

Best Practice Guideline article

# Clinical management of the baby with hypoxic ischaemic encephalopathy

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## ABSTRACT

The results of randomized clinical trials indicate that the optimal management for infants with hypoxic ischaemic encephalopathy is therapeutic hypothermia combined with high quality standard neonatal intensive care. In addition to therapeutic hypothermia clinical management of the infant with hypoxic ischaemic encephalopathy should include the management of multiorgan dysfunction, obtaining and documenting detailed clinical information and performing appropriate investigations and assessment to confirm the diagnosis and to help direct care, and providing counseling and support to the family. This article is a summary of the in hospital clinical management of infants with hypoxic ischaemic encephalopathy.

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In the UK, 10% of newborns (approximately 70,000 annually) require some form of resuscitative procedure after birth [3]. The majority respond promptly and make a full recovery, although it is concerning that infants who do not develop encephalopathy may have an increased risk of a low IQ score at 8 years if they required resuscitative efforts at birth, and infants with just brief depression of the Apgar score (<7 for 1 min after birth) may have poorer function in cognitive tests in later life [15,16].

Encephalopathy developing within hours of birth occurs in approximately 2–3/1000 births in the UK and is much more common in low resource settings [9,13]. Neonatal encephalopathy may have many etiologies. This paper focuses on the clinical management of infants who have a triad of: (1) intensive resuscitative intervention at birth (which is immediately followed by); (2) an abnormal neurological state characterized by abnormal behaviour, tone and reflexes, and usually seizures; and (3) evidence of a hypoxic ischaemic insult. This clinical scenario is most appropriately and commonly called hypoxic ischaemic encephalopathy

(HIE). The hypoxic ischaemic insult is assumed to have started intrapartum but this may be difficult to ascertain unless a sentinel event occurred; it is also accepted that other factors may be present [7,9]. In many cases the first indication of a problem is a non reassuring cardiotocograph or the presence of thick meconium staining of the liquor intra partum or a failure to establish spontaneous breathing after birth.

Although therapeutic hypothermia improves neurological outcomes in infants with HIE and is rapidly being introduced into clinical practice in many countries [11], meticulous standard medical and nursing intensive care is also critical. This includes: management of multiorgan dysfunction; obtaining and documenting detailed clinical information and performing appropriate investigations and assessment to confirm the diagnosis and to help direct care; and providing counseling and support to the family. Therapeutic hypothermia is discussed elsewhere in this issue.

## 1. Resuscitation

Our practice is based on our interpretation of the ILCOR 2005 neonatal guidelines [2]. Key points are listed in Box 1.

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Although the ILCOR guidelines are helpful, the circumstances will vary from case to case and it is important that experienced personnel attend if the infant does not respond promptly to standard resuscitative measures. Complications such as a tension pneumothorax may be difficult to ascertain in the full term infant in the delivery suite and some infants may have co existing abnormalities that may be undetected by inexperienced personnel.

It is generally accepted that if cardiac asystole persists despite adequate resuscitative efforts > 10 min the chance of neurologically intact survival is exceedingly low and international guidelines state that resuscitative efforts should be discontinued [2,27]. However, 24% of infants with an Apgar score 0 at 10 min were reported to survive without disability in one trial of therapeutic hypothermia [12] and in another trial 9/17 survivors had no disability at 18 months of age (The TOBY trial: unpublished data). Although these data are from a selected group of infants that responded to resuscitation and the denominator is unknown, they do indicate caution in specifying time points at which resuscitation efforts should be discontinued.

The ILCOR 2005 guidelines are not specific about starting ventilation with air, but the experimental and clinical evidence support this practice and we follow this policy [22]. Although none of the clinical trials of therapeutic hypothermia provide details of the resuscitation measures employed, in the UK most neonatal units aim to start resuscitation with air but this is only possible if air/oxygen blenders are routinely available.

## 2. Clinical management in the neonatal unit

The initial management of infants with HIE following admission to the neonatal unit consists of standard neonatal intensive care measures (Box 2), continuous core temperature monitoring using a rectal (most commonly practiced in the UK) or esophageal probe, initiation of therapeutic hypothermia if appropriate and neurological monitoring by regular clinical examination, continuous EEG or amplitude integrated EEG (aEEG) and regular cranial ultrasound examinations. Clinical management will depend on the severity of encephalopathy: infants with mild encephalopathy at about 6 h of age are likely to make a rapid recovery but may occasionally deteriorate and have brief seizures so observation (preferably including aEEG) for at least 24 h is appropriate. These infants may be enterally fed according to local protocols. More severely affected infants will require closer monitoring and enteral feeding can be cautiously introduced once the initial biochemical and metabolic disturbance are corrected, usually after about 24 h. It is our practice to cautiously feed even if the infant is receiving therapeutic hypothermia.

### Box 1

Key points in the resuscitation of full term infants

- Personnel experienced in advanced neonatal resuscitation should attend to the infant
- If the infant is apnoeic start mask or endotracheal tube ventilation; Progressively increase inspiratory pressure to achieve adequate chest inflation
- Start pulse oximetry; Oxygen saturation >80% is adequate
- Use air ventilation; Increase inspired oxygen concentration progressively if oxygen saturation <80% despite adequate chest inflation
- Start cardiac compression if heart rate is < 100 despite adequate chest inflation
- Look for complications such as a pneumothorax if there is no improvement despite adequate chest inflation
- Consider discontinuing resuscitation efforts if infant is asystolic >10 min

### Box 2

General medical management of infants with moderate/severe HIE:

On admission to the neonatal unit

- Reassess cardiovascular and respiratory status and perform neurological assessment
- Consider therapeutic hypothermia
  - Start passive cooling if appropriate – Follow local protocols
- Insert rectal thermometer at least 3 cm and start continuous rectal temperature monitoring

Correction of acidosis

- Correct respiratory acidosis by manipulating ventilatory support
- Severe metabolic acidosis (pH < 7.0) persisting > 4 h despite adequate ventilation may be treated with intravenous 4.2% bicarbonate over 30–60 min (mmol bicarbonate required = base deficit (mmol/L) \* weight (kg) \* 0.3. Initially give half this dose)

Cardio-respiratory management

- Start mechanical ventilation if repeated desaturation associated with seizures or incipient respiratory failure with rising oxygen requirements and increasing respiratory acidosis (eg pCO<sub>2</sub> > 8 kPa; Inspired oxygen concentration > 50%)
- Avoid hypocapnia. Aim for pCO<sub>2</sub> around 6 kPa during cooling
- Maintain SaO<sub>2</sub> ≥ 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 regular echocardiographic assessment of cardiac contractility and stroke volume to guide fluid/inotrope administration
- If echocardiographic assessment indicates adequate contractility but evidence of hypovolaemia, consider IV 0.9% saline (10–20 mls/kg). Check hematocrit and consider a blood transfusion if clinically hypovolaemic and hematocrit < 30
- Consider inotropes if echocardiographic assessment indicates poor contractility or BP is low despite volume replacement.
- Perform an electrocardiogram and check cardiac enzymes if hypotension is persistent

Fluid balance/metabolic management

- Hypoglycaemia can be a serious complicating factor in HIE. Monitor plasma glucose closely (4 hrly) and adjust glucose intake accordingly
- Oliguria/anuria is common following HIE;
  - Monitor urinary output and aim for urine output ≥ 1 ml/kg/h.
  - Observe for bladder retention. Urinary catheterisation may be useful.
  - Consider low dose dopamine (2.5–5 µg/kg/min) or fluid challenge (20 mls/kg 0.9% sodium chloride IV over 30 min) in incipient renal failure/anuria
- Initial intravenous fluid requirements are approximately 40 ml/kg/day 10% Dextrose solution. Monitor blood electrolyte levels 8 hrly for first 24–48 h
- Consider electrolyte additives or parenteral nutrition after 24–48 h when electrolytes/renal function stable
  - Give maintenance potassium supplementation if renal function is adequate (2 mmol/kg/day). Avoid potassium supplementation during cooling, as hyperkalaemia may occur on rewarming.

#### Monitoring for multiorgan failure

- Monitor haematologic, clotting, biochemical, renal and hepatic function parameters

### 3. Information gathering and documentation

Because many cases present unexpectedly and the focus following birth is on clinical management, communication and information sharing between obstetric and neonatal teams may be suboptimal. However, it is important to obtain a detailed structured clinical history to identify risk factors for HIE, and evidence of alternative diagnoses and comorbidities. This information needs to be carefully documented so that it is readily available to multidisciplinary teams that are often involved in the long term clinical management of affected children (Box 3).

### 4. Neurological monitoring

Regular neurological assessment is necessary to determine the severity of encephalopathy, detect deterioration and complications such as cerebral sinus thrombosis or haemorrhage, to assess the response to therapies such as anticonvulsant therapy, and to assess likely neurological outcome which is critical for planning further clinical management (Box 4).

#### Box 3

##### Documentation

- Document maternal and family history (eg maternal and paternal age, maternal and paternal health, consanguinity, ethnic background, parity, details of previous pregnancies, health of other children, a family history of thrombosis, any thyroid disease, active herpes infection, neurological disease, cerebral palsy, seizures, neonatal or infant deaths, travel abroad before or during pregnancy)
- Document details of current pregnancy (eg last menstrual period and expected date of delivery and certainty, conception whether natural or assisted, history of infertility, previous fetal losses and stillbirths, maternal medication/drugs, antenatal care, results of chorionic villous sampling/amniocentesis, results of antenatal scans, placental site, fetal position, fetal movements including time of onset and any changes, chorionicity of twins, history of twin to twin transfusion syndrome, presence of oligo/polyhydramnios, growth pattern, infection, essential hypertension/pre-eclampsia, diabetes mellitus/gestational diabetes, accidental injury, rhesus incompatibility, results of any cardiocogram in pregnancy).
- Document details of resuscitation (eg evidence for intrapartum fetal distress, cord blood gases and lactate from both arterial and venous samples, Apgar scores at 1, 5 and 10 min, need for intubation and duration, difficulties in intubation or ventilation, presence of meconium below the cords, onset of satisfactory heart rate, time to first gasp, onset of regular respirations, maximum ventilatory requirement, any drugs/fluids administered).
- Document details of care in the neonatal unit including specific documentation of care during therapeutic hypothermia eg using TOBY UK cooling register documentation ([www.npeu.ox.ac.uk/tobyregister](http://www.npeu.ox.ac.uk/tobyregister)).

Several clinical neonatal neurological examination methods have been described [5,8,21,24]. These systems help standardize the assessment of HIE and are part of the criteria for starting therapeutic hypothermia. Assessment may be complicated by anticonvulsant

#### Box 4

##### Neurological monitoring

- The clinical features of HIE evolve over a period of days. Perform daily neurological examinations and document clinical state and responsiveness
- Perform continuous aEEG/EEG according to local protocols
- Monitor for seizures: Correlate subtle signs such as lip smacking, head turning, eye turning, bradycardias and apnoeas with the aEEG. Subclinical seizures may be apparent on aEEG
- Treat clinical seizures according to local protocols: eg. if seizures are repetitive or interfere with respiration, or associated with systemic disturbance. Runs of subclinical seizures may need treatment
- Perform cranial ultrasound scan on admission and daily for first 4 days and before discharge. Measure cerebral flow velocities and calculate pulsatility index daily during the first 3 days
- Perform MRI according to local protocols. If only one scan can be performed the optimal timing is 4–14 days after birth

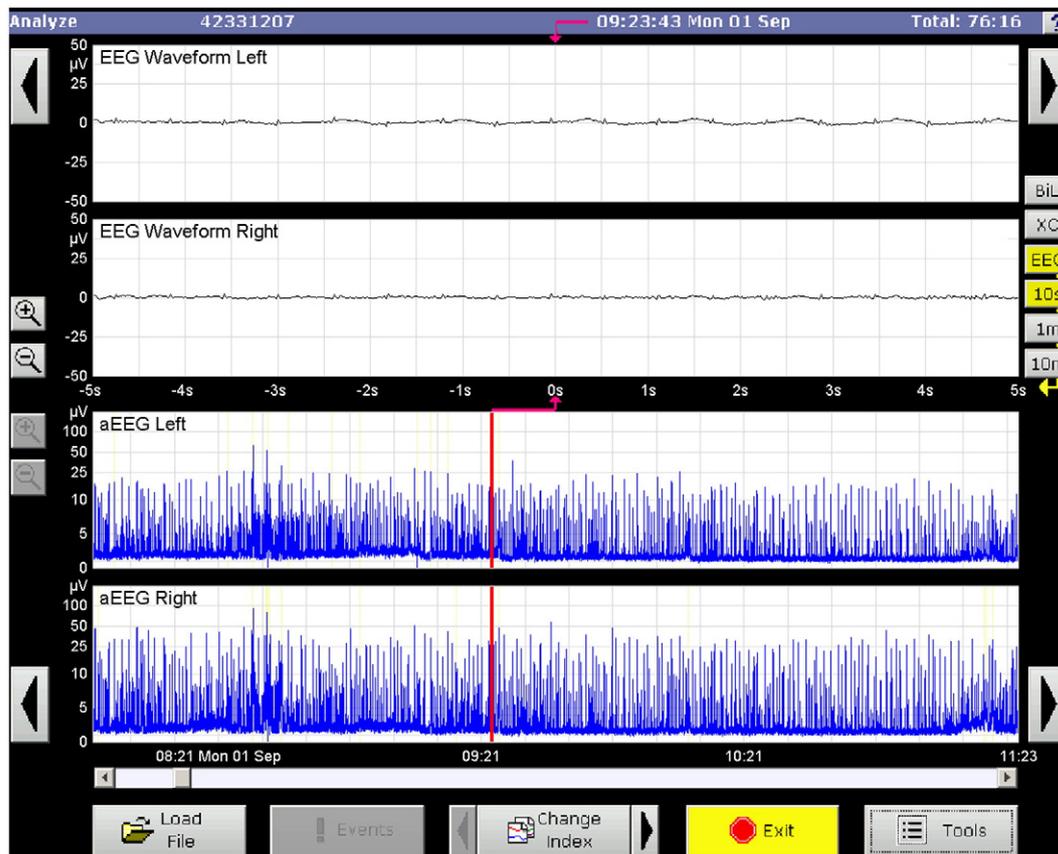
therapies, paralytic agents and co-morbidities. Our practice is to assess the Thompson score [24] and a modified optimality score [8] daily in moderately/severely affected infants.

Infants with the mildest degree of encephalopathy (usually called stage 1 encephalopathy) have transient irritability, hypertonia and poor feeding and a good neurological outcome, although there are concerns about learning and memory difficulties in later childhood even in infants who appear to do well [14]. More severely affected infants (stage 2 encephalopathy) have reduced tone and complex reflexes and often have seizures. Stage 2 encephalopathy is associated with a poor outcome in approximately 25% of the infants. The most severely affected infants (stage 3 encephalopathy) have profound stupor or coma and the EEG is usually severely suppressed. Stage 3 encephalopathy leads to death or a severely abnormal outcome in >75% of infants. In many infants clinical features intermediate between these stages are common.

Continuous monitoring of the aEEG is routinely used in our practice. It is easy and quick to apply, the patterns are relatively simple to analyse and correlate well with both standard EEG and MRI findings and neurological outcome [4,25,26]. Severely abnormal patterns such as burst suppression or low voltage patterns persisting for more than about 24 h after birth are associated with a poor neurodevelopmental outcome in about 70% of infants even in infants treated with hypothermia (Fig. 1). Visual and somatosensory evoked potentials have also been used to predict outcome in HIE, and whilst accurate are more difficult to perform than the CFM and do not give continuous data [23].

Cranial ultrasound scanning is helpful to exclude structural abnormality suggesting metabolic and other diagnoses, detect calcification and cysts suggestive of viral infection and detect atrophy suggestive of long standing damage. It will also identify cerebral haemorrhage. Sequential observation of the evolution of injury following a recent hypoxic ischaemic insult at birth is helpful both for defining the pattern of lesion and timing its onset.

Magnetic resonance imaging (MRI) may provide information about the timing of injury and specific patterns of abnormality that may suggest diagnoses other than HIE. MRI has shown that there is a low rate of established brain lesions acquired before birth in HIE and also a low rate of associated congenital abnormality [7]. The patterns of brain injury may not be apparent until after the first 4–7 days on



**Fig. 1.** Amplitude integrated EEG (aEEG) record from an infant with hypoxic ischaemic encephalopathy. The aEEG is everely abnormal and shows a burst suppression pattern (lower half of figure). The EEG waveform (upper half of figure) is very low or absent voltage with an artefact due to the ECG.

conventional MRI but may be readily seen with diffusion weighted imaging [20]. Proton magnetic resonance spectroscopy is increasingly available and provides important prognostic data during the first week [6,18]. A reduction in n acetyl aspartate and elevation of cerebral lactate correlate with later neurological problems.

## 5. Investigations

In most cases further investigations are warranted to support the diagnosis of HIE. When encephalopathy has developed following resuscitative efforts at birth with evidence of perinatal asphyxia [1] and following a sentinel event [17], a diagnosis of HIE is likely to be correct but co existing or precipitating/predisposing conditions such as infection or trauma also need to be considered. A protocol will help ensure only the most appropriate investigations are carried out (Box 5).

## 6. Counseling and redirecting care

The unexpected birth of a baby suffering severe neurological and multisystem injury must be one of the most traumatic experiences possible for parents. During the first few days after birth it is important that senior personnel talk to the parents regularly in a quiet

### Box 5

#### Investigations

- At birth/on admission to neonatal unit
  - Cord blood gases including blood lactate,
  - Routine haematology, biochemistry and metabolic parameters according to local protocols
  - Cardiac and hepatic enzymes
  - Screen for bacterial infection according to local protocols and including lumbar puncture if appropriate

- Tests for congenital infection
- Cranial ultrasound scan
- EEG/aEEG recording
- MRI scan within 14 days of age
- 2nd line investigations – In cases with clinical history not suggestive of HIE or with progressive or persistent encephalopathy
  - Investigation for metabolic or genetic disorders if any of dysmorphic features, parental consanguinity, abnormal intracranial anatomy, severe growth restriction, unusual pattern of injury on MRI scan, normal looking MRI scan in face of ongoing neurological problems
- 3rd line investigations – When previous investigations are non informative
  - Consider further investigation for metabolic disorders (eg non ketotic hyperglycinemia, sulfite oxidase deficiency, biotinidase deficiency, mitochondrial disorders, peroxisomal disorders, carbohydrate glycosylation defects, carnitine or acyl carnitine disorders, disorders of lysosomal enzymes)
  - Consider investigation for neuromuscular diseases (eg nerve conduction studies, electromyogram, muscle biopsy)
  - Consider thrombophilia screen in cases with focal haemorrhage, infarction or thrombosis
  - Store blood for future DNA analysis

environment away from the intensive care nursery. The senior attending physician should provide a full explanation of the infant's condition avoiding medical terminology. Parents will find it difficult to take in all the information in one session and several meetings are needed. The use of an interpreter may be required if one of the parents does not have a good command of the local language to ensure both

parents receive a full explanation. Other family members should be included in the discussions if the parents agree as this improves understanding amongst family members and reduces the need for the parents to explain the situation to others and may reduce the feeling of isolation. Nursing staff play a key role in providing further explanation, feeding back parents' feelings and thoughts to the medical team and to 'personalize' care, helping parents to adapt to the unfamiliar clinical environment and facilitating parental care of the baby. A clinical psychologist experienced in neonatal care plays an invaluable role, by providing a professional approach to counseling (Box 6).

### 6.1. Redirecting care

Approximately 30% of infants that meet the criteria used in the cooling trials protocols die following moderate/severe HIE. The majority of these infants die following a redirection of medical care and discontinuation of assisted ventilation. The possibility of redirecting care should be introduced when the prognosis is

#### Box 6

##### Counseling

- Talk to parents in a quiet setting away from nursery
- Avoid medical terminology, use simple terms and check that parents understand the information provided
- Use interpreting services if one of the parents does not have a good command of the language
- Seek feedback from nurses: Parents are more likely to discuss their feelings with the nursing staff
- Use professional counseling services if available
- Offer a meeting with the parents a few weeks following the death of an infant, preferably together with a senior obstetric physician to provide additional explanation and to assess need for further counseling

considered to be hopeless. The prognosis becomes increasingly poor the longer the infant remains in a severe encephalopathic state (stage 3 encephalopathy) and the aEEG/EEG severely suppressed (EEG voltage extremely low or absent). Persistence of this state beyond 48–72 h indicates that further life supporting treatment is futile. In our practice we almost always obtain an MRI to confirm the diagnosis and severity of brain injury either before ventilatory support is withdrawn or post mortem. In our experience the MRI almost invariably shows gross brain swelling and abnormal signal intensity throughout. Sinus thrombosis is sometimes observed.

Some severely affected infants have a partial recovery during the first 72 h after birth but the level of encephalopathy persists at an intermediate stage 2/3, with the aEEG/EEG remaining moderately or severely abnormal (burst suppression pattern of the EEG predominating). Clinical assessment of the prognosis is difficult and the prognosis may be better than expected following therapeutic hypothermia [10]. We aim to perform an MRI at around 4 days of age in all cases. The occurrence of severe basal ganglia and thalamic signal abnormalities usually together with moderate/severe white matter and cortical changes predicts a very poor prognosis with spastic quadriplegia, microcephaly, feeding and often visual and other communicative difficulties occurring in survivors, even in infants treated with hypothermia [19]. A decision to withdraw or withhold life supporting care may also be appropriate in these cases.

In these situations the senior attending physician together with the nurse looking after the infant should hold regular discussions with the parents; other members of the family or counselors can be present if the parents wish. A clear account of the infant's condition and prognosis and an explanation of the therapeutic options should be provided. The parents' views are critical but the infant's best interests

are paramount; in our experience it is almost always possible for a consensus decision to be reached.

The nursing staff play a leading role in the process of withdrawing life supporting care, focusing on ensuring dignity for the baby and support for the parents. Key points are to ensure that: a clear explanation of the process is given to the parents; parents have sufficient time for preparation and family members are allowed to be with the parents if they wish; a private quiet space is provided preferably separate from other intensive care cots; parents are encouraged and helped to hold the infant throughout; adequate analgesia and sedation is provided; and a nurse known to the parents stays with them throughout. A follow-up visit some weeks following the death of the infant should be arranged preferably together with a senior obstetric physician to provide additional explanation to the parents and to assess the need for further counseling.

## 7. Concluding remarks

Meticulous neonatal care provided by multidisciplinary teams is critical for ensuring the best outcomes for infants with HIE. This needs to be combined with a personalized approach that focuses on the emotional needs of the family. Clear protocols are important for standardizing and auditing care.

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