NETS
Part of the Sydney Children's Hospitals Network

HYPOXIC ISCHAEMIC ENCEPHALOPATHY IN THE NEWBORN - NETS

PRACTICE GUIDELINE ©

DOCUMENT SUMMARY/KEY POINTS

- Hypoxic-ischemic encephalopathy (HIE) is neonatal encephalopathy caused by systemic hypoxaemia and/or reduced cerebral blood flow resulting from an acute peri-partum event. To prevent secondary inflammatory mediated injury, moderate to severe encephalopathy is treated with therapeutic hypothermia (TH).
- TH reduces mortality without increasing major disability in newborns with HIE.[1]
- TH should be instituted in neonates ≥35 weeks of gestation with moderate-to-severe HIE if identified before six hours of age.[1,2] Neonates <35 weeks who otherwise meet the criteria for TH should be discussed with the NETS consultant and receiving neonatologist.
- Babies with HIE demonstrate poor thermoregulation[1,3], and it is essential to monitor temperatures closely either continuously via rectal probe or intermittently via axillary probe every 15 minutes.

Approved by:	SCHN Policy, Procedure and Guideline Committee	
Date Effective:	1st April 2022	**Review Period**: 3 years
Team Leader:	Staff Specialist	**Area/Dept**: NETS

Date of Publishing: 15 March 2022 1:13 PM Date of Printing: 15 March 2022

CHANGE SUMMARY

- Updated to include management of infants with HIE more broadly including TH
- Updated in line with the NSW Health Consensus Guideline
- Updated references
- Transferred to SCHN style and approval processes. Title changed, previous title 'Therapeutic Hypothermia In The Newborn – NETS'.

READ ACKNOWLEDGEMENT

- All NETS clinical staff are to read and acknowledge they understand the contents of this guideline.

TABLE OF CONTENTS

Approved by:	SCHN Policy, Procedure and Guideline Committee	
Date Effective:	1st April 2022	**Review Period**: 3 years
Team Leader:	Staff Specialist	**Area/Dept**: NETS

Rationale/Background

- Hypoxic-ischemic encephalopathy (HIE) is neonatal encephalopathy caused by systemic hypoxaemia and/or reduced cerebral blood flow resulting from an acute peri-partum event.
- For TH to be effective it is required to be instituted in neonates of ≥35weeks gestation with moderate-to-severe hypoxic ischaemic encephalopathy before six hours of postnatal age.[1,2]
- HIE can be classified as mild, moderate or severe based on the Sarnat criteria for encephalopathy. Early recognition of moderate or severe encephalopathy is required to allow timely initiation of TH. TH reduces mortality without increasing major disability in newborns with moderate-to-severe hypoxic ischaemic encephalopathy.[1]
- Benefits outweigh short-term adverse effects that most frequently manifest as sinus bradycardia and thrombocytopenia.
- The decision to commence TH is based on inclusion and exclusion criteria and should be made in consultation with a receiving hospital neonatologist/NETS consultant and referring consultant.
- Appropriate resuscitation with attention to airway, breathing and circulation should occur prior to consideration of TH.
- Babies who require TH also require transfer to a neonatal intensive care unit for aEEG monitoring, MRI and formal EEG.
- While some babies with actual or potential HIE may not meet criteria for this treatment, care should be taken to avoid hyperthermia.
- Decisions should be based on worst encephalopathy documented and once cooling commenced it is advisable for it to continue for 72hours to achieve the full benefit of the therapy.

Hypoxic-Ischemic Encephalopathy Detection and Management

Ensure appropriate resuscitation of the newborn, with attention to airway, breathing and circulation prior to considering therapeutic cooling. Aim for normothermia whilst the baby is being assessed for inclusion criteria. Cooling is an adjunct therapy and should not influence the decision to cease resuscitation attempts.

- Referring units should proactively identify all newborns at risk of encephalopathy, perform cord gases and commence monitoring for encephalopathy
- Target oxygen saturations 91-95%, arterial pCO_2 35-45mmHg, mean blood pressure 40-50mmHg and blood glucose 3-7mmol/L
    - Infants with HIE typically require respiratory support (CPAP or ventilation) given the metabolic load. Respiratory distress is often a sign of acidosis and not lung parenchymal pathology.

- Babies with HIE often have concomitant cardiac and renal dysfunction. Fluids are generally restricted to 40-60mL/kg/day with close monitoring of fluid balance. Consider urinary catherisation.
- Inotropic support with low dose adrenaline may be required if cardiac output is low leading to hypotension. Exercise caution with fluid boluses due to potential renal impairment. Ideally clinician performed ultrasound (CPU) will assist detection of poor contractility, low flow states and more rarely hypovolaemia.

- Avoid hyperthermia at all times – temperature >37.5ºC increases risk of death and disability
- Consider end-organ investigations if available at referring site – FBC, UEC, LFT, CMP, troponin
- Check coagulation if bleeding, thrombocytopaenic or petechiae are present
- Consider infection and cover with antibiotics after blood culture if risk of sepsis present
- Manage seizures as per seizure guidelines

Specific Requirements for therapeutic hypothermia

Eligibility criteria for TH in the near term/term neonate (≥ 35 weeks gestation) with moderate to severe HIE are adapted from the NSW Ministry of Health Policy Directive.[4] These criteria were also used in all the Cooling trials. [1]**Refer to NETS Clinical Calculator for eligibility criteria and Sarnat scoring for TH**

All of the following three criteria must be met to be eligible for TH

1. ≥ 35 weeks gestational age and < 6 hours old
2. Evidence of acidosis or depression at birth, with any ONE of the following:
   - **i.** pH < 7.00 or base excess ≤ -12 on any cord or baby blood gas in the first hour **OR**
   - **ii.** Apgar Score: < 6 at 10 minutes **OR**
   - **iii.** Mechanical ventilation or ongoing resuscitation for ≥ 10 minutes **OR**
   - **iv.** pH 7-7.1 or lactate >8mmol/L in the first hour
3. Presence of moderate or severe encephalopathy defined as:
   - **i.** 3 or more moderate or severe features of encephalopathy (Sarnat criteria) identified at any time from 1-6 hours **OR**
   - **ii.** Seizures (witnessed by a medical officer/nurse/midwife or seen on aEEG/EEG) **OR**
   - **iii.** 2 moderate or severe features of encephalopathy and abnormal aEEG (e.g. lower margin < 5µV)

The decision to cool the baby should be discussed with the NETS consultant and the receiving unit neonatologist. Cooling of babies who do not meet the standard criteria requires cautious consideration on a case-by-case basis with receiving neonatologist and NETS. Repeated examination and documentation of clinical signs of encephalopathy[6] is recommended. All infants commenced on therapeutic cooling require retrieval but it can be commenced prior to confirmation of destination.

	Normal	**Mild encephalopathy (HIE Grade 1)**	**Moderate encephalopathy (HIE Grade 2)**	**Severe encephalopathy (HIE Grade 3)**
Level of consciousness	Alert/arouses appropriately	Hyperalert	Lethargic	Stupor/coma
Spontaneous activity	Normal	Normal	Decreased activity	No Activity
Posture	Normal	Mild distal flexion	Arms flexed, legs extended (decorticate)	Arms and legs extended (decerebrate)
Tone	Normal	Normal	Hypotonia	Flaccid
Primitive Reflexes	Normal suck, Strong moro	Weak suck, normal Moro	Weak suck, incomplete Moro	Absent suck, absent Moro
Autonomic activity				
- Pupils	Equal, reactive	Dilated	Constricted	Dilated – reactive
- Heart rate	Normal	Tachycardia	Bradycardia	Variable heart rate
- Respiration	Normal	Normal respirations	Periodic breathing	Apnoea

Sarnat and Sarnat Staging criteria for defining mild, moderate and severe encephalopathy[5]

Exclusion Criteria (prevention of hyperthermia paramount)

- Uncontrolled severe hypoxia due to persistent pulmonary hypertension
- Uncontrolled bleeding due to severe coagulopathy
- Baby is 'in extremis' and unlikely to survive. Death seems imminent from multi-organ impairment and inability to resolve cardiovascular instability.

Equipment

- NETS neonatal transport system
- Rectal temperature probe (Philips grey disposable for 2012 series, thermistor/probe and cable to connect for N8/N9).
- Lubricant
- Cool packs from refrigerator; never from the freezer. Cloth covers.
- Cool bag with frozen bricks to transport cool packs.

Procedure

- Full cardiorespiratory monitoring
- Rectal probe continuous temperature monitoring
- Invasive arterial pressure monitoring is desirable
- Infant should remain nil by mouth

Passive Cooling

- Insert lubricated probe into the anus to 5cm to ensure accurate measurement of the newborn's core temperature. Tape to upper inner thigh. The probes are designed for this purpose and will not cause mucosal trauma if used as directed.
- Aim for rectal temperature of 33-34°C within one hour of commencing cooling. If rectal temperature drops below 33.5°C, set radiant warmer or transport incubator to **"ON"** to maintain the rectal or axillary temperature within target range.
- Nurse newborn on an open radiant warmer with heater **"OFF"**. When in NETS transport system, nurse with incubator **off** and porthole doors **open**.
- Nurse newborn naked - do not dress, no wraps- plastic or cloth.
- Leave nappy unfastened.
- Full cardio-respiratory monitoring.
- If newborn is ventilated normal humidifier settings should be used.
- Record start of passive cooling and then record temperature at 15 minutes intervals.

Active Cooling

If passive cooling has not reduced the newborns temperature to below 35.5°C within the first one hour, active cooling should be commenced. The above principles of care remain the same in active cooling

Active cooling algorithm:

- Target temperature range for rectal temperature 33 - 34°C to be reached within 1 hour of commencing cooling.

Rectal Temperature	Number cool packs to apply	Areas to apply
≥35.5°C	2*	Under shoulders
34.0-35.5°C	1	Under shoulders
<34.0°C	0	None

NSW Ministry of Health[3]

**More than 2 packs prevents radiant heat loss into the environment and therefore makes cooling the newborn increasingly difficult.*

- If the temperature falls (either rectal or axilla) to <33.5°C remove 1 or both cool packs and if necessary turn on radiant heater or transport incubator heater to maintain temperature in the required range.
- Consider using low dose morphine or fentanyl for infants with distress of excessive shivering. TH and altered organ function can impact pharmacokinetics so it is recommended to start at low dose and titrate to effect.

Risks and Complications

Short-term adverse outcomes in newborns treated with TH are primarily an increased incidence of sinus bradycardia and thrombocytopenia.[1] Other reports include:

- Pulmonary hypertension
- Hypotension with a requirement for inotropic support
- Severe coagulopathy – coagulation should be assessed at the referring hospital where 24hour pathology facility on site exists. If the specimen is required to be sent away, coagulation study can be collected at the destination. Visible signs of bleeding should be treated aggressively with FFP.
- Leucopoenia
- Subcutaneous fat necrosis – observe and document skin condition under packs
- Excessive cooling to temperatures below target range

Educational Notes

- Moderate to severe HIE after perinatal asphyxia contributes significantly to neonatal mortality and morbidity including long-term neurodevelopmental sequelae in 25%-60% of survivors.[4]
- There are two major phases of neuronal death following a perinatal hypoxic ischaemic insult.[2] Primary neuronal death occurs in relation to cellular hypoxia, there is a primary energy failure, an exhaustion of high energy metabolism and cellular depolarisation followed some hours later (6-100 hours) by a secondary loss of neurons. This allows a therapeutic 'window of opportunity' to initiate neuroprotective measures in the newborn such as passive or active TH.[2]
- This secondary phase of neuronal death is associated with increased seizure activity in the newborn with HIE.[2]
- Meta-analysis of 11 randomised controlled trials comprising 1,505 term and late preterm infants with moderate/severe encephalopathy and evidence of intrapartum asphyxia demonstrated that 72 hours of TH resulted in a statistically and clinically significant reduction in the combined outcome of mortality or major neurodevelopmental disability to 18 months of age (typical RR 0.75 (95% CI 0.68 to 0.83); number needed to treat to prevent death or major disability (NNT) 7 (95% CI 5 to 10).[1]
- TH continued for 72 hours at which time the baby is rewarmed slowly.
- Even though there is no current evidence to support TH in newborns with mild HIE or those born before 35 weeks gestation,[1] in the years since the publication of results of RCTs, there is gradual indication creep towards treating these neonates with TH. A systematic review of this practice in 2018 found 4 RCTs in which 95 babies were inadvertently included in cooling trials for moderate to severe encephalopathy and demonstrated no evidence to support this practice[6]. However, these studies were not powered to study the outcome in mild encephalopathy.

- In spite of lack of evidence, some neonatologists prefer to treat babies with mild encephalopathy with TH and some paediatricians at referring nurseries are not comfortable in monitoring them locally with anticipation of progression of clinical symptoms. NETS would support these paediatricians by retrieving them to a NICU for close observation without TH.

References

1. Jacobs. S.E, Berg. M, Hunt. R, Tarnow-Mordi. W.O, Inder. T.E, Davis. P.G. Cooling for newborns with hypoxic ischaemic encephalopathy. Cochrane Database of Systematic Reviews 2013, Issue 1. Art. No.:CD003311. DOI:10.1002/14651858. CD003311.pub3.
2. Royal Prince Alfred Hospital Newborn Care Guidelines. Moderate systemic hypothermia for neonatal hypoxic ischaemic encephalopathy (HIE). Accessed 23/09/2021 http://www.sswahs.nsw.gov.au/rpa/neonatal%5Ccontent/pdf/guidelines/hypothermia.pdf
3. O'Reilly, K,M., Tooley, J,. Winterbottom, S Therapeutic Hypothermia during Neonatal Transport. Acta Paediatricia 2011 Vol 100(8) 1084-1086
4. Buckmaster. A, Evans. N, Tarnow-Mordi. W and Jacobs. S. Whole Body Cooling for Neonates >35 weeks Gestation with Moderate or Severe Hypoxic Ischaemic Encephalopathy (HIE) 2010. Hypothermia Guideline reference Group. NSW Ministry of Health Policy Directive PD2010_006. Accessed 17/03/2013 http://www0.health.nsw.gov.au/policies/pd/2010/pdf/PD2010_006.pdf
5. Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress. A clinical and electroencephalographic study. Archives of Neurology 1976;33(10):696-705.
6. Conway JM, Walsh BH, Boylan GB et al. Mild hpoxic ischaemic encephalopathy and long term neurodevelopmental outcome – A systematic review. Early Human Development 2018;120: 80-87
7. Queensland Health Clinical Guidelines. Hypoxic-Ischemic encephalopathy (HIE). Accessed 23/09/2021. https://www.health.qld.gov.au/__data/assets/pdf_file/0014/140162/g-hie.pdf