Therapeutic Hypothermia for Hypoxic Ischaemic Encephalopathy

1. Overview / Description

- Hypoxic ischaemic encephalopathy (HIE) remains a significant cause of neonatal morbidity and mortality.
  - **Therapeutic hypothermia (TH)** has an established role in reducing morbidity/mortality when commenced **within 6 hours of birth.**
- Infants at risk of HIE require thorough and repeated neurological assessments in order to:
  - Establish or exclude the diagnosis of HIE
    - This includes establishing a diagnosis of mild HIE which confers a risk of neurological injury and neurodevelopmental sequelae
  - Assesses for eligibility for TH
- There is currently **inadequate evidence** to support the use of TH in
  - **Mild HIE**
  - **Preterm infants <35 weeks gestational age**

This guideline relates to the **PIPER retrieval aspects of HIE assessment and management**. For further information on HIE, please refer to the guidelines in Section 2 and References section.

2. Related Documents

- PIPER Neonatal - Hypoxic Ischaemic Encephalopathy (HIE) Assessment Form
- The following guidelines provide extensive background and references for further reference and reading:
  - Queensland Clinical Guidelines - Hypoxic ischaemic encephalopathy (HIE)
  - Hypoxic ischaemic encephalopathy in newborns – recognition, monitoring and early management | Agency for Clinical Innovation (nsw.gov.au)
- ANZNN will soon be releasing guidance on data collection, screening and assessment for infants at risk of HIE.

3. Definition of Terms

ANZNN:	Australian New Zealand Neonatal Network
aEEG	Amplitude-integrated electroencephalography
HIE:	Hypoxic ischaemic encephalopathy
TH:	Therapeutic Hypothermia

4. Responsibility

All PIPER Medical and Nursing staff

5. Procedure

5.1 SCREENING AND NEUROLOGICAL ASSESSMENT OF INFANTS AT RISK OF HIE

- **The PIPER Neonatal - Hypoxic Ischaemic Encephalopathy (HIE) Assessment Form** should be used for infants at risk of HIE
- **All newly born or collapsed term/near term infants should be screened for risk factors for HIE, including:**
  - Acute peripartum event (eg. placental abruption, cord prolapse, shoulder dystocia etc.)

- Fetal heart rate abnormality (eg. fetal bradycardia etc.)
- Resuscitation at birth OR depressed Apgar scores
- Cord blood gas or blood gas within 60min of life with pH <7.0 OR base deficit ≥ 12
- **Postnatal collapse** in first few days of life may be considered although evidence is limited in this setting

- **If ANY risk factor is identified:**
  1. Obtain **cord gas or blood gas** within 60min of life (or postnatal collapse) AND
  2. Complete a **neurological exam** (Table 1) AND
  3. Document **eligibility/ineligibility for Therapeutic Hypothermia** (Table 2)

5.1.1 PIPER Considerations for the Assessment of HIE:

- Infants with a risk of HIE require close monitoring and repeated neurological examination. The capability and resources of the referring centre should be considered. Infants may need to be transferred for neurological monitoring, even if they do not meet the criteria for TH.
- PIPER telehealth at the time of neurological examination can be used to assist with scoring as required.
- Some Victorian non-tertiary centres have access to aEEG neuromonitoring. Use of this equipment should be driven by the local team who can ensure there is adequate medical and nursing expertise in the use and interpretation of aEEG.

5.2 THERAPEUTIC HYPOTHERMIA

- Infants at risk of HIE should be scored hourly for the first 6 hours of life using the Modified Sarnat Criteria (see Table 1).
  - Clinical encephalopathy cannot be accurately assessed during resuscitation or while the infant is critically hypoxic or hypotensive. Perform examination as soon as possible after infant is resuscitated and stabilised.
  - Hourly scoring is performed due to the evolving nature of encephalopathy in HIE. Some newborns may deteriorate, whereas other infants may improve. **Therapeutic hypothermia should be considered for all infants who meet the criteria at any stage during scoring, regardless of whether their neurology subsequently improves**.
- Infants at risk of HIE should have their eligibility for TH scored as per Table 2.
- **Joint decision making** with the Receiving NICU Consultant should be undertaken for borderline cases, postnatal collapses and TH commencement >6H life.

TABLE 1 NEUROLOGICAL EXAM: Modified Sarnat Criteria

Modified Sarnat Criteria **Assess neonatal signs against each criterion (N = Normal / MILD = Mild / MOD = Moderate / S = Severe / or N/A = Not Available)**										
Assessment Criteria	**Encephalopathy Severity**				**Hours post birth** Record severity of each criterion hourly **(N, Mild, Mod, S or N/A)**					
	Normal (N)	**Mild (MILD)**	**Moderate (MOD)**	**Severe (S)**	**0-1hrs**	**1-2hrs**	**2-3hrs**	**3-4hrs**	**4-5hrs**	**5-6hrs**
Alertness / Level of consciousness	Alert Arouses appropriately	Hyperalert	Lethargic Difficulty waking	Stupor or coma						
Spontaneous activity	Normal	Normal or increased	Decreased activity	No activity						
Posture	Normal	Normal	Distal flexion*	Decerebrate†						
Tone	Normal	Normal or increased tone in limbs or trunk	Hypotonia (focal or general) in limbs, trunk or neck	Flaccid						
Suck reflex	Normal	Normal or incomplete suck or biting	Weak suck	Absent						
Moro reflex	Normal	Exaggerated, low threshold	Incomplete	Absent						
Autonomic	Pupils equal/ reactive, normal HR, normal RR	Pupils equal/ reactive, tachycardia, normal RR	Pupils constricted or bradycardia or periodic/ Irregular breathing	Pupils dilated or deviated, or variable HR or apnoea						
Total moderate or severe features										
Seizures (tick if observed)										
Date and time of assessment										
Clinician signature and designation (hourly)										
Telehealth / Video assessment (tick if undertaken)										

Source: Hypoxic ischaemic encephalopathy in newborns – recognition, monitoring and early management (NSW Health, 2024).

TABLE 2 ELIGIBILITY CRITERIA FOR THERAPEUTIC HYPOTHERMIA (TH)

CRITERIA **Criteria A, B and C** should all be met to qualify for TH, unless at PIPER Consultant discretion. **Joint decision making** with the Receiving NICU Consultant should be undertaken for borderline cases, postnatal collapses and TH commencement >6H life.	
A. **Gestational** age **≥ 35 weeks** AND **≥1800g** AND **<6 hours old**	**Yes** ☐ **No** ☐
B. **Evidence of perinatal hypoxia-ischaemia** as defined by the presence of **≥TWO** of the following: • Apgar ≤5 at 10 minutes • Chest compressions or ventilation (ETT/SGA or Face Mask) at 10 minutes • Cord or blood gas (within 60min life/postnatal collapse) with ○ pH < 7.0 OR base deficit ≥ 12	**Yes** ☐ **No** ☐

C. **Presence of moderate/severe encephalopathy** with **≥ONE** of:
• ≥3 moderate or severe features of encephalopathy (Table 1)
  ○ identified **at any time** after initial stabilisation to 6 hours of life
  ○ **regardless of whether infant's neurology subsequently improves**
• 2 moderate OR severe features of encephalopathy AND abnormal aEEG[#]
• Seizures (witnessed by a trained healthcare worker or seen on aEEG)
	Yes ☐
	No ☐

CONTRAINDICATIONS	
There are no absolute contraindications to therapeutic hypothermia; however, relative contraindications include uncontrolled **bleeding**, uncontrolled severe hypoxia due to **persistent pulmonary hypertension**, or **imminent end of life care** planned.	**Yes** ☐ **No** ☐

[#]eg. aEEG lower margin <5uV for >1H. Consider discussing with receiving NICU Consultant.

5.2.1 PIPER Considerations regarding the institution of TH:

- Therapeutic Hypothermia should be commenced **within 6 hours of birth**.
  - **Commencing TH after 6H life** should be discussed the Receiving NICU Consultant for **joint decision making.**
- Qualifying infants should **reach target temperature as soon as safely possible**. However, where there are competing demands (eg. airway and circulatory management), it may be appropriate to maintain normothermia, and reassess for commencement of cooling when resources allow.
- Neonates undergoing TH should have **baseline bloods tests** taken: blood glucose level, blood gas, lactate, FBC and ideally coagulation studies, UEC and LFT.

5.2.2 Temperature management in referral centres

- The implementation of TH requires adequate resources (time, personal, equipment) to avoid overshooting and monitor for risks of TH.
- The decision to commence TH at a referring centre prior to PIPER's arrival depends on the clinical situation, anticipated retrieval time, and local capabilities/resources. The risks and benefits of each approach should be considered with attention to the 6H window in which TH should be commenced. Guidance is provided in Table below.

Therapeutic Hypothermia for Hypoxic Ischaemic Encephalopathy

Types	Strategy for Referring Team	Resources and Monitoring
Passive hypothermia at Referring Centre • Preferred strategy to expedite cooling for infants in Level 3-5 centres with sufficient resources.	**Removal of all heat sources** The **target core temperature** is 33°C to 34°C à Where infant falls below 33°C, radiant warmer should be increased by 25%, and temperature rechecked in 15 minutes	• 1:1 Nursing • Full cardiorespiratory, saturation and blood pressure monitoring • Access to rectal thermometer probe for continuous monitoring; or rectal/axillary temperature every 15 minutes • Baseline blood glucose level, blood gas, lactate and FBC. Coagulation screen, UEC and LFT are desirable
Deferred until PIPER arrival. • Preferred strategy in Level 1-2 centres	Maintain normothermia (preferably 36.5 – 37.0 degrees)	• Primary aim is to avoid temperature instability. ○ Especially avoid HYPERthermia • Regular temperature monitoring • Rectal/axillary temperature every 30 minutes

5.2.3 Temperature management with PIPER

Equipment

- Rectal thermistor (disposable/single use 'Vital Temp general purpose probe 9 FR')
- Cable to connect rectal thermistor to temperature module
- Lubricant
- Sleek tape
- Cold packs (6) at refrigerator temperature (NEVER from the freezer) transported in insulated carry bag
- Covers for cold packs (kept in insulated carry bag)

5.2.4 Procedure

Preparation

- Ensure baseline blood tests collected as detailed in Section 5.2.1
- Ensure airway is secure (intubation is not a prerequisite), breathing is adequate, and any circulatory compromise is addressed.
- Ensure adequate intravenous access, preferably with a dual lumen UVC and UAC.

5.2.5 Procedure for controlled passive hypothermia:

1. Nurse the baby **naked** on a radiant warmer with the warmer turned off or in the transport incubator turned off or to its lowest setting if the baby is not ventilated
   a) No sheepskin
   b) Do not dress, or use a hat or any form of wrap (plastic or cloth)
   c) Leave the nappy unfastened.
2. Insert rectal temperature probe ≥5cm into anus and secure at the 10cm mark to the inner thigh.
3. Continuously monitor rectal temperature on Zoll monitor and record 15 minutely.
4. Ensure continuous cardiorespiratory, saturation and blood pressure (if applicable) monitoring and record at least half hourly.
5. If ventilated or on respiratory support, use humidified and heated gas at usual temperature.
6. Once loaded in transport incubator, nurse with cot turned off and doors open (when possible).

7. If infant not ventilated, set temperature on transport incubator to lowest possible and leave portholes open (when possible).
8. Record time hypothermia treatment commenced and rectal temperature every 15 minutes.
9. All other documentation/care/treatment should be the same as in any asphyxiated baby with HIE.
10. If rectal temperature drops **below 33.5°C**, set radiant warmer on manual or turn on incubator (or increase incubator temperature if already on) and gradually adjust heater output to maintain rectal temperature between 33°C - 34°C
11. If hypothermia has been underway for **one hour** and the rectal temperature is still **>35.5°C**, discuss the use of refrigerated gel packs with the PIPER consultant
12. **Refrigerated gel packs:**
    a) Refrigerated at ~ 4°C (never frozen)
    b) Wrapped in cotton covers or equivalent; they should never be applied directly to the skin
    c) Placed:
        i. One under the shoulders/upper back/head
        ii. The second across the chest/body
        iii. Using more than 2 packs prevents radiant loss of heat into the environment and makes it more difficult to cool the baby.
    d) Record the time the gel packs were applied and continue to record rectal temperature 15 minutely.
    e) Algorithm to achieve the 33°C - 34°C target rectal temperature range

Temperature	Number of refrigerated gel packs to be applied	Areas to apply
≥ 35.5°C	2	Under shoulders, across chest
34.0 – 35.5°C	1	Across chest
< 34.0°C	0	Nil

    f) If rectal temperature drops below **33.5°C**, remove all gel packs and repeat temperature in 15 minutes. If the temperature continues to fall, set radiant warmer on manual or turn on transport incubator and gradually adjust heater output to maintain rectal temperature at 33.0°C – 34.0°C.
13. Aim is to achieve target rectal temperature range 33.0°C – 34.0°C within 1 hour, but more importantly continue to manage airway, breathing, circulation.
14. Advise/reassure parents about their baby's appearance and that the baby will feel cool to touch.
15. If infant appears uncomfortable, consider Morphine and/or Midazolam (if ventilated) or Paracetamol.
16. Irritability is common and often related to HIE.

*5.2.6 **Other considerations:***

- Ensure parents are well informed about the diagnosis and treatment plan for their baby.
- Advise parents about their baby's appearance and that their baby will feel cool to touch and may shiver. Explain management of discomfort/pain.
- Advise parents that the cooling period will be 72 hours and then the baby will be rewarmed over 8-12 hours.

5.3 SYSTEMIC MANAGEMENT OF HIE

Table: Multisystem Management of HIE

	Considerations

Airway	• **Consider intubation**, especially if:
	  ○ Cardiorespiratory instability
	  ○ Significant encephalopathy (including inability to protect airway)
	  ○ Seizures

Breathing	• **Use the standard PIPER saturation targets**
	  ○ Avoid HYPOxia or HYPERoxia
	  ○ Use minimum FiO2 possible to achieve saturation targets
	• **Target CO2 40-50 mmHg** in the ventilated patient to optimise cerebral perfusion pressure

Circulation	• **Target normotension and normovolaemia** to optimise cerebral perfusion pressure ○ Hypoxia-ischaemia may lead to depressed cardiac function and cardiovascular support medications may be required

Disability	• Temperature management as per **Therapeutic Hypothermia guideline**
	  ○ Avoid overshooting HYPOthermia OR HYPERrthermia
	• **Monitor for seizures**
	  ○ Treat seizures as per PIPER Neonatal Seizures guideline
	• Monitor **patient comfort**
	  ○ Prioritise non-pharmacological comfort measures
	  ○ In the ventilated patient, consider morphine +/- midazolam. Titrate to avoid excessive use.
	  ○ In the non-ventilated patient, consider paracetamol +/- low dose morphine (eg. IV Infusion at 5 microg/kg/hr)

Exposure	• **Temperature management** ○ **Therapeutic Hypothermia** if meeting criteria • **Commence empiric IV antibiotics** (caution Gentamicin in infant with acute kidney injury; consider Cefotaxime)

Fluid and Electrolytes	• Cease feeds
	• **Check blood glucose level, blood gas, lactate, and electrolytes** and correct as required
	  ○ **Fluid management** to maintain normoglycaemia and euvolaemia
	  ○ **Avoid hyPO and hyPER glycaemia**. Target BGL during transport 3-7mmol/L
	  ▪ Extra caution if fluid restriction and risk factors for hypoglycaemia
	  ▪ Commence IV 10% Dextrose at TFI 40-60ml/kg/day
	  ▪ Consider higher concentration dextrose +/- central lines if issues with hypoglycaemia
	  ○ Fluid balance monitoring

Haematology	• Vitamin K • Send FBC (and ideally coagulation studies) and corrected as required
Other	• **Consider differential/co-existing diagnoses** and investigate as appropriate

Access	• **Check vascular access**
	  ○ 1-2 PIVCs may be sufficient.
	  ○ Consider additional access if cardiovascular instability or refractory hypoglycaemia

References

N/A

Disclaimer

The Paediatric, Infant Perinatal Emergency Retrieval (PIPER) Neonatal and Paediatric guidelines were developed by PIPER clinicians for the sole use within the PIPER service at The Royal Children's Hospital Melbourne.

The authors of these guidelines have made considerable effort to ensure the information upon which they are based is accurate and up to date. Users of these guidelines are strongly recommended to confirm that the information contained within them especially drug doses is correct by way of independent resources. The authors accept no responsibility for any inaccuracies or information perceived as misleading.

Appendices

N/A

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