Queensland Clinical Guidelines

Translating evidence into best clinical practice

Maternity and Neonatal **Clinical Guideline**

Hypoxic ischaemic encephalopathy (HIE)

Queensland Government

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Cultural acknowledgement

The Department of Health acknowledges the Traditional Custodians of the lands, waters and seas across the State of Queensland on which we work and live. We also acknowledge First Nations peoples in Queensland are both Aboriginal Peoples and Torres Strait Islander Peoples and pay respect to the Aboriginal and Torres Strait Islander Elders past, present and emerging.

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Flow Chart: HIE clinical features, investigations and management

Hypoxic insult
- Low cardiac output
- Decreased tissue perfusion
- Ischaemia

Multi-organ dysfunction

Clinical features	Investigations
Neurological • Abnormal neurological exam • Seizures	• Continuous aEEG/EEG • Monitor for seizures • MRI
Respiratory • Hypoxaemia • Respiratory acidosis	• Cord blood gas • Arterial blood gas • CXR
Cardiovascular • Hypotension • Shock • Arrythmias • Heart failure • Ischaemia	• Blood gas • Echocardiography
Metabolic • Hypo/hyperglycaemia • Hypocalcaemia • Hypomagnesaemia • Lactic acidosis • Hyponatraemia	• Blood glucose • Calcium • Lactate • Electrolytes
Renal failure • Acute tubular or cortical necrosis • Oliguria • Polyuria • Haematuria	• Urea • Creatinine
Haematology • Elevated nucleated RBC • Thrombocytopenia • Bleeding–DIC • Thrombosis	• FBC including platelets • LFTs • Coagulation profile • Blood culture
Gastrointestinal • Feeding intolerance • Bleeding • Gut ischaemia–NEC	

Differential diagnosis investigations, consider:
- Lumbar puncture (if coagulation profile normal)
- Bloods for chromosome analysis, ammonia, amino acids
- Urine for amino and organic acids, ketones, reducing substances
- Early NBST [repeat at usual collection date]
- Cranial US

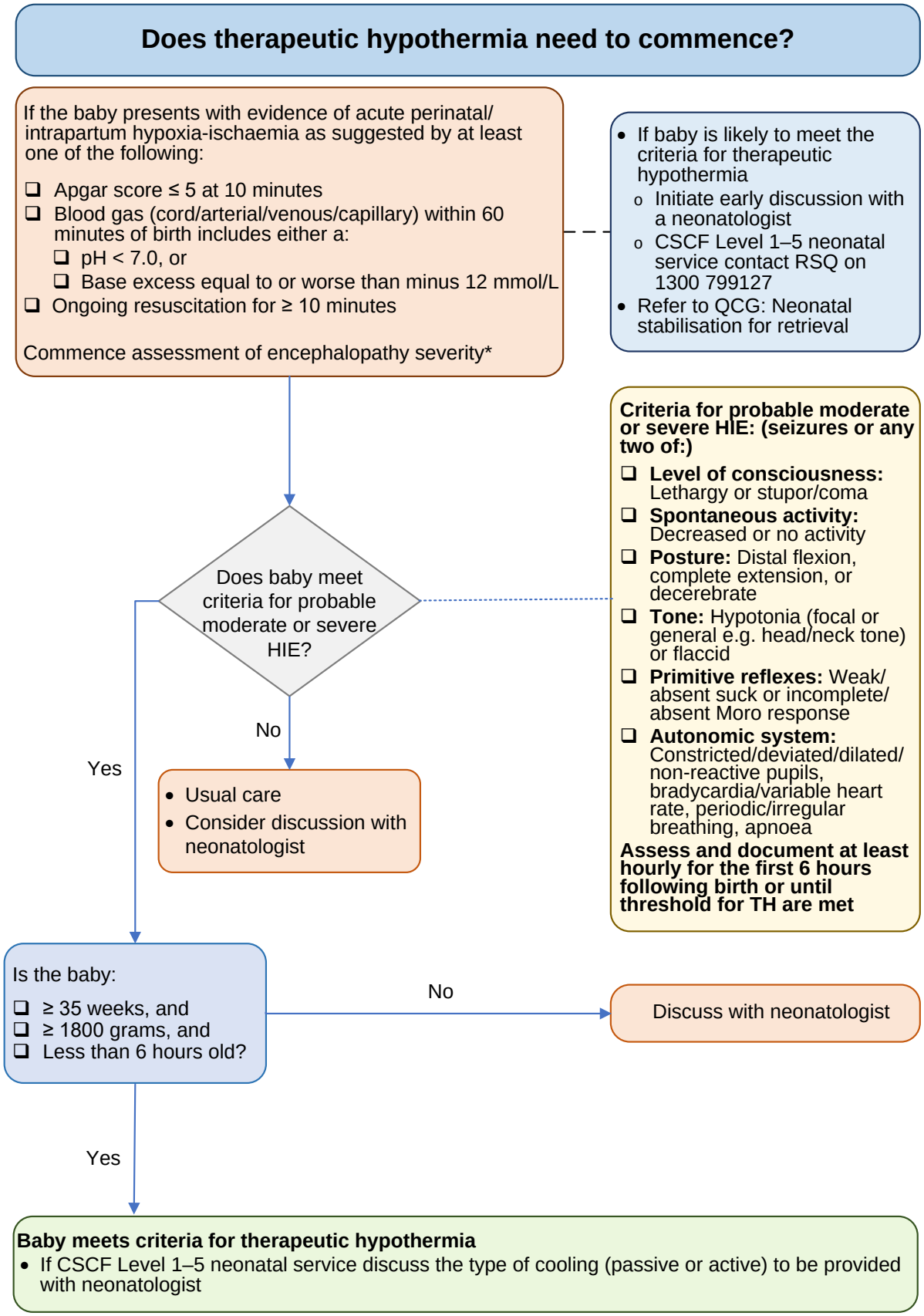
Management
- Anticipate need for resuscitation from maternal/obstetric/labour history (including CTG trace)
- Refer to QCG: *Neonatal resuscitation*
- Maintain breathing and circulation
- Commence Sarnat scoring for 6 hours after birth or until TH begins
- Record vital signs (TPR, BP, SpO_2)
- Supportive care
- Treat seizures [refer to QCG: *Neonatal seizures*]
- Avoid:
  - o Hypo/hyper ventilation
  - o Hypoxaemia/hyperoxia (keep $SpO_2 \geq 92\%$)
  - o Hyperthermia
  - o Hypotension
    - ▪ Inotropes as indicated
- Correct underlying causes of metabolic acidosis
- Nil by mouth (insert OGT/NGT)
- Maintain normal blood glucose [refer to QCG: *Newborn hypoglycaemia*], calcium and magnesium
- Restrict fluid intake
  - o Commence glucose 10% IV at 40–50 mL/kg/day
  - o Monitor urine output
  - o Maintain accurate fluid balance record
- Nutritional support: TPN if/when required
- Therapeutic hypothermia (if criteria met)
  - o Core temperature of 33–34 °C within 6 hours of birth for 72 hours from target temperature

Ongoing care and assessment
- Family support
- Developmental assessment
- Physiotherapy and speech therapy

aEEG: amplitude integrated electroencephalogram; **BP** blood pressure; **CTG** cardiotocograph; **CXR:** chest x-ray; **DIC:** disseminated intravascular coagulation; **EEG:** electroencephalogram; **FBC:** full blood count; **IV:** intravenous; **LFTS:** liver function tests; **MRI:** magnetic resonance imaging; **NEC:** necrotising enterocolitis; **NGT:** nasogastric tube; **NBST:** neonatal bloodspot screening test; **OGT:** orogastric tube; **QCG:** Queensland Clinical Guidelines; **RBC:** red blood cells;**SpO_2:** oxygen saturation; **TPN:** total parenteral nutrition; **TPR :** temperature, pulse, respirations; **US:** ultrasound scan

Flowchart: F21.11-3-V10-R26

Flow Chart: Assessing baby for therapeutic hypothermia

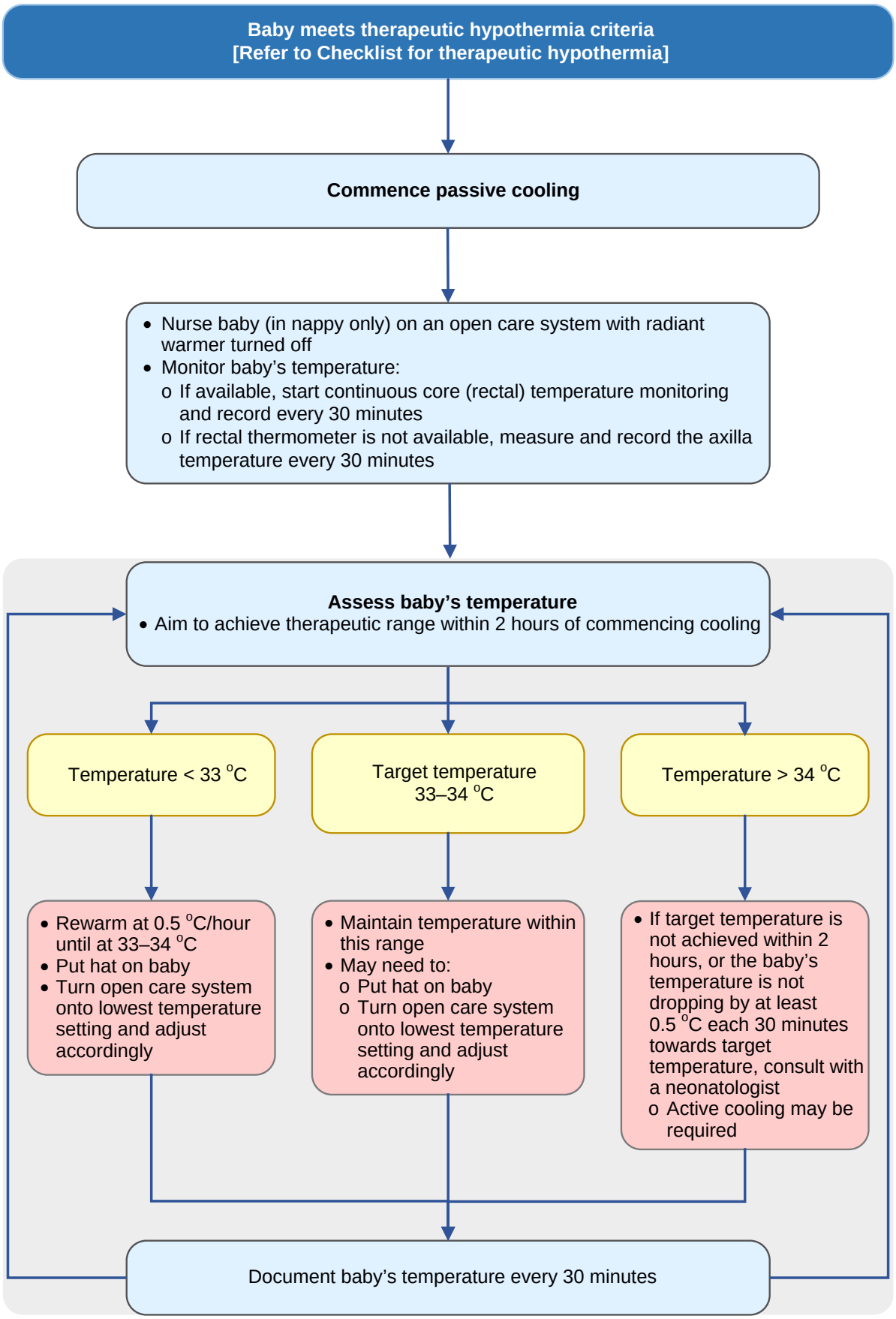


CSCF: Clinical Services Capability Framework; **HIE:** hypoxic ischaemic encephalopathy; **QCG:** Queensland Clinical Guidelines; **RSQ:** Retrieval Services Queensland

*Use Sarnat scoring form

Flowchart: F21.11-2-V9-R26

Flow Chart: Passive cooling



>: greater than; **<:** less than

Flowchart: F21.11-4-V8-R26

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Abbreviations

aEEG	Amplitude-integrated electroencephalograph
BP	Blood pressure
CUS	Cranial ultrasound
EEG	Electroencephalograph
EPO	Erythropoietin
FBC	Full blood count
FGR	Fetal growth restriction
HIE	Hypoxic-ischaemic encephalopathy
ISC	Infant servo control
IQ	Intelligence quotient
MRI	Magnetic resonance imaging
NBST	Newborn screening test
RSQ	Retrieval Services Queensland
SpO_2	Peripheral capillary oxygen saturation
TDM	Therapeutic drug monitoring
TH	Therapeutic hypothermia

1 Introduction

1.1 Definition

Neonatal encephalopathy is a condition that occurs in a newborn baby born at or after 35 weeks gestation, that has features of disturbed neurological function. It is characterised by a reduced level of consciousness or seizures, often with difficulty initiating and maintaining respiration, and with depressed tone and reflexes.[1,2] While infants born at less than 35 weeks gestation can experience hypoxic ischaemic injury, their assessment and clinical management differs from that of late preterm and term infants.

Hypoxic-ischaemic encephalopathy (HIE) is a type of neonatal encephalopathy caused by systemic hypoxaemia and/or reduced cerebral blood flow resulting from an acute peripartum or intrapartum event. [3] It is a condition which can cause significant mortality and long-term morbidity.[4] HIE can be a clinical consequence of perinatal, birth and/or neonatal asphyxia.

1.2 Incidence

In Queensland, from 2015–2019, the incidence of “Intrauterine hypoxia and birth asphyxia” was between 1.3% to 1.7% of all live preterm and term births.[5] In developed countries, noting differences in definitions between studies and countries, the incidence of:

- Intrapartum hypoxia-ischaemia is 3.7 (range 2.9–8.3) per 1000 term births[6], and
- HIE is 2.5 per 1000 live term births[6]
- Moderate or severe HIE requiring therapeutic hypothermia (TH) is 1.3 per 1000 live births[7]

1.3 Clinical standards

If baby with suspected HIE is not born in a facility with a neonatal intensive care unit as described in the Clinical Services Capability Framework[8], contact Retrieval Services Queensland (RSQ) for referral to a neonatologist and service that is capable of providing comprehensive clinical care including[9,10]:

- Mechanical ventilation
- Core temperature and vital signs monitoring
- Biochemical, coagulation and haematological monitoring
- Detection and monitoring of seizures including with an amplitude-integrated electroencephalograph (aEEG) or electroencephalograph (EEG)
- Neuroimaging including magnetic resonance imaging (MRI)
- Neurologic consultation
- Systems for monitoring of longitudinal neurodevelopmental outcomes

If active TH is indicated refer to Section 3.6 Management of baby born in level 1–5 facility.

1.4 Communication

- Parents of babies with HIE usually experience acute distress due to the seriousness of their baby’s condition
- Early accurate prognosis in the first few days after birth is uncertain
- Facilitate regular discussions between the baby’s parents and other identified support persons, neonatologist, other medical teams, nursing and other support staff (e.g. social worker)
- Involve parents in decisions about their baby including:
  - HIE and treatment options [refer to Appendix A Points for discussion with parents]
- Facilitate the parents involvement in their baby’s care[11]:
  - Explain tests and procedures, comfort measures, pain management, equipment
  - If the baby’s condition allows, assist the parents to provide care measures
- Refer to local support services where required (e.g. social work)
- Provide written parent information on HIE (e.g. Queensland Clinical Guideline Parent Information: *Hypoxic-ischaemic encephalopathy*)
- If required, provide palliative and bereavement care and support

2 Risk factors

2.1 Maternal

Table 1. Maternal risk factors

Aspect	Consideration
Medical conditions	• Thyroid disease[12] • Hypertension disorder in pregnancy[1,3] o Refer to Queensland Clinical Guideline *Hypertension and pregnancy*[13] • Diabetes[12]–pre-existing or gestational o Refer to Queensland Clinical Guideline: *Gestational diabetes mellitus*[14] • Immune disorders[15] (e.g. antiphospholipid syndrome) • Chronic conditions[15] (e.g. renal disease) • Exposure to infections or drugs[15]
In-utero	• Elevated temperature[3,16] (e.g. chorioamnionitis[12], funisitis[17]) • Ante/intrapartum haemorrhage or uterine rupture[2,16-19] • Hypotension[12] • Trauma[12]
Predisposing factors[12]	• Illicit substance use[15,16] • Potential for birthing complications: o Shoulder dystocia[18,20] o Nulliparous women[16,18,20] o Overweight[20] o Short stature[20] • History of: o Pre-eclampsia o Placental vasculopathy • Previous caesarean section associated with uterine rupture[20] • Multiple pregnancy[1]

2.2 Fetal/baby

Table 2. Fetal/baby risk factors

Aspect	Consideration
Antepartum assessment	• Fetal movements: o Useful indicator of fetal health o Detection by maternal perception or real-time ultrasound scan (USS)[15] o Refer to Queensland Clinical Guideline: *Fetal movements*[20] • Fetal heart rate[3,12] • Biophysical profile–fetal breathing, movement, tone and amniotic fluid volume[15] • Growth–identification of fetal growth restriction (FGR)[3,15] • Blood flow velocity–Doppler flows in umbilical and fetal cerebral and systemic vessels[15]
Fetoplacental[15]	• Oligohydramnios or polyhydramnios • Multiple pregnancy (in particular monochorionic) where cerebral perfusion may be compromised • Previous fetal death • Uteroplacental failure resulting in FGR and consequent intrapartum asphyxia
Intrapartum assessment	• Fetal heart rate • Fetal blood lactate • Cardiotocograph (CTG)
Postpartum	• Paired umbilical cord blood gas • Low Apgar scores[3] • Presence of comorbidities o Severe pulmonary hypertension of the newborn[12] o Severe recurrent apnoeic events[12] o Severe pulmonary disease[12]

2.3 Intrapartum events

The risk of HIE is increased by significant intrapartum events leading to metabolic acidosis and an hypoxic-ischaemic fetal insult.[12] However, these events occur in less than half of the babies with HIE, and their absence does not preclude this diagnosis.

Table 3. Intrapartum events

Aspect	Consideration
Context	• An absence of an intrapartum sentinel event does not exclude the diagnosis of HIE
Significant events	• Peripartum or intrapartum hypoxic-ischaemic event[15,21,22], e.g.: o Uterine rupture[15] o Placental abruption[15] o Cord accident including prolapse[3,17,18] o Hypotension o Amniotic fluid embolism[17] o Fetal exsanguination from a vasa praevia or large feto-maternal haemorrhage[21] • Prolonged shoulder dystocia • Prolonged labour with transverse arrest[15] • Difficult instrumental birth
Intrapartum fetal heart rate pattern	• Abnormal fetal heart rate patterns associated with fetal hypoxia o Refer to Queensland Clinical Guideline: *Intrapartum fetal surveillance*[23]
Other	• Meconium in liquor

3 HIE assessment, diagnosis and management

3.1 Signs of HIE/diagnostic criteria

There is no 'gold standard' test or early biomarker for the diagnosis of HIE.[2] Clinical signs assist diagnosis and determine if the encephalopathy is mild, moderate or severe. A prompt assessment during the first six hours of life is required to determine if the baby is eligible for TH. In all cases discuss options for treatment with a neonatologist by contacting Retrieval Services Queensland (RSQ).

Currently, there is no internationally agreed definition of mild HIE.[24] Some babies with mild HIE may benefit from TH.[25] Due to a lack of certainty about the benefits and harms, treating them with TH is not routinely recommended outside of clinical trials and it is suggested that it is discussed with a neonatologist.

Consider the possibility of other causes of neonatal encephalopathy, rather than HIE, especially until there is evidence of a hypoxic and/or ischaemic injury during the perinatal and/or intrapartum period. Suspect neonatal encephalopathy in the baby who is depressed at birth and who, in the earliest hours of life, presents with disturbed neurological function.[21] Refer to Table 4. Signs of HIE and Appendix C Assessment of encephalopathy severity (Sarnat scoring).

Table 4. Signs of HIE

Aspect	Consideration
Clinical features	• Abnormal state of consciousness o If mild HIE may be hyperalert/irritable • Reduced spontaneous movements • Respiratory difficulties (initiating and maintaining breathing) • Increased or reduced tone • Abnormal posturing • Abnormal primitive reflexes–suck and Moro • Seizure activity[26] • Poor feeding
Differential diagnosis	• Metabolic abnormalities, congenital abnormalities, meningitis, hypoglycaemia, severe hyperbilirubinaemia[27] • Other causes of seizures/encephalopathy in newborn babies (e.g. intracranial haemorrhage, perinatal stroke, drug withdrawal, genetic encephalopathies, epilepsies))
Blood gas	• Paired cord blood gas (venous and arterial) to identify metabolic acidosis[26] o Refer to Queensland Clinical Guideline: *Intrapartum fetal surveillance*[22] • Neonatal blood gas within in first hour after birth indicated if: o Cord blood gas not obtained o Baby's condition deteriorates after birth o Cord blood gas pH less than 7.0 and/or base excess worse than or equal to minus 12 mmol/L • If cord or early neonatal blood gas pH less than 7.0[28] and/or base excess worse than or equal to minus 12 mmol/L (capillary, arterial or venous) commence encephalopathy screening
Apgar score	• Less than or equal to 5 at 5 and 10 minutes
Examination	• Consistent with signs of mild, moderate or severe encephalopathy • Refer to Table 7. Clinical staging criteria and/or • Hourly and systematic neurological examinations to help establish prognosis[1,12], and determine if TH is indicated
Onset of multisystem organ failure	• May include a combination of renal injury, hepatic injury, hematologic abnormalities, cardiac dysfunction, metabolic derangements, and gastrointestinal injury[4,21] • HIE can occur in the absence of failure of other organs
Placenta and umbilical cord	• Gross and histological examination may show signs of contributing cause, (e.g. umbilical cord thrombosis, placental vascular lesion, infection or inflammation)[2] • Refer to Table 2. Fetal/baby risk factors
Investigations	• Refer to Table 5. Investigations

3.2 Investigations

Table 5. Investigations

Aspect	Consideration
Routine investigations	• Paired cord blood gas from umbilical and venous samples for pH and base deficit, to identify respiratory and metabolic acidosis in the baby and placental function[2,29] o Lower pH and more negative base deficit are prognostic of poorer short term outcomes[30]–longer term outcomes may be modified by treatment including TH o Refer to Queensland Clinical Guidelines Intrapartum fetal surveillance[22] • Electrolytes, glucose and lactate (from blood gas sample)[1,2] o Higher and more persistently elevated levels of serum lactate seen in babies with poor outcomes[30] • Full blood count (FBC) to identify infection, haemorrhage, thrombocytopaenia[1,2] [refer to Table 5. Investigations] • If there is bleeding, thrombocytopenia or petechiae: o Perform a coagulation profile–prothrombin time measured by international normalised ratio (INR) and activated partial thromboplastin time (APTT)[1,2] ▪ Consider also for babies with features of moderate or severe HIE even in the absence of bleeding, thrombocytopenia or petechiae • Calcium (can be ionised calcium on a blood gas) • Septic work-up o Blood culture • Liver function tests[1,2] on day one or two o Higher liver enzymes correlate with severity of HIE[30], although severe HIE can occur with normal liver enzymes • Renal function tests (urea and creatine) on day one to two[1,2] o Serum creatinine and urea concentrations correlate with the severity of HIE[30] o Serum creatinine rise of more than 26.5 micromol/L or rise of 150–200% over the first 48 hours is considered stage one acute renal failure[31] • If blood results are abnormal, or if there is ongoing moderate or severe encephalopathy, or signs of dysfunction of other organs (e.g. oliguria) repeat daily or more often
Differential diagnosis	• Cranial ultrasound (CUS)–consider on day 1 to exclude/examine neurosurgical cause for HIE, ventricular size, haemorrhage, structural brain abnormality, vertebral lesions and obvious cystic lesions[2] • Consider: o Lumbar puncture (if coagulation profile normal and platelet count greater than 50 per microlitre) o Blood for ammonia, amino acids and microarray to identify chromosomal anomalies ▪ If baby has characteristic dysmorphism (e.g. trisomy) consider a rapid FISH (fluorescence in situ hybridisation) o Inborn errors of metabolism–urine for amino and organic acids, reducing substances, (e.g. ketones[1], blood for ammonia[1], amino acids) o Metabolic genetic disorders–early newborn screening test (NBST) ▪ Repeat NBST when it would usually be collected ▪ Discuss as indicated with metabolic specialist /neurologist
Neuroimaging	• Is unable to determine aetiology of HIE[21] but may be essential to rule out alternative diagnoses (e.g. brain malformation, intracranial haemorrhage, tumour) and contribute to assessment of severity and outcome • Refer to Table 20. Neuroimaging
EEG	• Commence aEEG or EEG if available to determine clinical or electrographic seizures[1,2] • Refer to Table 21. EEG

3.3 HIE staging

Table 6. HIE staging

Aspect	Consideration
Context	• HIE is classified in stages, which if applied consistently provide useful information about the magnitude of injury and prognosis • Refer to Table 7. Clinical staging for HIE staging criteria • It is important to note this was originally described when no early therapeutic intervention was available • Refer to Appendix B Checklist for therapeutic hypothermia
Timing of assessment	• Undertake assessment of HIE stage as soon as possible after the baby is resuscitated and stabilised, and continue for at least six hours o Level of encephalopathy cannot be accurately assessed during resuscitation or while the baby is critically hypoxic or hypotensive o If evidence of encephalopathy identified, repeat assessment at least daily for several days • If baby is high risk, perform frequent (at least hourly) assessment of neurological status within the first six hours of birth o Refer to Appendix C Assessment of encephalopathy severity (Sarnat scoring) • A baby may deteriorate and move from Stage 1 to Stage 2 HIE • As signs may evolve over the first hours after birth: o Repeat assessment of baby even if no signs evident at initial examination • If two or more signs of moderate or severe HIE or seizures at any time in first six hours consult with neonatologist regarding commencing TH • TH will require the baby to be transferred to a Level 6 neonatal service
Clinical interpretation	• In Stage 1 HIE (mild), the baby will usually require minimal support and will have a normal neurological examination within three to four days • In Stage 2 and 3 (moderate and severe), the baby will be significantly unwell and the level of support required is dependent on the degree of organ compromise

3.4 Staging criteria

Table 7. Clinical staging criteria

Stage of HIE	Features
Mild (Stage 1)[4]	• Muscle tone may be increased and deep tendon reflexes may be brisk during the first few days • Transient behavioural abnormalities, such as poor feeding, irritability, or excessive crying or sleepiness, may be observed • By three to four days of life, the central nervous system examination findings become normal • Long term follow up studies indicate some babies will have some neurodevelopmental compromise[32-34] o Refer to Table 22. Outcomes
Moderate (Stage 2)[4]	• The baby is lethargic or has reduced arousal, with significant hypotonia and diminished deep tendon reflexes • The grasping, Moro, and sucking reflexes may be sluggish or absent • The baby may experience periods of apnoea • Seizures may occur within the first 48 hours of life • Full recovery within one to two weeks is possible and is associated with a better long-term outcome o Improvement of baseline EEG or aEEG (to normal voltages and with restoration of sleep-wake cycling) by 48–72 hours is associated with better neurological outcomes
Severe (Stage 3)[4]	• Stupor or coma is typical: o The baby may not respond to any physical stimulus • Breathing may be irregular and the baby often requires respiratory support • Generalised hypotonia and depressed deep tendon reflexes are common • Newborn reflexes, (e.g. sucking, swallowing, grasping and Moro) are absent • Disturbances of ocular motion, (e.g. skewed deviation of the eyes, nystagmus, loss of conjugate movements ("doll's eye") and bobbing) may be revealed by cranial nerve examination • Pupils may be dilated, fixed or poorly reactive to light • Seizures occur early and often and may be initially resistant to conventional treatments o The seizures are usually generalised, and their frequency may increase during the 24–48 hours after onset, correlating with the phase of reperfusion injury o As the injury progresses, seizures may subside and the EEG remains or becomes isoelectric or shows a burst suppression pattern ▪ At that time, coma may progress, and the fontanelle may bulge, suggesting increasing cerebral oedema

3.5 Initial management

Clinical management is primarily supportive, with the addition of TH for neuroprotection in those babies who meet the criteria [refer to Table 10. Criteria for therapeutic hypothermia]. Consider if the baby requires transfer to a Level 6 neonatal service. Contact RSQ promptly for advice and discussion with a neonatologist.

Table 8. Initial and ongoing management

Aspect	Consideration
Resuscitation	• Babies with HIE typically require respiratory support (continuous positive airway pressure (CPAP) or positive pressure ventilation) at birth o Some babies need cardiac compressions and/or IV adrenaline o Aim for normothermia until the baby meets the inclusion criteria for TH o Monitor temperature to avoid hyperthermia[35] (greater than 37.5 ^{o}C[36]) • Refer to the Queensland Clinical Guidelines: *Neonatal resuscitation*[37] and *Stabilisation for retrieval–neonatal*[38]
Blood gases	• Measure cord blood gases • Take a capillary, venous or arterial blood gas within one hour of birth
Serial assessments	• Continue serial assessments for encephalopathy (Sarnat scoring) for all babies where there has been any one of: o Continued need for resuscitation equal to or greater than 10 minutes o 10 minute Apgar score of less than or equal to 5 o pH of less than 7.0 and/or base excess worse than or equal to minus 12 mmol/L (cord gas or gas measured within an hour of birth) • If criteria for moderate or severe encephalopathy are met within six hours of birth commence TH o Refer to Table 8. Initial and ongoing management
Monitoring	• Record observations hourly (or more frequently if indicated) • Continuous monitoring of heart rate, respiration rate, oxygen saturation (SpO_2)–record hourly • Measure and record BP and temperature hourly o Avoid hyperthermia[35] (greater than 37.5 ^{o}C)[36] • Measure and record HIE staging criteria hourly until a decision is made about TH [refer to Table 7. Clinical staging criteria]

3.6 Management of baby born in level 1–5 facility

If baby with suspected HIE is not born in a facility with a neonatal intensive care unit as described in the Clinical Services Capability Framework, contact RSQ[8] for referral to a neonatologist.

Table 9. Non-tertiary birthing facility

Aspect	Consideration
Resuscitation	• Attention to airway, breathing and circulation takes priority over cooling • Refer to Queensland Clinical Guideline: *Neonatal resuscitation*[37]
Identify eligibility	• Consider all babies who meet the eligibility criteria for TH o Refer to Table 10. Criteria for therapeutic hypothermia • If the blood gas pH is less than 7.0 or base excess is equal to or worse than minus 12 at birth or soon after, identify if the baby is suitable for TH • If baby has one or more signs of HIE consider mild neonatal encephalopathy[25,39] discuss management with neonatologist by contacting RSQ [refer to Table 7. Clinical staging criteria
Inter-hospital transfer	• Contact RSQ for o Consultation and decision by neonatologist about commencement of TH o Retrieval to a neonatal intensive care unit (NICU) • Refer to Queensland Clinical Guideline: *Neonatal stabilisation for retrieval*[38]
Therapeutic hypothermia	• If TH is deemed appropriate by the neonatologist, target the baby's temperature between 33.0 °C and 34.0 °C • Required core temperature can usually be achieved by turning the heater off (passive cooling) • Refer to Table 15. Cooling and Table 17. Rewarming baby

4 Therapeutic hypothermia

When provided in the context of good supportive care such as assisted ventilation and cardiovascular support, TH is currently the only proven treatment for moderate and severe HIE that improves mortality and long-term outcomes for babies.[40] If TH is started within six hours of birth babies with moderate and severe HIE have better outcomes.[41] Discuss with a neonatologist the options for treatment of a baby with signs of mild HIE.

Discuss with a neonatologist the options for treatment for a baby who does not meet the criteria used in clinical trials of TH. These include infants with signs of mild HIE, if the six-hour window has been missed, where there are congenital anomalies or a suspected surgical condition, or in settings of post-natal asphyxia (e.g. accidental smothering). In certain cases, TH may still be appropriate, and in others, supportive care without TH will be the best approach.

4.1 Criteria

Table 10. Criteria for therapeutic hypothermia

Aspect	Consideration
Context	• If TH is provided for moderate to severe HIE, there is a statistically significant: o Improvement in survival[42] o Proportion of babies with normal neurological function at follow-up[43] o Reduction in– ▪ Major disability[42];[43] ▪ Neurodevelopmental disability[42] including cerebral palsy[42,43] ▪ Developmental delay[42,43] ▪ Blindness[43] ▪ Risk of death in the neonatal period and at 18 months[43] ▪ Refer to Table 22. Outcomes
Commencement	• If criteria for TH are met, commence within 6 hours of birth
Inclusion criteria[40,44]	• Baby is greater than or equal to 35+0 weeks gestational age • Birth weight greater than or equal to 1800 g • Evidence of perinatal/intrapartum hypoxia, as indicated by at least one of: o Apgar score of less than or equal to 5 at 10 minutes of age[9] o Ongoing resuscitation at 10 minutes of age or more[9] o pH less than 7.0[9] or a base excess worse than or equal to minus 12 mmol/L on cord/arterial/venous/capillary blood gas obtained[22] within 60 minutes of birth[12] • Evidence of either: o Moderate or severe encephalopathy [refer to Table 7. Clinical staging] *or* o Mild encephalopathy–discuss with neonatologist [25,45] or o Seizures (witnessed by medical officer, nurse or midwife, or seen on aEEG or EEG) • No contraindications to TH o Refer to Section 4.2 Contraindications and cautions • Cooling can begin before 6 hours of age • Refer to Appendix B Checklist for therapeutic hypothermia

4.2 Contraindications and cautions

Consider the benefits versus risk of TH including management of PPHN, medications the baby is receiving and other treatments including extracorporeal membrane oxygenation (ECMO).

Table 11. Contraindications and cautions

Aspect	Consideration
Conditions in which TH not contraindicated (if other inclusion criteria met)	• PPHN (controlled) o May have more complicated respiratory and circulatory course, and require higher oxygen o Combined adverse outcome (mortality and/or severe brain injury) not different to babies with PPHN who have not had TH[46] o Nitric oxide use is not contraindicated for managing PPHN during TH • Suspected or confirmed sepsis[47] • Coagulation profile abnormalities (not causing uncontrolled or critical bleeding) • Until diagnosis is confirmed and discussed with parents: o Suspected neuromuscular disorders o Chromosomal abnormalities
Conditions to discuss with neonatologist (contact RSQ)	• If gestation 35 weeks or more, and birthweight less than 1800 grams (severe fetal growth restriction) • If baby does not meet criteria for TH consider cautiously on a case-by-case basis as these babies o Have not been studied in randomised controlled trials o Evidence of benefit or harm is limited in these groups
Contraindications	• Baby with uncontrolled PPHN despite maximum therapy (e.g. nitric oxide, prostacyclin) • Major congenital abnormalities identified[9,42] including: o Life threatening abnormalities of the cardiovascular or respiratory systems • Critical bleeding [9] • Baby is moribund[9] (e.g. very low BP or severe acidosis unresponsive to treatment, imminent withdrawal of life support planned) or so severely affected that there is little hope for acceptable quality of life [42,48,49] o Following counselling and agreement with parents • Severe head trauma or intracranial bleeding[9] o In babies who have had intracranial haemorrhage, cooling has not proven to be beneficial[50], and may worsen coagulopathy

4.3 Management

4.3.1 Initial stabilisation

- Assess and stabilise baby prior to commencing TH
- Commence passive cooling once criteria for TH are met [refer to Table 10. Criteria for therapeutic hypothermia]
  - o Nurse baby (in nappy only) on an open care system cot with radiant warmer turned off
- Insert (preferably umbilical) venous and arterial catheters (arterial catheter insertion usually to occur at a Level 5 or 6 neonatal service–follow local policies)
  - o Hypothermia may make vascular access more difficult
  - o Collect blood samples as advised by neonatologist [refer to Table 5. Investigations]
- Insert nasogastric tube and leave on free drainage
- Use servo-controlled cooling device (if available)
- Refer to Queensland Clinical Guideline: *Neonatal resuscitation*[37] and Queensland Clinical Guideline: *Stabilisation for retrieval–neonatal*[40]

4.3.2 Assessment and monitoring

Table 12. Assessment and monitoring

Aspect	Consideration
Clinical assessment and monitoring	• Commence continuous monitoring[31] with hourly documentation o Cardio-respiratory signs and SpO_2[31] o If invasive BP monitoring is not available, record manual BP every 15 minutes • Assess capillary refill[31] • Assess for generalised oedema[31] • Chest x-ray • Blood gas
Temperature	• Monitor temperature • If active cooling–continuous core monitoring[31] • If passive cooling–if rectal probe unavailable intermittent axilla temperature every 30 minutes
Neurological	• aEEG/EEG monitoring[31] • Observe for seizure activity o Refer to Queensland Clinical Guideline: Neonatal seizures[47] • Daily neurological examinations as HIE may evolve over 1–4 days • MRI and/or cranial ultrasound [refer to Table 20. Neuroimaging]
Urine	• Monitor urine output[31] • Consider testing for amino and organic acids, ketones, reducing substances
Infection	• May co-exist with HIE[31,51] • Investigations include a septic work-up • Refer to Queensland Clinical Guideline: *Early onset Group B streptococcal disease* [52]
Pathology	• Baseline electrolytes, renal function and liver function tests, full blood count[31] (including platelets) • Monitor electrolytes and platelets every 8–12 hours in first 24–48 hours[31] • Check blood glucose level o Refer to Queensland Clinical Guideline: *Hypoglycaemia–newborn*[53] • Coagulation profile[31] • Refer to Table 5. Investigations • Early NNST (repeat at usual time)
Sarnat scoring and staging	• Assess and record during TH[31] • Follow local policies regarding clinician proficiency to perform assessment • Refer to Table 7. Clinical staging criteria

4.3.3 Supportive care

Babies will often exhibit effects in one or more organ systems including renal, hepatic, haematologic, cardiac, metabolic and gastrointestinal. Individualise each baby's management with continuous monitoring of cardiorespiratory status and early identification and treatment of seizures and multi-organ compromise (a characteristic of HIE).

Table 13. Supportive care during therapeutic hypothermia

Aspect	Consideration
Respiratory	• Ventilatory support as required • Avoid: o Hyperoxia as it is a risk factor for adverse outcomes in babies with HIE treated with TH[2,31] o Over-ventilation and consequent hypocarbia and high pH that may lead to severe brain hypoperfusion, cellular alkalosis and worse neurodevelopmental outcomes • Maintain SpO_2 greater than or equal to 92%[31,54]
Cardiovascular	• Hypotension, shock, cardiomegaly, arrhythmias or heart failure (rare) may occur[31] o Avoid systemic hypotension or hypertension[2] • Maintain mean arterial pressure above 35–40 mmHg for term babies • Inotropes may be required if hypotensive o Discuss with neonatologist by contacting RSQ • Exercise caution before giving fluid boluses in the absence of suspected hypovolaemia [refer to Renal row below] • Avoid iatrogenic hypertension • Consider echocardiography as it may identify hypovolaemia, poor myocardial contractility and low flow states • Sinus bradycardia is common during TH and may not require treatment if cardiac output is adequate
Infection	• Start empirical antibiotics (benzylpenicillin, or ampicillin and gentamicin)[31] o Refer to Queensland Clinical Guidelines: *NeomedQ Benzylpenicillin*[55], *NeomedQ Ampicillin*[56] and *NeomedQ Gentamicin*[57] available at http://www.health.qld.gov.au/qcg • Refer to Queensland Clinical Guideline: *Early onset Group B streptococcal disease* [52]
Neurological	• Moderate to severe HIE: o If available, commence continuous amplitude integrated electro-encephalogram (aEEG) for 96 hours or EEG with simultaneous video recording (if available) to confirm clinical seizures, detect subclinical seizures and assess background • Manage seizures[2] including the use of anti-epileptic medications[9] o Refer to the Queensland Clinical Guideline: *Neonatal seizures*[47]
Neuro-developmental care[58-60]	• Minimise parent/baby separation • Reduce environmental stimulation–noise, light • Minimal handling–cluster cares • Protect sleep time • Avoid and manage pain and stress • Re-position baby to prevent pressure areas and support comfort

Table 14. Supportive care (continued)

Aspect	Consideration
Renal	• Oliguria, haematuria, proteinuria, myoglobinuria, polyuria or renal failure may occur [refer to Table 5. Investigations] • Commence 10% glucose IV at 40–50 mL/kg/day • Monitor fluid balance • Consider avoiding nephrotoxic drugs o If gentamicin is used: ▪ Monitor levels of gentamicin[31]—longer dosing intervals (e.g. 36–48 hours) may be required in babies receiving TH[61] ▪ Consider therapeutic drug monitoring (TDM) before the second dose ▪ Refer to Queensland Clinical Guideline: *NeoMedQ Gentamicin*[57] • If oliguria/anuria present consider: o Urinary catheterisation o Circulating blood volume–discuss with neonatologist o Withholding the subsequent dose of aminoglycoside (gentamicin) if prescribed until results of TDM are available
Metabolic	• Maintain normal metabolic status[2] o Hypo/hyperglycaemia[31], hypocalcaemia, hyponatraemia, hypomagnesaemia, lactic acidosis may occur [refer to Table 5. Investigations] • Maintain blood glucose levels within normal physiological ranges o Perform regular blood glucose levels o Refer to Queensland Clinical Guideline: *Hypoglycaemia–newborn*[53]
Haematology	• Thrombocytopenia[62], thrombosis, bleeding or elevated nucleated red blood cells may be present • Disseminated intravascular coagulopathy (DIC)[31] is a significant risk after hypoxic injury to the liver[4] • Perform a coagulation profile o Consider fresh frozen plasma (FFP)[31] or other component therapy as required, and a second dose of vitamin K given IV [refer to Table 5. Investigations]
Gastrointestinal	• Nil by mouth • Monitor liver function tests (LFTs)[63] • Baby is at risk of necrotising enterocolitis[31] • If receiving TH do not feed baby • Cautiously reintroduce feeds following rewarming o Use breast milk (if available) o Feed intolerance may occur post TH[64]

4.3.4 Allied health

- Provide neurodevelopmental input and education for parents
- Refer for initial and ongoing neurological examination including assessment of tone, movement, behaviour and oro-motor responses to track progress

4.4 Cooling and re-warming

4.4.1 Cooling baby

Table 15. Cooling standards and methods

Aspect	Consideration
Clinical standard	• Cooling is commenced within 6 hours of birth to limit secondary reperfusion injury • Cooling is continued for 72 hours at target temperature[2] unless complications develop • Core temperature of 33.0–34.0 °C is targeted by 2 hours from commencement[42,48,49] • Any baby receiving TH has temperature monitored
Clinical practice	• Commence continuous core (rectal) temperature monitoring o Record baby's temperature every 30 minutes (rectal) ▪ If rectal temperature monitoring not available record axilla temperature every 30 minutes • Achieve cooling primarily by passive methods: o Nurse the baby on an open care system and turn the radiant warmer off o Nurse the baby naked with only a nappy on, and no sheepskin, water bags, cloth or occlusive wraps • If active cooling–use a servo controlled device if available • If the baby is ventilated maintain the humidifier temperature at the temperature recommended by the manufacturer • Refer to Queensland Clinical Guideline: *Respiratory distress and CPAP*[65]
Passive cooling	• If baby's temperature is: o Less than 34 °C ▪ Rewarm 0.5°C per hour until 33–34°C ▪ Put hat on baby ▪ Turn overhead heater to lowest temperature and adjust as required o 33–34 °C ▪ Maintain temperature within this range ▪ Consider reducing temperature of overhead heater o If greater than 34°C after two hours or not dropping by 0.5 °C every 30 minutes ▪ Discuss with neonatologist as active cooling using cooling packs or servo- controlled device (if available), may be required
Active cooling–servo controlled (option 1)	• Preferred method if available • Initiate servo-controlled cooling and rewarming mattress as programmed, or as per manufacturer instructions
Active cooling–manually (option 2)	• Apply the cool pack to the back of the baby's neck and head, and across the torso as required • If the rectal temperature is: o Less than 34.5 °C: remove one/some/all cool packs o Less than 34.0 °C: remove all cool packs o Less than 33.0 °C: manually adjust the heater output on the radiant warmer to regain a core temperature 33 °C–34 °C • The cool pack temperature guide is 10 °C (acquire from the fridge, never the freezer) • Cover cool packs with a cotton sheet or other appropriate cover • Observe and documents baby's skin in contact with cool packs every 15 minutes [refer to Table 18. Adverse effects]
Ceasing cooling prior to 72 hours	• Complications that may require cooling to cease prior to 72 hours include: o Life threatening bleeding–coagulopathy uncontrolled by blood products o Uncontrolled pulmonary hypertension o A cardiac arrhythmia requiring treatment (excluding sinus bradycardia) • Deterioration in condition which leads to redirected/palliative care based on discussions between the baby's parents and the treating team

4.4.2 Care of baby during TH

Table 16. Care of baby

Aspect	Consideration
Sedation/pain relief	• If the baby shows any signs of distress or if there is excessive shivering (may not be present in babies)[31]causing difficulties maintaining the desired baby temperature, consider: o Low dose morphine o Paracetamol–use with caution and preferably administer intravenously • Metabolism of most drugs, including analgesics and sedatives, is altered by TH[9,31,66,67] • Refer to Queensland Clinical Guidelines: *NeoMedQ Morphine sulfate*[68] and *NeoMedQ Paracetamol*[69] available at https://www.health.qld.gov.au or consulate with a neonatal pharmacist as required
Feeding	• Withhold enteral feeds due to the risk of gastrointestinal tract compromise (e.g. necrotising enterocolitis)[64] • If indicated, consider total parenteral nutrition

4.4.3 Rewarming baby

Table 17. Rewarming baby

Aspect	Consideration
Principles of rewarming	• After 72 hours of cooling, rewarm baby at a rate not exceeding 0.5 °C every 2 hours • Target rectal temperature is 37 °C • Babies will take 12–16 hours to rewarm to normothermia • Rectal probe measurements may cease after the baby has maintained the target rectal temperature of 37 °C for at least 6 hours • Continue monitoring other vital signs as hypotension and apnoea may occur[31] • Prevent rebound hyperthermia which is detrimental in moderate to severe HIE • If aEEG is used, continue during rewarming (or EEG, ideally accompanied by video) o Rebound seizure activity may be seen during or after rewarming[29,70]
Cooling and warming mattress (option 1)	• Rewarm baby on the proprietary servo-controlled cooling and rewarming mattress as programmed, or as per manufacturer instructions • Document every 30 minutes: o Rewarming times o Temperature increments o Temperature of baby o Temperature of cot • When rectal temperature of 37 °C is reached: o Attach a skin temperature probe to the baby, connect to open care system and set skin infant servo control (ISC) mode to required temperature • Connect rectal temperature probe to the relevant monitoring system for ongoing continuous display

4.6 Adverse effects of TH

Table 18. Adverse effects

Aspect	Consideration
Cardiovascular	• Arrhythmias[71]–sinus bradycardia[9 72] (common) • Decreased cardiac output[31] • Hypotension requiring inotropic treatment [9,72](common co-morbidity) • Persistent pulmonary hypertension[9,31] (uncommon)
Apnoea	• Consequence of: o Hypothermia or underlying HIE o Delayed metabolism of sedative medications
Haematological	• Bleeding risk due to inhibitory effects on the clotting cascade exacerbating coagulopathy common in HIE including: o Thrombocytopenia[9,71] o Blood hyperviscosity syndrome[29]
Metabolic disturbances	• Alterations in medication pharmacokinetics (e.g. medication metabolised and/or eliminated by liver or kidney)[66] • May be due to hypoxic organ damage common in HIE as well as TH
Skin or soft tissue injury	• Scalp oedema[48] • Subcutaneous fat necrosis[9,73]: o Rare, inflammatory, transient skin disorder[74,75] o Can occur from tissue exposure to excessively cold temperatures[71,75] • Sclerema from exposure to water filled mattress[76] • Case report of skin breakdown and local haemorrhage under cooling cap[48]
Gastrointestinal	• Ileus
Infections	• Systematic review identified no statistically significant effect of TH on sepsis[42] • Immunosuppression has been demonstrated in babies receiving TH[77]
Hypocalcaemia	• One RCT reported increased risk when compared with standard care 28% v 19%[49] • Symptomatic or requiring treatment uncommon

5 Prognosis following HIE

Early prediction of long term outcome requires a multimodal approach (i.e. combination of clinical assessment, neurological examination, EEG, aEEG, MRI). Older prognostic studies such as Sarnat and Sarnat[78] do not take into consideration the benefits of TH and other improvements in neonatal intensive care.

The 2013 Cochrane review reported outcomes for babies with moderate or severe HIE who were cooled according to study protocols.[42] The number of babies needed to treat to reduce the combined outcome of mortality or major neurodevelopmental disability at 18 months of age was 7.[42] Outcomes following treatment with whole body TH included[42]:

- Death or major neurodevelopmental disability–48%
- Mortality–27%
- Major neurodevelopmental disability (in surviving babies)–28%

Children born prior to the TH era with moderate encephalopathy had a disability rate of 6–21% while children with severe encephalopathy had a rate of 42–100%.[79] More recent outcomes may differ as the confidence in TH has increased and the profile of babies with moderate or severe HIE treated with TH may differ from those enrolled in large clinical trials. Other supportive care has also evolved over time.[50]

5.1 Clinical

Table 19. Clinical

Aspect	Consideration
10 minute Apgar score[80,81]	• Among babies with moderate or severe HIE o A 10 minute Apgar of 0–3 is more likely to be associated with a poor outcome (death or moderate/severe disability) o Risk of poor outcome is reduced in babies who subsequently have TH o Each point increase in 10 minute Apgar is associated with a lower risk of death or disability
Clinical biomarkers[82]	• If moderate or severe HIE occurred at less than 6 hours of age, the risk of poor outcome (death or moderate/severe disability) was increased if: o Signs of severe HIE persisted at 72 hours of age o At discharge examination, abnormal neurology was noted (e.g. clonus, fisted hand, abnormal hand movements, absent gag, presence of asymmetric tonic neck reflex) or gavage or gastrostomy feeding was needed
Cooled babies[82]	• If baby with moderate or severe HIE has TH, then at 18–22 months of age (when compared to no TH), the rate of: o Death, or moderate or severe disability is less o Moderate or severe cerebral palsy is less o Blindness is less o Hearing impairment is less • A core temperature less than 32 ºC during induction or maintenance phase: o Was more likely in babies with lower birth weight o Increased risk of needing BP support compared to other cooled babies o If promptly resolved, no increase in death or disability, or the Bayley II Mental Development Index (MDI) at 18 months of age

5.2 Neuroimaging

Table 20. Neuroimaging

Aspect	Consideration
Context	• Does not determine aetiology of HIE[21] but may be essential to rule out alternative diagnoses (e.g. brain malformation, intracranial haemorrhage, tumour) • Babies treated with TH are more likely to have a normal brain MRI than similarly-affected babies not treated with TH[2]
CUS	• Consider on day 1 to exclude haemorrhage, neurosurgical cause or structural brain abnormality for cause of encephalopathy • CUS lacks sensitivity in newborn babies for evaluating the nature and extent of the hypoxic ischaemic injury[21] • Poor characteristics as a prognostic indicator in baby with HIE[1]
Computerised tomography (CT) scan	• Lacks sensitivity for evaluating the nature and extent of the injury[21] • May assist with differential diagnosis • Not usually performed on babies in the neonatal period due to radiation dose exposure
Magnetic resonance imaging (MRI)	• Best form of imaging for prediction of outcome[83]–depends on: o Clinical context o Timing of the MRI o Sequence run o Scoring system applied o Location of brain injury • Routinely perform at 5–10 days of life to better define and assess the extent of the injury which may aid prognosis[1,21] • Cerebral injury scores are predictive of adverse outcome in baby with HIE treated with TH[84] • Patterns of brain injury consistent with HIE include deep nuclear grey matter or watershed cortical injury • Certain findings are prognostic of neurodevelopmental outcomes beyond infancy[85] o Pontine and cerebellar injury with basal ganglia thalamus injury are indicators of poor neurodevelopmental outcome[86] • Valuable in predicting long-term neurodevelopmental outcome • Magnetic resonance spectroscopy lacks specificity and sensitivity[87] • Prognostic value of scans performed after rewarming not changed by TH[85] • Prognostic value highest in clinically moderate and severe HIE[85]

5.3 Electrophysiology

Table 21. EEG/aEEG

Aspect	Consideration
Context	• Both conventional EEG and aEEG provide information about severity of HIE and perform well in predicting outcome[88-91] o Can be implemented soon after birth (where available)[89] o Provides real time measure of cerebral function[89] • Can contribute to early diagnosis and classification of HIE severity[89] when used in context of clinical features • A normal EEG/aEEG is highly predictive of normal outcome[89]
Severe encephalopathy	• Continuous low-voltage, flat and burst suppression tracings • A baby may have normal neurological outcome if aEEG background voltage activity recovers by 48 hours of life[12,91]
Prediction of outcome	• In babies receiving TH by 6 hours of age, the aEEG background has a sensitivity of 96% (95% CI 89–97%) for predicting moderate to severe adverse outcomes, but poor specificity 39% (95% CI 32-45%)[92] • Severely abnormal background activity on aEEG at 36 and 48 hours of life associated with severe injury on MRI and abnormal neurodevelopmental outcome[83]

5.4 Outcomes

Neurological outcomes of concern include spasticity, choreoathetosis, dystonia and ataxia that are often grouped together as cerebral palsy (CP). Seizures, neurosensory deficits (deafness or blindness) and cognitive deficits are also reported.[93,94]

Table 22. Outcomes

Aspect	Consideration
Benefits of TH	• Babies with moderate or severe HIE who receive TH are more likely to have a normal brain MRI and favourable neurodevelopmental outcomes at 36 months of age compared with those who do not receive TH[95,96] o Associated with an increased rate of normal survival—no cerebral palsy or seizures, and intact vision and hearing o Risk of developing cerebral palsy is reduced with TH compared to standard care: RR 0.67 [95% CI 0.52 to 0.86][42]
Outcomes after TH at 6–7 years of age	• Children who received TH for HIE continue to have better outcomes at 18 months of age and into childhood than those not treated with TH • If baby with moderate or severe HIE is treated with TH their survival rate at 6–7 years of age is better than those who have not received TH[79]
Mild HIE	• In a prospective study 16% of babies with mild HIE not treated with TH had neurodevelopmental impairment at 18–22 months of age[34] • Accurate prediction of outcomes difficult[87] because of lack of consensus case definition and likely important detection bias in reported studies • Abnormal short term outcomes may manifest after mild HIE o Functional impact on neurodevelopment is unclear but has been associated with lower rates but similar types of outcomes as babies with moderate or severe HIE[34] • No evidence as to whether TH modifies outcomes

5.5 Discharge planning

Table 23.Discharge planning

Aspect	Consideration
Preparation for discharge	• Arrange a discharge and follow-up meeting with the parents o Plan for when parents are ready to take their baby home (or shortly after discharge) and are better able to take in information and ask questions o Discuss what happened to their baby, treatments and ongoing follow-up
Parent education	• As early prognosis of long term outcome is difficult, inform parents that long term follow-up is important to enable appropriate referrals (if indicated) to specialised services • Provide the parents with written information on the follow-up procedures as this may be difficult information to retain
Follow-up	• Babies with moderate to severe HIE or who received TH require a neurodevelopmental review by early intervention specialists skilled in infant neuromotor and behavioural development (e.g. medical, allied health) o Make referrals are prior to discharge • Enrol babies with moderate to severe HIE into a standardised follow-up program from birth to 2 years of age that can provide assessment, appropriate follow-up and data collection on outcomes[9] • Babies with mild HIE also require neurodevelopmental follow up[33]
If baby dies	• Discuss the purpose and/or value of an autopsy with the parent(s) o If autopsy declined, parents may consent to post-mortem MRI • Suggest and refer parents to social worker for emotional/psychological support • Refer to appropriate support groups (e.g. SANDS) • Discuss and refer to the Coroner if required

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Appendix A Points for discussion with parents

The following discussion points may be useful when counselling parent(s) about aspects of HIE and therapeutic hypothermia. For associated parent information, refer to the Queensland Clinical Guidelines website (http://www.health.qld.gov.au/qcg).

Aspect	Consideration
Resuscitation	• Your baby needed significant resuscitation at birth to help him/her breathe. He/she appears to have suffered from the effects of lack of oxygen and blood supply to the brain
Incidence	• About 1–4 in 1000 newborn babies suffer from the effects of reduced blood flow or oxygen supply to their brain around the time of birth
Consequences	• This can result in brain damage from direct injury and from changes within the brain that occur after birth • If treatment is started within 6 hours from birth there is a chance to lessen the secondary changes
Prognosis	• Babies with mild brain injury often have a normal outcome • Approximately 30 to 60% of those babies who survive after more severe damage to their brain may develop long-term disabilities. These disabilities include cerebral palsy and severe learning difficulties
Treatment	• Your baby will be assessed to see if cooling can be used as a treatment • If started within 6 hours of birth research has shown that cooling babies with moderate or severe brain injury may reduce the brain injury, increase the chance of survival and reduce the severity of possible long-term disability
Cooling	• Your baby will continue to receive standard intensive care support • Your baby's temperature will be slowly lowered and kept between 33 and 34 °C for 72 hours • Cooling will be achieved by either: o Exposing your baby to the ambient air temperature and if required, cool gel packs can be applied or o Placing a sensor on your baby's skin to automatically monitor and control their temperature • Your baby's temperature and other vital signs will be closely monitored throughout while they are being cooled • If your baby shows any signs of discomfort during cooling, he/she will be given medication to reduce this • After 72 hours of cooling your baby will be gradually rewarmed to a temperature of 37 °C
Research	• Research is ongoing on the best ways to prevent, treat and care for newborn babies with brain injuries • You may be asked to consider participating in research trials that are happening at this time

Appendix B Checklist for therapeutic hypothermia

If baby has a perinatal event and/or acidosis and meets the criteria below, therapeutic hypothermia may be indicated.

Call Retrieval Services Queensland immediately on 1300 799 127 to discuss with a neonatologist the need for transfer and therapeutic hypothermia.

Therapeutic hypothermia criteria

- ❑ Evidence of acidosis or depression at birth, as indicated by at least **one** of the following:
  - ❑ Apgar score ≤ 5 at 10 minutes
  - ❑ pH < 7.0 or a base excess equal to or worse than minus 12 mmol/L on a cord/arterial/venous/capillary blood gas obtained within 60 minutes of birth
  - ❑ Mechanical ventilation or ongoing resuscitation for ≥ 10 minutes

AND either of:

- ❑ Evidence of moderate or severe encephalopathy **at any time** from 1–6 hours of age (use modified Sarnat assessment)*

  OR:
- ❑ Seizures (witnessed by medical officer/nurse/midwife or as seen on aEEG/EEG)

AND

- ❑ No absolute contraindications to therapeutic hypothermia:
  - ❑ Uncontrolled critical bleeding
  - ❑ Uncontrolled hypoxia due to persistent pulmonary hypertension
  - ❑ Imminent withdrawal of life support planned

AND

- ❑ Meets the following criteria:
  - ❑ ≥ 35 weeks**
  - ❑ Birth weight ≥ 1800 grams***
  - ❑ Able to begin cooling before 6 hours of age
  - ❑ Assessment made of relative contraindications (e.g. uncontrolled pulmonary hypertension, critical bleeding or coagulopathy, major congenital abnormalities, conditions requiring major surgery in the first 72 hours of life)
  - ❑ Assessed as not moribund and with plans for full care

*If baby has evidence of **mild encephalopathy** discuss with neonatologist
If baby is **< 35 weeks gestational age discuss with neonatologist
***If baby is **< 1800 grams** discuss with neonatologist

Adapted from:
Jacobs SE, Berg M, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG. Cooling for newborns with hypoxic ischaemic encephalopathy. Cochrane Database of Systematic Reviews. 2013; Issue 1. Art.No.:CD003311.DOI: 10.1002/14651858.CD003311.pub3:CD003311.
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Abbreviations: **aEEG:** amplitude-integrated electroencephalograph; **EEG**: electroencephalograph**;**
≥: greater than or equal to; **<**: less than; **≤**: less than or equal to

Appendix C Assessment of encephalopathy severity (Sarnat scoring)

Assessment criteria	Encephalopathy severity • Assess baby's signs against each criterion • Record each hour the **actual time** of assessment during the first 6 hours of life • Record **severity** for each sign: normal **(n)**, mild **(mild)**, moderate **(mod)** or severe **(s)** or **N/A** (if criterion not assessable)				Hours from birth					
	Normal (N)	**Mild (Mild)**	**Moderate (Mod)**	**Severe (S)**	**1h**	**2h**	**3h**	**4h**	**5h**	**6h**
					:	**:**	**:**	**:**	**:**	**:**
Level of consciousness	Alert/arouses appropriately	Hyperalert	Lethargic	Stupor or coma						
Spontaneous activity	Normal	Normal or increased	Decreased	None						
Posture	Normal	Normal or mild distal flexion	Distal flexion, complete extension	Decerebrate						
Tone*	Normal	Normal or increased in trunk and extremities	Hypotonia (focal or general)	Flaccid						
Suck reflex	Normal	Normal or incomplete	Weak	Absent						
Moro reflex	Strong	Strong, low threshold	Incomplete	Absent						
Autonomic system	Pupils equal and reacting to light; normal heart rate and respirations	Pupils equal and reacting to light; tachycardia; normal respirations	Pupils constricted; bradycardia or periodic/irregular breathing	Pupils deviated/ dilated/non-reactive; variable heart rate or apnoea						
Seizures	None	None	Common, focal or multifocal	Uncommon (excluding decerebration)						

*Assess tone in both limbs and trunk/neck–presence of hypotonia in either meets the criteria.

Appendix D Sarnat and Sarnat staging of HIE

Clinical feature	Stage 1 (mild)	Stage 2 (moderate)	Stage 3 (severe)
Level of consciousness	Hyperalert	Lethargic or obtund	Stuporous
Neuromuscular control			
Muscle tone	Normal	Mild hypotonia	Flaccid
Posture	Mild distal flexion	Strong distal flexion	Intermittent decerebration
Stretch reflexes	Overactive	Overactive	Decreased or absent
Segmental myoclonus	Present	Present	Absent
Complex reflexes			
Suck	Weak	Weak or absent	Absent
Moro	Strong, low threshold	Weak, incomplete, high threshold	Absent
Oculo vestibular	Normal	Overactive	Weak or absent
Tonic neck	Slight	Strong	Absent
Autonomic function	Generalised sympathetic	Generalised parasympathetic	Both systems depressed
Pupils	Mydriasis	Miosis	Variable, often unequal, poor light reflex
Heart rate	Tachycardia	Bradycardia	Variable
Bronchial and salivary secretions	Sparse	Profuse	Variable
Gastrointestinal motility	Normal or decreased	Increased, diarrhoea	Variable
Other			
Seizures	None	Common, focal or multifocal	Uncommon (excluding decerebration)
EEG findings	Normal (awake)	**Early:** low-voltage continuous delta and theta **Later:** periodic pattern (awake) **Seizures:** focal 1-to 1½-Hz spike-and-wave	**Early:** periodic pattern with isopotential phases **Later:** totally isopotential
Duration	Less than 24 hours	2–14 days	Hours to weeks

Source: Sarnat grading scale for neonatal encephalopathy after 45 years: an update proposal Pediatric Neurology 2020 113 (75-79). Sarnat, H; Flores-Sarnat, L; Fajardo, C;
Leijser, L; Wusthoff, C; Mohammad, K.

Abbreviations**: EEG:** electroencephalograph

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