in resistive index  $\leq 0.55$  which is a measure of cerebral blood flow can be identified. It is however a poor prognostic indicator.
- MRI: useful prognostication tool in HIE and optimal timing for MRI in these babies is 5-14 days as earlier scans may miss HIE related findings as they change over time. Brain metabolite concentrations using magnetic resonance spectroscopy.
- Placental Histology

## PROGNOSIS

Hypoxic–ischaemic encephalopathy (HIE) may be associated with mortality and long term neurological sequelae. Hence assessing its severity and possible outcome is useful to guide management as well as parental counselling.

Poor prognosis is defined as death or moderate to severe disability. Disability is often defined as cerebral palsy, hearing or visual deficits and neurodevelopmental scores less than 2 standard deviations below the mean.

Factors associated with poor prognosis include:

- APGAR score of  $\leq 4$  at 10 min
- Severity of HIE: HIE grade 2 or more is associated with poor outcome
- Neurological exam: Abnormal neurological findings on day 7
- aEEG: Persisting abnormal EEG beyond 36hrs is a poor prognostic sign while rapid recovery within 6-12hrs is a good prognostic indicator.
- Seizures: continuous or repetitive seizures suggest poor prognosis despite cooling
- Neuro-imaging: abnormalities in the thalamus or basal ganglia are associated with abnormal neurodevelopmental outcomes. A resistance index of  $\leq 0.55$  within 24 to 72 hours after birth has a high predictive value for abnormal outcome. Brain metabolite concentrations including N acetyl aspartate concentration may improve the prognostication.
- multiorgan dysfunction is associated with high risk of mortality.

Biochemical parameters such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH) and creatine kinase (CK) have previously been thought to be useful in predicting outcomes. However, recent meta-analysis debunks this as most are not specific to HIE and correlate poorly with neurological outcomes.

## **RE-ORIENTATION OF CARE**

Though TH has been shown to be effective in reducing mortality and moderate–severe disability at 18-24 months of age, there is still a risk of mortality and major morbidity in about 30% of babies. Though difficult, it is important to identify these high-risk babies with poor outcomes so as to guide discussions with parents about end of life care and re-orientation of goals of care to palliative measures.

These discussions should be held by day 2 of life if there is lack of recovery of severity of clinical encephalopathy and aEEG. MRI could be undertaken to augment the prognostication although the validity is higher soon after rewarming. MRI findings it can be used as an adjunct to other poor prognostic predictors listed above.

## **FOLLOW UP**

HIE is associated with long term adverse outcomes such as developmental delay with cerebral palsy, learning problems, visual problems, hearing deficits, feeding problems, epilepsy or behavioural problems. Hence these patients require follow up after discharge to assess for these complications.

Optimal follow up includes 6-8 weeks of age and every 6 months until 2 years of age, when a neurodevelopmental assessment using standardised scales including Bayley scales of infant and Toddler development or Griffiths scale of infant development should be undertaken. There should be a coordinated follow up with community Paediatric team for children with difficulties. All cooled children should ideally undergo pre-school developmental follow up.

## **PRACTICE POINTS**

- Majority of cases of NE are due to acute hypoxic ischaemia secondary to perinatal asphyxia.
- Therapeutic hypothermia has been effective in reducing the risk of associated mortality and major morbidity
- Criteria for TH include evidence of perinatal asphyxia and encephalopathy on neurological examination.
- In addition to TH, supportive therapy is necessary to improve outcomes in them.

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## Figure legends

Fig 1. Pathophysiology following hypoxic-ischaemic insult. NTP/EPP: Nucleotide triphosphate (mainly ATP)/ high energy phosphate pool .

Table : 1 Modified Sarnat and Sarnat clinical encephalopathy grade.

Fig 2. Amplitude integrated electroencephalogram categories based on amplitude and pattern types.