CLINICAL PRACTICE GUIDELINE
Guideline coverage includes NICU KEMH, NICU PCH and NETS WA

Hypoxic Ischaemic Encephalopathy (HIE)

This document should be read in conjunction with the Disclaimer

Definition

Lack of sufficient oxygen and blood perfusion to the brain, resulting in brain injury.

Pathophysiology

Following a hypoxic-ischaemic insult, neuronal death occurs in two phases:

- **Primary neuronal death** - This is related to cellular hypoxia leading to primary energy failure and cellular depolarisation.
- **Secondary phase** - after a latent period (at 6-100 hours) neuronal death may be initiated by a cascade of pathologic processes and is associated with marked encephalopathy. This involves cytotoxic oedema, mitochondrial failure, accumulation of excito-toxins, active cell death, nitric oxide synthesis and cytotoxic actions of activated microglia. Seizure activity is increased during this phase.

Clinical Presentation

Infants with HIE present with neurological symptoms, whose severity is classified based on the modified Sarnat staging (see table below). There may be evidence of other end-organ damage such as coagulopathy, raised liver enzymes, acute renal failure, hypotension, persistent foetal circulation and/or respiratory failure.

Investigations

- Frequent neurological examination.
- Blood tests to exclude other organ dysfunction - Blood gases, FBC, coagulation profile, liver enzymes, urea and creatinine, glucose, electrolytes (including Ca, Mg, and PO_4), lactate.
- Sepsis screen.
- Cerebral Function monitoring, EEG. It is very important to apply the leads and start recording the amplitude integrated EEG using the cerebral function monitor as soon as possible after admission. a-EEG will assist in the diagnosis of HIE. It has also been shown to be a good prognostic indicator in infants with HIE (del Rio 2016).
- Lumbar puncture if sepsis suspected.
- Urgent head Ultrasound should be requested in all cases of HIE. It will help identify any subdural/extradural haematomas that can be associated with HIE or mimic HIE. Sometimes infants with such haematomas require urgent neurosurgical intervention.
- MRI of brain.

Table: Staging of HIE based on the modified Sarnat Classification (Sarnat 1976)

Variable	Stage I	Stage II	Stage III
Level of consciousness	Alert	Lethargic	Comatose
Muscle tone	Normal or hypertonic	Hypotonic	Flaccid
Tendon reflexes	Increased	Increased	Depressed or absent
Myoclonus	Present	Present	Absent
Seizures	Absent	Frequent	Frequent
Complex reflexes			
Suck	Active	Weak	Absent
Moro	Exaggerated	Incomplete	Absent
Grasp	Normal to exaggerated	Exaggerated	Absent
Oculocephalic (doll eye)	Normal	Overactive	Reduced or absent
Autonomic function			
Pupils	Dilated, reactive	Small, reactive	Variable/fixed
Respiration	Regular	Periodic	Ataxic, apnoeic
Heart rate	Normal or tachycardia	Bradycardia	Bradycardia
EEG	Normal	Low voltage, periodic or paroxysmal	Periodic or isoelectric

Prognosis

- Mild (stage I): Survival is expected. In the past it was considered that mild HIE will not adversely affect long term outcomes. However, recent evidence indicates that infants with mild HIE have increased incidence of abnormal findings on the MRI of the brain as well as long term neurodevelopmental outcomes (Conway 2018)
- Data from our unit showed that infants with moderate to severe HIE undergoing therapeutic hypothermia have a mortality rate of around 14-17%. Majority of the deaths were in severe HIE (Gardiner 2014, Buchiboyina 2017).
- Data from our units showed that cooled infants with moderate to severe HIE who survive have around 18-23% incidence of moderate to severe disability (Gardiner 2014, Buchiboyina 2017).

Management

Therapeutic hypothermia (to maintain core temperature between 33-34C for 72 hours followed by gradual rewarming over 12 hours).

Evidence from high quality RCTs indicates that cooling of neonates with moderate to severe HIE is safe and reduces the risk of death or disability at 18 to 22 months of age (Jacobs 2013). Hence infants with stage 2 or 3 HIE should receive therapeutic hypothermia to maintain core temperature at 33-34^{0}C. Sometimes, while receiving calls from peripheral hospitals, it may be difficult to assess the presence or absence

of HIE. In such situations, neonatologists may consider offering mild hypothermia (approximately 35.5^0c) until the picture becomes clear.

Refer to Cooling Guideline: Systemic Cooling for Neuroprotection in Neonates ≥ 35 Weeks Gestational Age with HIE. Cooling for mild HIE is not standard practice because there are no RCTs that have evaluated cooling in mild HIE. Hence we do not know if cooling is beneficial or harmful in mild HIE. However, a recent survey found that many units cool infants with mild HIE (Oliveira V 2018). Hence the decision to cool mild HIE is up to the discretion of individual clinicians.

Avoid Hypoglycaemia

Hypoglycaemia is known to worsen the neurodevelopmental outcomes of infants with HIE. Hence it is very important to avoid hypoglycaemia (Tan 2017).

To prevent hypoglycaemia:

- Provide 6-8 mg/kg/min of glucose infusion IV and Check blood glucose levels hourly for the first 4 hours.
- Increase concentration of dextrose to maintain above Glucose Infusion Rate, if fluid restriction required.
- Aim for blood glucose levels between 3.5-6 mmol/L
- If blood glucose levels are maintained well above 3.5 mmol/L frequency of checking may be reduced, but should remain at least 4 hourly for the first 24 hours. Refer to Hypoglycaemia.

Appropriate Management of Associated Problems

Refer to: Infection in the Neonate and Sepsis: Septic Screening Procedures.

Fluid Restriction

50-60 mL/kg/day; there is no strong evidence to support fluid restriction in HIE (Kecskecs 2005).

Respiratory Support

May be needed if the infant does not have adequate respiratory efforts. The use of multiple anticonvulsant medications will also necessitate respiratory support.

Blood Pressure Support

Volume expansion or Inotrope may be required. The infant should remain normotensive to maintain cerebral perfusion.

Seizure Control

Higher seizure burden is known to be associated with worse outcomes in HIE (Kharoshankaya 2016). Hence efforts should be made to identify and treat seizures. However, overzealous treatment with multiple anticonvulsants has the potential to cause side effects. The question remains how aggressively neonatal seizures should be treated (van Rooij 2013). Hence a balanced approach is essential. The commonly used anticonvulsants are phenobarbitone, phenytoin, levetiracetam, midazolam and lignocaine (El-Dib 2017). Refer to Seizures: Neonatal.

Feeding: Our current practice is to keep the infants nil by mouth during the period of cooling and rewarming. A recent survey found that many units offer small volumes of enteral feeds (breastmilk) during the period of therapeutic hypothermia (Hazeldine 2018). A recent retrospective study found that administration of minimal enteral feeds is safe in infants undergoing therapeutic hypothermia for HIE (Thyagarajan 2015). If clinicians would like to give enteral feeds, it is preferable to use expressed breast milk and the volume should be minimal (5-10 ml/kg/day).

Other intensive care management: Optimise electrolyte and fluid balance, correct coagulopathy with FFP, cryoprecipitate and platelets as appropriate.

Follow-Up:

All infants showing signs of HIE require developmental follow-up with Griffiths Scales at one year and Bayley Scales.at two years of age.

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Related WNHS policies, procedures and guidelines

Neonatal Clinical Guidelines - Cooling Guideline: Systemic Cooling for Neuroprotection in Neonates > 35 Weeks Gestational Age with HIE
- Seizures: Neonatal
- Hypoglycaemia
- Sepsis: Infection In The Neonate
- Sepsis: Septic Screening Procedures

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