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SUMMARY	To guide clinicians in the management of newborns with moderate-severe Hypoxic-ischaemic encephalopathy
Key Words	Therapeutic Hypothermia (TH), Hypoxic-ischaemic encephalopathy (HIE)

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Hypoxic-Ischaemic Encephalopathy (HIE) in Infants ≥ 35 Weeks Gestation

RHW CLIN070

Contents

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RHW CLIN070

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Within this document we will use the term woman, this is not to exclude those who give birth and do not identify as female. It is crucial to use the preferred language and terminology as described and guided by each individual person when providing care.

1 BACKGROUND

The aim of this CBR is to recognise infants at risk of moderate-severe Hypoxic Ischaemic Encephalopathy (HIE) after birth and guide Therapeutic Hypothermia (TH) treatment options for the at-risk neonate. Severe hypoxia with impaired cerebral blood flow is thought to be the main mechanism causing brain injury after intrapartum hypoxia-ischaemia. Following resuscitation and reperfusion, there is a latent period of 1 to 6 hours where the impairment of cerebral oxidative metabolism can at least partially recover before irreversible failure of cellular and mitochondrial function occurs.[1] TH appears to have its effect by reducing this delayed secondary injury to the brain.

2 RESPONSIBILITIES

2.1 Staff (medical, midwifery, Nursing, Allied health)

2.1.1 Medical – diagnosis and management of infants suspected of HIE

2.1.2 Nursing – management of infants suspected of HIE, observation, application of rectal temperature probe, application of aEEG, application of Temperature Management System device when indicated

2.1.3 Midwifery – notification to neonatal medical staff of infants at risk of HIE

3 PROCEDURE

3.1 Equipment

- Arctic Sun Temperature Management System device
- Arctic Gel Pad Neonatal (1.8-4.5 kg) - Single use
- Rectal Temperature Probe
- aEEG (Olympic BRAINZ) with electrodes

3.2 Clinical Practice

3.2.1 At Delivery

- Determine/estimate gestational age (≥35 weeks) and birthweight (≥1800g) to ensure the eligibility for cooling.
- Identify any risk factors indicating peripartum hypoxia (e.g. placental abruption, cord prolapse, uterine rupture)
- Follow the neonatal resuscitation principles as per the Neonatal Intensive Care Unit (NICU)guidelines
    - Ensure airway, breathing and circulation are restored before commencing either passive or active cooling.
    - Maintain normothermia but avoid hyperthermia during resuscitation and stabilisation.
    - Avoid commencing cooling (e.g. turning off radiant warmer) while providing active resuscitation.
- Obtain cord arterial and venous gas to determine any abnormal acid base status suggestive of perinatal hypoxia. Follow the pathway given in Appendix 2 (Figure 1) as a guide
- Admit the following infants to NICU for close observation and monitoring:
    - All neonates in “Red pathway” in Appendix 2 (Figure 1)
    - Any neonate in ‘Yellow pathway’ but developing concerns suggesting evolving encephalopathy (Appendix 2, Figure 1)

3.2.2 Post Resuscitation/during transport to NICU

- May commence passive cooling by turning off the warmer if the infant is deemed to have achieved haemodynamic and respiratory stability with FiO2 requirement <0.80 and fit the criteria for TH.

3.2.3 In NICU

- Perform neurological assessment at admission using Modified SARNAT criteria (Appendix 2 - Figure 2).
- Connect aEEG/EEG monitor if infant is neurologically abnormal.
- Clinician trained in Modified SARNAT Examination (Neonatal Fellow/Consultant/NNP/Registrar) to perform hourly (at the minimum) neurological assessment for the first 6 hours of life using Modified SARNAT criteria (use Appendix 2 Figure 2).
- Monitor cerebral function and any electrical seizure activity on aEEG.
- Monitor for any worsening of Modified SARNAT criteria, for example, starting as mild encephalopathy but progressing towards moderate encephalopathy.
- Perform the following tests- preferably prior to the commencement of TH where possible:
    - Tests for end-organ dysfunction: FBC, UEC, CMP, LFT, coagulation studies, troponin T
    - Blood cultures
    - Head ultrasound (to rule out haemorrhage)

- Consider urine metabolic screen / chromosome array with DNA storage.

NOTE: Neurological monitoring is a continuum and infant may deteriorate in between formal hourly assessment and in these cases assessment will need to be more frequent than hourly

3.2.4 Eligibility Criteria for TH [3,4]

- The following 4 criteria need to be met:
  - Gestation ≥ 35 weeks gestation, and birth weight ≥1800g
  - <6 hours post birth
  - Perinatal depression defined by at least **ONE** of the following:
    - Apgar score ≤5 at 10 minutes
    - pH <7.00 OR base excess > -12 mmol/L (on cord blood or if cord blood not available, arterial/capillary blood gas within first hour)
    - Continued need for resuscitation: IPPV or cardiac massage at ≥ 10 minutes of life
    - Lactate > 8 mmol/L on cord blood or if cord blood not available, on first blood gas collected within the first hour of life.
  - Presence of moderate-severe encephalopathy with any **ONE** of the following:
    - 3 or more criteria in moderate or severe category of Modified SARNAT score
    - 2 criteria in moderate or severe category **PLUS** abnormal aEEG (e.g. lower margin < 5μV for >1 hour, electrical seizures)
    - 2 criteria in moderate category **PLUS** seizures (confirmed clinically or EEG/aEEG)
- NICU team may consider other criteria for commencement of cooling if benefits are perceived to outweigh any potential harm from cooling. These may include:
  - Newborns progressing to moderate HIE with prior criteria of neonatal depression as above

NOTE:
Initiation of TH should not be delayed awaiting aEEG data.
Newborns requiring sedation (e.g. opiates) or muscle relaxation require careful assessment, including careful neurological examination before initiating muscle relaxation. aEEG/EEG monitoring is particularly important in these circumstances.[1]

3.2.5 Prior to commencement of TH

- Ensure adequate resuscitation and support for the infant including airway, breathing, circulation and glucose. Exercise caution with fluid boluses
- Commence Intravenous fluid therapy at 40 mL/kg/day with either 10% (Glucose infusion rate (GIR) 2.7 mmol/kg/min) or 12.5% glucose (Glucose infusion rate 3.5 mmol/kg/min) to avoid hypoglycaemia and maintain blood glucose at ≥3.5 mmol/L
- Secure good venous (if peripheral x 2) and/or arterial access (consider umbilical lines) prior to commencing TH.
- Inform parents and provide them with the parent information sheet (Appendix 1)
- AVOID Hyperthermia (Temp > 37ºC > 37.5ºC)

NOTE:
Peripheral IV access may become difficult once cooling is commenced.

3.2.6 TH Procedure

- Please refer to RHW NCC Nursing Clinical Business Rule - Cooling Therapy - Arctic Sun set up
- Target rectal temperature during TH: 33.0^0C – 34.0^0C to achieve within 30 minutes of commencement.

3.2.7 Amplitude-Integrated Electroencephalogram (aEEG)

- Apply aEEG at the earliest suspicion of encephalopathy, preferably soon after arrival to NICU to monitor background activity and seizures.
- Moderate to severely abnormal background activity on aEEG is defined as any of the following:
  - Discontinuous normal voltage (DNV)
  - Burst suppression pattern.
  - Moderate or severely depressed voltage +/- seizure activity
- Infants who have a normal aEEG showing sleep wake cycling throughout the first 6 hours and are showing no ongoing signs of encephalopathy may not require TH.

NOTE:
aEEG may be suppressed after administration of phenobarbitone.
Abnormal aEEG in the first 6 hours of life may assist in decision making for TH but may not be a good predictor of long-term outcomes for neonates treated with hypothermia.
Return of normal aEEG background activity within 48 hours of age is a good outcome for neonates undergoing hypothermia.[7,8]

3.2.8 Early discontinuation of TH is appropriate after discussion with parents if:

- Unfavourable outcome is highly likely (e.g. severe uncorrectable hypotension, severe metabolic acidosis not responding to treatment, Grade 3-4 IVH, Intracerebral Haemorrhage)
- Persistent extreme severe encephalopathy such that further treatment is likely to be futile
- Life threatening uncontrolled bleeding due to coagulopathy
- Uncontrolled pulmonary hypertension.
- Persistent hypoxaemia in 100% oxygen
- Cardiac arrhythmia resistant to pharmacological treatment
- Established metabolic disorders or overwhelming septicaemia

3.2.9 Contraindications for TH

- Major congenital anomalies, including life threatening abnormalities of the cardiovascular or respiratory systems – Decision of TH can be made on a case by case basis in discussions with NICU team and families
- Uncontrolled bleeding

- Uncontrolled severe hypoxia due to persistent pulmonary hypertension (Oxygen requirement > 80% and not responding to treatment)
- Moribund condition with little hope of acceptable quality of life and imminent end of life care planned
- Severe head trauma (e.g. severe subgaleal haemorrhage) or intracranial bleeding, in whom clinicians are concerned about worsening coagulopathy or bleeding.[3]

3.2.10 Differential Diagnosis of HIE

- Sepsis, meningitis, hypoglycaemia, hyperbilirubinaemia.
- Inborn errors of metabolism
- Congenital abnormalities (central and peripheral nervous system disorders)
- Intracranial haemorrhage, perinatal stroke
- Neonatal abstinence syndrome

3.2.11 Ongoing Monitoring

- Continuous rectal temperature
- Continuous arterial blood pressure wherever possible or at least 2-4 hourly non-invasive blood pressure monitoring. Target mean BP: 38-45 mm Hg
- Continuous aEEG monitoring for the duration of cooling
- Blood gas (arterial preferred): Minimum 6-hourly for the first 24 hours, and then, as indicated.
  - Heel prick samples in babies undergoing TH may give inaccurate results due to poor perfusion. If gas results do not correlate with clinical signs/symptoms, please correlate with alternate sampling method (e.g. proper arterial or venous sampling)
- Avoid respiratory alkalosis with hypocarbia (<35 mmHg) if on respiratory support.
- Severe metabolic acidosis – Improves with time, however, may need correction over 6-12 hours in refractory cases.
  - Sodium acetate intra-arterial or intravenous infusion can be considered. Refer to sodium acetate ANMF formulary.
- Blood Glucose – Aim for 3.5—8.0 mmol/L.[9] Avoid hypoglycaemia and hyperglycaemia.
- Oxygen saturation – Aim for 91--98%.
- Renal function and electrolytes (UEC) – 6-12 hourly initially, and then as required, but at least daily until day 3-5 of life.
- Calcium and Magnesium every 6-12 hourly initially and then as required.
  - Aim to avoid hypocalcaemia (ionised Ca <1.1 mmol/L) and hypomagnesemia (Serum Mg <0.7 mmol/L).[10]
- Full Blood count – 12 hourly initially, and then as required, but at least daily until day 3-5 of life
- INR and APPT – on day 1 and at least daily until normal. Maintain INR<2.0.
  - Consider Fresh Frozen Plasma: if INR>1.5 with bleeding or INR>2.0 with or without bleeding.
- LFTs and Troponin T – Prior to commencement of cooling and on daily basis if required.
- Trophic feeding
  - Minimal enteral feeding (10 mL/kg/day, progressing to 20 mL/kg/day) during hypothermia is thought to be safe and feasible for newborns with HIE. Giving more than minimal feeds is not advised because gut perfusion may be reduced during cooling.[11]

- Sedatives
  - Signs of distress include tachycardia, facial grimacing and irritability
  - A heart rate consistently above 110 bpm in cooled infants suggests the infant may be distressed.
  - Sedation with intravenous morphine infusion at 10 microg/kg/hr may be warranted.[12] Refer to ANMF formulary for further information.
- Skin monitoring to minimise the risk of subcutaneous fat necrosis.
  - Watch for indurated erythematous nodules and plaques, particularly over the back, arms, buttocks, thighs and chest.

3.2.11 Electroencephalogram (EEG) and Magnetic Resonance Imaging (MRI)

- All cooled infants should have a formal EEG after birth
- All infants with moderate-severe HIE who are cooled and have an initial abnormal neurologic examination should have MRI with DWI±MRS between 4 to 7 days of life
- Early MRI may help with decision making regarding palliation/redirection of care

3.2.12 Adverse effects associated withTH

- Sinus bradycardia (HR 80-100/min) and cardiac arrhythmias
- Hypotension
- Thrombocytopenia - mild thrombocytopenia (50,000-150,000) does not require active management unless clinical evidence of bleeding.
- Increased oxygen requirements and/or PPHN
- Low pCO2 (check arterial or capillary pCO2 on ventilated infants regularly and ensure the low temperature is entered when putting a gas into the blood gas machine) – an infant's pCO2 can be up to 20% lower at 33.5ºC than at 37ºC.
- Hypoglycaemia
- Urinary retention
- Prolonged drug half-lives – e.g. morphine[12], antibiotics and phenobarbitone. Refer to ANMF formulary for further information on dose adjustment for specific drugs
- Increased bleeding tendency or coagulopathy
- Hypocalcaemia

3.2.13 Follow-Up

- All babies that are cooled are to be followed up at Growth and Development clinic at either RHW or their local clinic until at least 2 years of age.

3.3 Documentation

- eRIC

3.4 Education Notes

3.4.1 Background

- Moderate to severe HIE is a significant cause of early mortality and permanent major disability in term infants. It occurs in 1-3 per 1000 live births in resource rich countries.[1,13]

- A variety of conditions decrease placental perfusion or disrupt the delivery of oxygen and glucose in the umbilical cord (e.g. placental abruption, cord prolapse, uterine rupture, shoulder dystocia). However, only a small fraction of patients with HIE (15%-29%) have a documented sentinel event.[14]
- Hypoxia eventually leads to a decrease in fetal cardiac output, which reduces cerebral blood flow. If the decrease in cerebral blood flow is moderate, cerebral arteries shunt blood flow from the anterior circulation to the posterior circulation to maintain adequate perfusion of the brainstem, cerebellum, and basal ganglia. As a result, damage is restricted to the cerebral cortex and watershed areas of the cerebral hemispheres. In some cases, acute severe hypoxia and abrupt decrease in cerebral blood flow produces injury to the basal ganglia and thalami.[14]
- Decreased cerebral perfusion sets in motion a sequence of changes in brain, which can be divided into phases. However, these phases can be overlapping depending on the injury, medical intervention and recovery[14]:
  - Acute phase: First 30 minutes after injury. Decreased cerebral blood flow results in decreased delivery of oxygen and glucose to the brain, leading to anaerobic metabolism. As a result, production of adenosine triphosphate (ATP) decreases and that of lactic acid increases.
  - Latent phase (30minutes to 6 hours after injury): During this phase, partial recovery occurs, but there is continuation of inflammation, cell death and processes leading to cell death.
  - Secondary phase (6 hours – 15 hours): Ongoing cytotoxic edema, excitotoxicity, secondary energy failure due to mitochondrial shutdown, and ongoing cell death.
  - Tertiary phase (from ≈12 hours, particularly after 72 hours to months): Late cell death, remodelling of injured brain, and astrogliosis (proliferation of surrounding astrocytes as a defence mechanism to minimise or repair the damaged CNS).

3.4.2 Cooling (TH) in HIE

- In 2020, 358 (6.0%) of the Australian and New Zealand Neonatal Network (ANZNN) registrants born at more than 34 weeks gestation received therapeutic hypothermia.
- Cooling (TH) appears to have its effect by reducing the delayed secondary phase of injury to the brain. It has been shown to be effective in both animal and human studies and is the current standard of treatment for newborns 35-36 weeks gestation or greater with moderate-severe neonatal encephalopathy related to intrapartum hypoxic events.[15- 18]
- The 2013 Cochrane review demonstrated reduced mortality with better neurodevelopmental outcomes among term and near-term neonates. Cooling decreased the combined outcome of mortality or major neurodevelopmental disability at 18 months of age (46% vs 61%, typical risk ratio (RR), 0.75; 95% CI, 0.68–0.83).[19] The number needed to treat (NNT) with cooling to benefit 1 newborn is 7 (95% CI, 5–10). Cooling also decreased disability in infants who survived (26% vs 39%, typical RR, 0.77; 95% CI, 0.63–0.94; NNT of 8 (95% CI, 5–14).[19]
- Rutherford and colleagues, from the TOBY cooling trial (TOtal Body hYpothermia), found that infants treated with therapeutic hypothermia showed less basal ganglia/thalamus lesions and fewer abnormalities in the posterior limb of internal capsule. Infants who were cooled were more likely to have normal scans.[20]

- It is important to state that although cooling has been effective at improving outcomes and has no increased the rate of infants surviving with disability, infants with moderate to severe HIE remain at a 30-70% risk of death or disability despite being cooled.
- Hourly neurological assessment from one to six hours of life is recommended because of the evolving nature of HIE in the first hours after birth.[3,4] Over time some newborns may deteriorate and others improve and so therapeutic hypothermia must be considered for all newborns who meet criteria at any time in the first six hours after birth, even if their condition subsequently improves.[3,4]
- Recent retrospective studies suggest that infants with mild HIE may have sequelae. However, at this point, there is insufficient data to make a recommendation on TH for mild HIE.[21,22]
- Adverse effects: Meta-analysis by Zhang et al found that TH increases the risk of thrombocytopenia and cardiac arrhythmia during intervention.[62]

3.4.3 Late TH started after 6hrs of age in perinatal HIE

- Current evidence suggests that cooling initiated later than 6 hours after birth may result in a small reduction in death or disability however there remains uncertainty as to its effectiveness.[5,6] Given the relative safety of cooling and the lack of alternatives cooling can be considered in these infants on an individual basis after discussion with the consultant.

3.4.4 TH following sudden unexpected postnatal collapse (SUPC)

- Sudden unexpected postnatal collapse (SUPC), is a rare, but well described entity with potentially catastrophic consequences including death or severe disability.[63] SUPC is generally defined as 'a term or near-term infant who is well at birth, assigned to routine postnatal care and who collapses unexpectedly within the first 7 days of life, requiring resuscitation with intermittent positive pressure ventilation and who either dies, requires ongoing intensive care or develops an encephalopathy'. The majority of cases of SUPC occur within the first 24 hours of life: 36% within the first 2 hours of birth, 29% between 2 and 24 hours after birth, while 24% occur between 24 and 72 hours after birth and 9% between day 4–7 of life.[63] In Australia, the incidence of SUPC is reported as 5.6 per 100,000 livebirths.[64]It has been observed that SUPC most commonly occurs from asphyxial position of the infant in the context of skin to skin care, either with the infant breast feeding or in the prone position.[63]
- No clinical trial has assessed the role of TH in the context of encephalopathy resulting from SUPC, and such a trial would be difficult to undertake in view of the rare nature of SUPC and the subsequent small numbers of eligible infants.[63] There is uncertainty about whether to offer TH after SUPC, as such infants were excluded from the original cooling trials. However, there are emerging case reports of infants undergoing TH in this context.[61,65] Whilst these data report 'success', the outcomes reported are variable and long-term data is lacking. Moreover, the potential limitations and even harm that may arise should be acknowledged.[63] There is however, a theoretical plausibility for benefit from TH in such context and so it should be carefully considered on an individual case basis. Importantly, TH should only be instigated after exclusion of conditions which may be adversely affected by TH (e.g. sepsis, inborn errors of metabolism) and after discussion of the potential benefits and risks with parents.

3.4.5 TH in Late Preterm infants

- Cooling in late preterm infants born at 34-35 weeks gestational age appears feasible. The paucity of studies and the possible increased risks of mortality and side effects mean it is currently not recommended in this group of infants.[38]

3.4.6 TH in mild HIE

- Recent retrospective studies suggest that infants with mild HIE may have a different perinatal insult. At this point, there is insufficient data to make this recommendation, but cooling may be considered on individual basis after discussion with consultant and families.[21,22,39-41]

3.4.7 aEEG/EEG in HIE

- Seizures occur in 45-55% of infants with HIE receiving cooling. aEEG is useful in monitoring (1) cerebral background activity, (2) seizures and (3) sleep-wake cycle. aEEG assists in the prediction of neurodevelopmental outcomes for term infants with HIE.[23-28] Seizures may be subclinical in up to 50% of cases. Cooling does not seem to significantly affect aEEG background activity. We use a 2-channel aEEG set up that is filtered and time compressed.
- aEEG after Phenobarbitone: Phenobarbitone induces significant suppression on aEEG in infants with HIE undergoing TH. Development of severe aEEG background patterns after phenobarbitone may unmask a population at greater risk of abnormal outcome.[8]
- Abnormal aEEG patterns in the early hours of life treated with hypothermia do not accurately predict outcome, however infants with a good outcome had normal background patterns return by 48 h of age.[7]
- **Background activity:** Classification of aEEG background activity is by looking at the lower and upper margin amplitudes of the activity band.[29]

Background Pattern	Lower Margin of aEEG trace*	Upper Margin of aEEG trace*	Comments
NORMAL			
Continuous Normal Voltage (CNV)	> 5 µV	> 10–25 µV	Sleep Wake Cycling (SWC) is present (this usually indicates a healthy brain)
ABNORMAL			
Discontinuous	< 5 µV	>10 µV	Minimum amplitude may be variable in both
Burst suppression	<5 µV	-	Bursts with amplitudes >25 µV
Low voltage	<5 µV	<5 µV	Some variability
Flat	<5 µV	<5 µV	Isoelectric

*These values refer to the cross-cerebral aEEG activity band for term neonates

- In a recent meta-analysis of 21 studies using EEGs, burst-suppression, low voltage, and flat trace most accurately predicted long-term neuro-developmental outcome.(25), but time to recovery to normal background activity is an important prognosticator. Even infants with

a severely abnormal background pattern (e.g. burst suppression) in the first 6 hours of life had a good likelihood of survival without significant disability if the pattern normalised within the first 24 hours of life.[18] A persistently abnormal aEEG at 48hr or more is associated with a high risk of adverse neurodevelopmental outcomes.[25-28]

- While a normal aEEG at 6hrs has a good negative predictive value it does not exclude an adverse outcome. Time of onset of sleep-wake cycles (SWC) may also be predictive of later outcomes. SWC is a good sign of a healthy brain. Even in infants with absent SWC initially onset of SWC within the first 36 hours of life was associated with normal outcomes, whereas those who never had normal SWC were more likely to have significant disability at 18 to 22 months.[35]
- **Seizures:** Seizures are manifested on EEG as a sudden, repetitive, pattern with a clear beginning, middle and end. By definition, neonatal seizures have a minimum duration of 10 seconds. On aEEG, seizures may appear as an abrupt rise in minimum and maximum amplitude in the background activity band (upper half of the screen), often followed by a postictal phase of decreased amplitude. The raw EEG tracing on the bottom half can often be helpful in evaluating segments suspicious for seizures. Seizures can be classified as single, repetitive or status epilepticus (defined as ongoing seizure activity >30 min).[29]
- **Sleep-Wake Cycle**: Sleep-wake cycling refers to cyclic fluctuation in the amplitude and degree of discontinuity as the neonate enters various stages of sleep or wakefulness. On aEEG, this is reflected by the presence of smooth sinusoidal variation, mostly in the minimal amplitude. Periods of wider bandwidth represent discontinuous activity during quiet sleep, whereas periods with a narrow bandwidth represent more continuous activity when awake or in active sleep. Sleep-wake cycles can be classified as absent, immature or developed.[29]

3.4.8 Metabolic acidosis in HIE

- Raised serum lactate levels in neonates with HIE are thought to be from (1) anaerobic cerebral metabolism and other ischaemic organs such as bowels during hypoxia and (2) delayed lactate clearance from liver and kidneys due to end organ dysfunction. Sustained lactic acidosis may suggest ongoing abnormal cerebral metabolism and delayed recovery of circulation and liver.[31] However metabolic acidosis and base deficit may also get worse initially after resuscitation. This is due to the “flush-out” of organic acids from cells and interstitial fluid into vascular space with improved perfusion and circulation with resuscitation.[30] It is important to take other clinical and laboratory parameters into consideration in interpreting whether persistent lactic acidosis is a result of “flush out” effect, or delayed recovery of circulation.
- Two studies evaluated the relation of lactic acidosis with severity of HIE and adverse neurodevelopmental outcomes. However these 2 studies were published pre TH era.[30,31]
- There was no confirmed association between disappearance of lactic acidosis and low cardiac output. A low rate of disappearance of lactate may rather be an indicator of organ injury due to asphyxia.[67] But a low rate of disappearance of lactate have been reported to be associated with poor neurodevelopmental outcomes.[32,66]
- A 2022 report by Puthuraya et al included infants with HIE treated with TH. The aim of the study was to correlate time for correction (ToC) from metabolic acidosis in HIE with short- and long-term outcomes. ToC of HCO3, BD and lactate were significantly longer in severe HIE, compared to mild HIE. Seizures were significantly higher in infants who corrected their HCO3, BD and lactate ≤24 hours. But, mean composite scores for cognition motor (MCS)

at 18-26 months were lower in infants who corrected their pH, BD and lactate at >24 hours.[32] Similarly a report by Chiang et al, showed persistent lactic acidosis beyond 72 hours of TH was associated with poorer neurodevelopmental outcomes.[66] Further studies are needed to explore ToC of acidemia as a prognostic marker.

3.4.9 Magnesium therapy in HIE

- A systematic review[51] of RCTs that compared magnesium to controls in newborns with HIE included 5 studies.[52-56] All used magnesium sulfate given within 24 hours of birth. The dose varied: 250mg/kg every 24 hours for 3 doses in 2 studies, 250mg/kg followed by two doses of 125mg/kg every 24 hours for 2 doses in another 2 studies and a single dose of 250mg/kg in 1 study. Magnesium was administered over 30 min in one study, over 1 hour in 3 studies. There was no difference in the death or moderate-to-severe neurodevelopmental disability at 18 months between the magnesium and the control groups (RR 0.81, 95% CI 0.36 to 1.84). There was significant reduction in the unfavourable short-term composite outcome (survival with abnormalities in any of the following: neurodevelopmental exam, neuroimaging or neurophysiologic studies), (RR 0.48, 95% CI 0.30 to 0.77) but no difference in mortality (RR 1.39, 95% CI 0.85 to 2.27), seizures (RR 0.84, 95% CI 0.59 to 1.19) or hypotension (RR 1.28, 95% CI 0.69 to 2.38) between the magnesium and the control groups. Review concluded there is insufficient evidence to determine if magnesium therapy given shortly after birth to newborns with HIE reduces death or moderate-to-severe disability. The improvement in short-term outcomes without significant increase in adverse effects supports the need for further adequately powered trials to determine if there are long-term benefits of magnesium and to confirm its safety. The publication of a few additional small trials is unlikely to change this conclusion.[57-60]
- The findings of the above studies suggest that regular monitoring and maintenance of normal serum magnesium concentrations is an important clinical measure in the management of neonates with HIE.

3.4.10 MRI in HIE

3.4.10.1 MRI technique:

- MRI is the most sensitive and specific imaging for evaluating neonatal HIE.[33,34]
- Currently 3 MRI modalities are performed with suspected HIE: (1) Conventional T1 and T2-weighed MRI, (2) Diffusion Weighted Image (DWI), and (3) Magnetic Resonance Spectroscopy (MRS).
- Conventional MRI is less sensitive than DWI and MRS in diagnosing early acute brain injury but can help to exclude other causes of encephalopathy such as congenital malformation, neoplasm, cerebral infarction and haemorrhage. On conventional MRI, HI injury to grey matter (cortex and deep grey matter) demonstrates characteristic T1-hyperintensity. White matter injury results in T1-hypointensity and T2-hyperintensity due to ischemia-induced oedema or cystic encephalomalacia.
- DWI: Early DWI is excellent for the detection of white matter injury. DWI can demonstrate cytotoxic oedema in acute phase before the conventional T1- or T2-weighted images with increased signal. The limitation of DWI is that it may give false negative result if performed within first 24 h of HI injury. DWI changes can be typically seen for only 10–12 days after tissue death and “pseudonormalisation” occurs thereafter. However, DWI cannot detect the severity of HI brain injury or predict adverse clinical outcome.

- MRS performed within first 24 h after birth is very sensitive to the severity of HI brain injury and can predict adverse outcome. Elevated lactate/creatine ratio on day 1 of life is a predictor of adverse neurological outcome, whereas absence of lactate predicts a normal outcome. Decreased N-acetylaspartate (NAA), increased choline and glutamine-glutamate peaks are also seen in neonatal HIE. MRS is not recommended in preterm neonates as they usually show higher lactate and lower NAA peaks.[33] In our facility MRI scoring and MRS are not routinely done as part of feed and wrap MRI. MRS is difficult to perform and interpret with motion artefacts in a feed and wrap modality.

3.4.10.2 Type of injury and MRI:

- Often, MRI demonstrates multiple injury patterns, making hard for clinicians to accurately assess the time, duration and extent of hypoxic insult prior to birth.
- In acute and profound asphyxia – injury in basal ganglia and thalamus are evident on MRI.
- In prolonged and partial asphyxia, MRI demonstrates white matter injury particularly in watershed area.[35,36]
- Basal ganglia/thalamic injury places neonates at increased risk of cerebral palsy and motor problems. Basal ganglia/thalamic (BG/T) predominant injury on MRI developed spastic quadriplegia in 56% of infants, whereas 11% of infants with the watershed predominant pattern had severe cerebral palsy (CP).[37]
- Abnormal signal intensity in the posterior limb of the internal capsule (PLIC) on T1/T2 imaging has been found to be an accurate predictor of motor outcome after birth asphyxia. Rutherford and colleagues[38] reported that all who had abnormal signal intensity in the PLIC on T1/T2-weighted images had neurodevelopmental impairment (defined as any Griffith score < 85 or any neurologic abnormality on examination) at 12 months of age.[37] Cognitive deficits on the other hand were more apparent in infants with the watershed-predominant pattern and these cognitive deficits often occurred in the absence of motor problems.[35]

3.4.10.3 Duration of injury and MRI

- MRI changes in isolation may not be reflective of severity/duration and type of injury and clinicians should always correlate with corroborative obstetric/intrapartum history and clinical presentation of the neonates.
- Severe and prolonged injury is usually demonstrated as widespread diffuse neuronal injury involving cortical and deep nuclei (basal ganglia and thalami) as well as white matter on MRI.
- Partial and prolonged injury may show predominantly white matter injury in watershed areas.

3.4.10.4 Challenges in recognising Encephalopathy

- **Neonates presenting late:** Not all neonates with hypoxic brain injury are symptomatic soon after birth. Some neonates who may be depressed at birth seem to make a clinical recovery in the first few hours, may go unrecognised initially, but then become symptomatic, manifesting seizure activity after the 6-hr window period for TH.[3,4,42] In these cases, the insult likely occurred in a subacute fashion, allowing the foetus to "self-resuscitate" in utero. Labour is often uncomplicated and the infant does not require serious intervention at delivery. As a result, severe acidaemia is not apparent, but encephalopathy may be present.

- **Neonates presenting as an unexpected encephalopathy at birth with no obvious intrapartum event:** Neonates often present with unexpected severe depression at birth without the need for active cardiopulmonary resuscitation and no documented acute intrapartum event, such as placental abruption, uterine rupture, or umbilical cord event. In such cases, a detailed maternal history may reveal subacute injury (e.g. decreased fetal movements at least 6-several hours before delivery). These infants were often less acidotic at birth on cord gases with no significant difference in initial postnatal pH or base deficit, but were more severely encephalopathic with severe aEEG suppression, and may result in serious adverse outcome.[43] Kasdorf, et al reported the outcomes of such infants treated with TH. They found that TH is unlikely to be of any benefit in neonates with early severe encephalopathy in the absence of a known acute perinatal event. However this was a small retrospective chart review comprising only 7 neonates with unexpected encephalopathy, and 26 neonates with documented acute injury.[43]

3.4.11 Challenges with drug therapy during TH

- TH affects pharmacokinetics of drugs. Recent review identified a significant decrease in clearance in neonates during therapeutic hypothermia, most pronounced for renal elimination: Phenobarbitone no difference, midazolam metabolite −21%, lidocaine −24%; morphine −21% to −47%, gentamicin −25% to −35%, amikacin −40%) during hypothermia. We suggest regular therapeutic drug monitoring (TDM) for phenobarbital, gentamicin and amikacin, for which TDM is readily available in our campus. For other drugs that may be impacted by TH, clinical monitoring for efficacy and safety is recommended.[68]
  - refer to ANMF governance guideline for further drug information

3.4.12 End-organ dysfunction

- **Troponin-T** is a component of the tropomyosin complex, which regulates cardiac muscle contractility. Troponin-T is the best marker of myocardial damage.[44] Compared to creatine kinase MB (CK-MB), Troponin-T increases earlier in myocardial damage and remains high for longer in the blood. Troponin-T is known to be more specific to the heart muscle than CK-MB. Healthy-term newborns have a higher upper reference limit for troponin T compared to adults. Using the 99th percentile, the upper reference limit in healthy term newborns was 0.097 µg/L. Compared to the adult values, the newborn upper limit was tripled for troponin-T. This circumstance must be taken into account when interpreting slightly “elevated” troponin values in newborns.[45] Troponin levels are reported higher in neonates with Sarnat stage 2 (median: 125 ng/L) and 3 (250 ng/L). Higher troponin levels were associated with higher mortality: 2.8% if troponin T ≤99 mg/dl; 5.4% if troponin -T 99-180 mg/dL; and 16% if Troponin -T ≥181 mg/dL. In this study, they further identified that a cut-off value of 164 ng/L for Troponin-T was determined to predict mortality with 77% sensitivity and 67% specificity.

3.4.13 Parent information, communication & care of family

- Moderate-Severe HIE can be a potentially devastating and life-changing event for families and care providers. Parents of newborns with HIE experience trauma both from the birth and from their concern about their baby and the need for therapeutic hypothermia treatment.

- Face-to-face meetings with clinicians with clear, compassionate and transparent communication about their newborn's condition and need for therapeutic hypothermia, together with encouraging parental involvement can help to reduce this trauma.[46]
- Advise/reassure re: infant's skin appearance and that they will be cool to touch and may shiver
- Provide parent information sheet on Therapeutic Hypothermia ('cooling') to Protect Newborns with HIE (appendix 1 or via www.aci.health.nsw.gov.au[2] + Hope for HIE website)
- Separation or isolation from their newborn may be a trigger for some parents, including Aboriginal families and refugees. Identify parents and families that may require additional support and provide referral early in the admission.

3.4.14 Parents Feedback to Clinicians

- Parents generally want clinicians to use simple, lay language.[47-49]
- Parents remember feeling bombarded with technical information that confused the "big picture" about why their infant was being cooled and what the cooling was expected to do. Parents felt that clinicians prioritised practical or technical details with less discussion of their overall relevance.[47-49]
- Information overload can make it challenging for parents to process information and think about what questions they want to ask.
- At the start of TH, most parents are preoccupied with the possibility of their infant's death & only after the infant began to stabilise could they process information about long-term outcomes.[47-49]
- Parents value simple invitations from clinicians to share emotions such as "How are you doing?"
- Parents appreciate when clinicians prompt question-asking & provide more time to understand what they were being told - In addition they appreciate written information they could refer to as they begin to process information – usually not immediately (Hope for HIE website – has an Australian branch)
- Don't delay talking about prognosis - Parents appreciate transparent and honest discussion of prognostic uncertainty - while prognostic uncertainty can be a source of distress for families, it can also allow for the provision of hope - the future is inherently unpredictable especially in neonates.
- MRI Day: The importance of showing parents the pictures or making representative drawings of the injury but also highlighting the not-injured brain was mentioned by parents.[50]
- Prognosis in HIE infants is extremely unpredictable as many factors such as the plasticity of the brain in development and the impact of the family environment can modulate long-term outcomes and their impact on quality of life - THUS avoid certainty in prognostication.

3.5 Abbreviations

TH	Therapeutic Hypothermia	HIE	Hypoxic- Ischaemic Encephalopathy
NCC	Newborn Care Centre	LFTs	Liver Function Tests
APTT	Activated Partial Thromboplastin Time	aEEG	Amplitude- Integrated Electroencephalogram
MRI	Magnetic Resonance Imaging	NICU	Neonatal Intensive Care Unit

DWI	Diffusion Weighted Imaging	MRS	Magnetic Resonance Spectroscopy
INR	International Normalised Ratio	PPHN	Persistent Pulmonary Hypertension of the Newborn
pC02	Partial Pressure of Carbon Dioxide		

3.6 CBR Implementation Plan

The revised CBR will be distributed to all medical, nursing and midwifery staff via @health email. The CBR will be discussed at ward meetings, education and patient quality and safety meetings. Education will occur through in-services, open forum and local ward implementation strategies to address changes to practice. The staff are asked to respond to an email or sign an audit sheet in their clinical area to acknowledge they have read and understood the revised CBR. The CBR will be uploaded to the CBR tab on the intranet and staff are informed how to access.

3.7 Related Policies/procedures

- RHW NCC Nursing - Clinical Business Rule – Cooling therapy – Arctic Sun Set Up
- RHW NCC Nursing CBR - Olympic BRAINZ Monitor (aEEG)
- NSW Health ACI Clinical Practice Guideline - Hypoxic ischaemic encephalopathy in newborns – recognition, monitoring and early management.

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4 ABORIGINAL HEALTH IMPACT STATEMENT DOCUMENTATION

- Considerations for culturally safe and appropriate care provision have been made in the development of this Business Rule and will be accounted for in its implementation.
- When clinical risks are identified for an Aboriginal and/or Torres Strait Islander woman or family, they may require additional supports. This may include Aboriginal health professionals such as Aboriginal liaison officers, health workers or other culturally specific services

5 CULTURAL SUPPORT

- For a Culturally and Linguistically Diverse CALD woman, notify the nominated cross-cultural health worker during Monday to Friday business hours
- If the woman is from a non-English speaking background, call the interpreter service: NSW Ministry of Health Policy Directive PD2017_044-Interpreters Standard Procedures for Working with Health Care Interpreters.

6 NATIONAL STANDARDS

- Standard 1 Clinical Governance
- Standard 2 Partnering with Consumers
- Standard 4 Medication Safety
- Standard 5 Comprehensive Care
- Standard 6 Communicating for Safety
- Standard 8 Recognising and Responding to Acute Deterioration

7 REVISION AND APPROVAL HISTORY

Date	Revision No.	Author and Approval
18/8/2011	1	J Smyth (Neonatologist) Approved by Newborn Care Management Committee and RHW Quality & Patient safety
28/8/2018	2	J Smyth (Neonatologist) Approved by NCC LOPs Committee
16/02/2024 1.7.24	3	J Smyth (Neonatologist), S Bolisetty (Neonatologist), R Jackson, (Neonatal Nurse Educator) Endorsed by NCC CBRs Committee Endorsed BRGC

Appendix 1: Parent Information

aci.health.nsw.gov.au

Therapeutic hypothermia (cooling) to protect babies with hypoxic ischaemic encephalopathy (HIE)

Parent information sheet

MAY 2023

The information provided here will answer some of the questions you may have about therapeutic hypothermia (cooling) and how it is used to care for babies with hypoxic ischaemic encephalopathy (HIE).

What is hypoxic ischaemic encephalopathy (HIE)?

Hypoxic means not enough oxygen; ischaemic means not enough blood flow; and encephalopathy means brain injury. This means your baby may be at risk of a brain injury caused by a lack of oxygen or blood flow.

What causes HIE?

HIE can occur because of a lack of oxygen supply to the brain around the time of birth. The brain can be injured if there is a lack of oxygen. The brain injury may be mild, moderate or severe. A lack of oxygen or blood flow can also cause problems with the lungs, liver, heart and kidneys.

What is therapeutic hypothermia or cooling?

Babies with moderate or severe HIE may benefit from therapeutic hypothermia or cooling. Cooling is a treatment that lowers your baby's body temperature from 37 degrees to 33.5 degrees to prevent further brain injury and help with recovery. Cooling may be started just after your baby's birth and continue for three days before a gradual rewarming process occurs.

Where will my baby be cooled?

Babies who need cooling should be cared for in a neonatal intensive care unit (NICU). If your hospital does not have a NICU, a specialised transport team known as the Newborn and Paediatric Emergency Transport Service (NETS) will transfer your baby to a NICU for cooling and intensive care support.

What happens to my baby during cooling?

Your baby will be cooled using carefully placed cold gel packs or a special cooling blanket. Your baby's heart rate, breathing, blood pressure and temperature will be monitored closely. A special monitor may also be placed on your baby's head to record the activity of your baby's brain. When it is time for the cooling to stop, your baby will be slowly and gently warmed back up to their normal temperature over several hours.

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Your baby will feel cold to touch and have a lower heart rate. Cooling is not painful, but your baby will be closely watched for discomfort, as babies who are cooled may sometimes shiver or be upset. If this happens, your baby may be given medications to keep them comfortable and you will be shown ways to settle your baby and help with these symptoms. You may be asked to not cuddle your baby during this time as it may warm the baby up too quickly. You can help your baby by talking to them and by holding their hand or foot to let them know you are there.

Your baby will not be able to feed as cooling can affect their stomach and bowel. If you are breastfeeding, the nurses or midwife can help you express your breast milk. This will be stored in the fridge or freezer until your baby is ready to be fed.

There may be mild side effects from cooling. Your baby will be watched closely for side effects. Rarely, cooling may need to be stopped before the whole three days is completed.

Your baby's care

The first few days of your baby's hospital stay may be worrying for you and your family. If your baby has been transferred from the birth hospital, you should also transfer there as soon as it is safe to do so.

The type of treatment your baby might need varies, but might include help with breathing and blood tests.

Outcomes after HIE

Your baby will be closely watched for lasting effects from brain injury. Some babies will make a full recovery, but others may have problems when they are older. It is important that you go to the follow-up appointments to watch for problems with learning, speaking, walking and movement.

Sadly, some babies will have a very severe injury and they may not survive in intensive care or may die after going home.

Comfort, support and information

Ask the care team as many questions as you need to ask. The team caring for your baby will include doctors, nurses and midwives. It can be difficult for you and your family if you have been separated from your baby. Your healthcare team, including social workers and Aboriginal liaison officers, will help your family with organising transport, accommodation and financial help.

You may also wish to speak to a social worker or to arrange a meeting with your midwife and obstetrician to discuss the birth of your baby.

During this difficult time, it is important that you take care of yourself. The following resources can be helpful.

Australian Breastfeeding Association

This organisation provides counselling and breastfeeding information to any person seeking help. **1800 686 2 686**

Bliss

Parent information is provided in Bliss Charity Hypoxic-ischaemic encephalopathy (HIE) – information for parents. Please note the contact information provided in this publication is for the United Kingdom.

Hope for HIE

An international organisation that has an Australian branch. www.hopeforhie.org

Life's Little Treasures Foundation

A charity dedicated to providing support, friendship and information specifically tailored for families of premature or sick babies. Life's little treasures Foundation **1300 697 736**

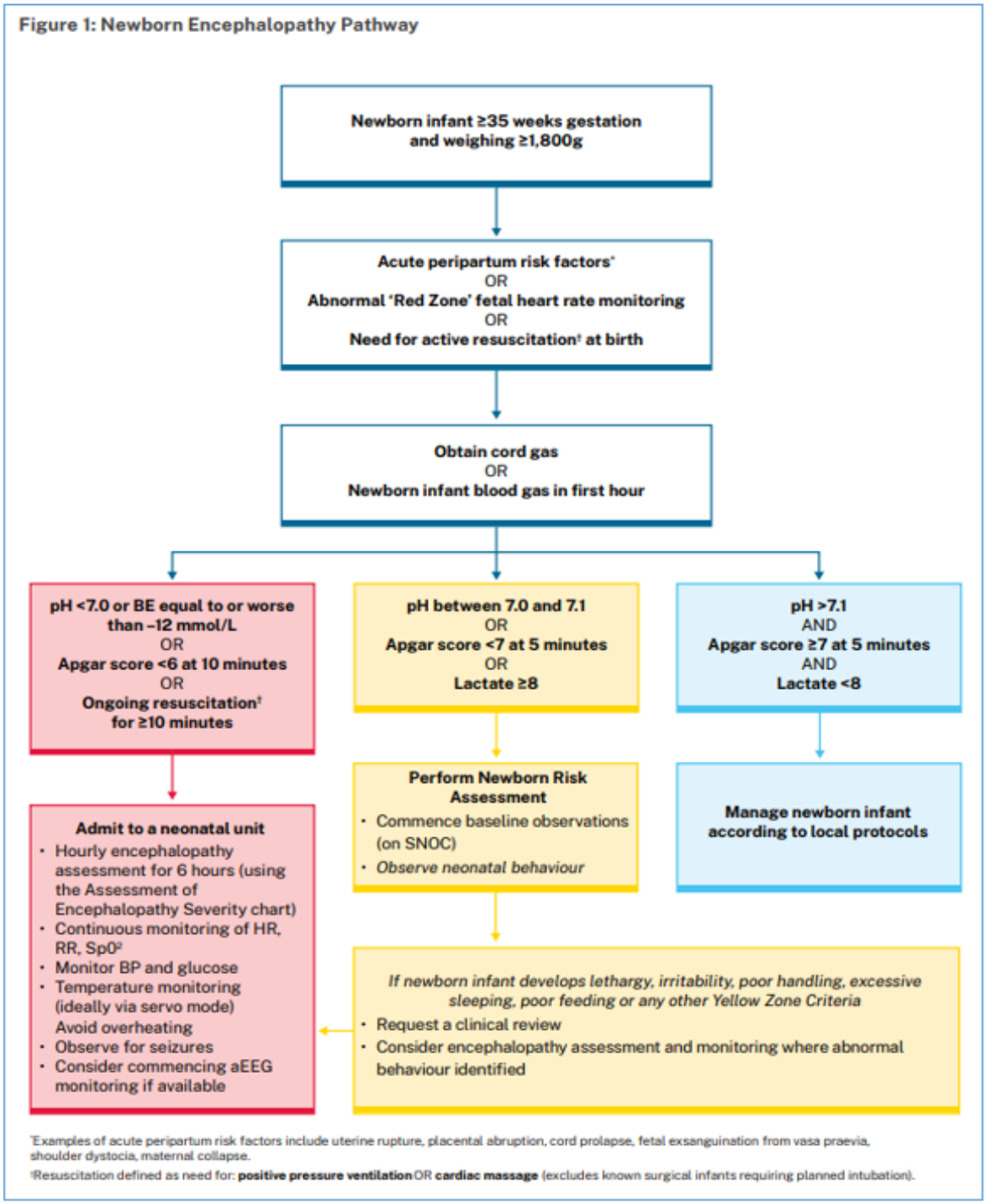
Miracle Babies Foundation

The foundation supports premature and sick newborns and their families. It offers an online information hub, hospital visits and support groups in the community after discharge. Miracle Babies Foundation
24-hour family support helpline **1300 622 243**

Pregnancy, Birth and Baby Helpline

This offers free, confidential, professional information and counselling for women, their partners and families relating to issues of conception, pregnancy, birthing and postnatal care.
pregnancybirthbaby.org.au **1800 882436**

Appendix 2: Figure 1.



Hypoxic ischaemic encephalopathy in newborns – recognition, monitoring and early management. - Clinical Practice Guideline NSW Health ACI May 2023. https://aci.health.nsw.gov.au/networks/maternity-and-neonatal/resources/hypoxic-ischaemic-encephalopathy

Appendix 2: Figure 2.

Figure 2: Assessment of Encephalopathy Severity Tool

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: **Normal:** pupils equal/reactive, normal HR, normal RR **Mild:** Pupils equal/reactive, increased HR, normal RR **Moderate:** Pupils constricted or bradycardia or periodic/irregular breathing **Severe:** 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)										

Request Senior Medical Review, discuss with Tertiary Centre Neonatologist/NETS consultant and consider Therapeutic Hypothermia if the newborn has 2 or more features of moderate or severe encephalopathy OR has seizures at any time from 1 to 6 hours post birth

References: Sarnat HB and Sarnat MS Neonatal Encephalopathy following Fetal Distress. Arch Neurol 1976:33,696-705 Queensland HIE Guideline 2019, NZ Consensus Statement for Treatment of Encephalopathy

*Thumb flexed under fingers or decorticate - arms flexed/legs extended

†arms and legs extended or sustained tonic postures

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