Queensland Clinical Guidelines

Translating evidence into best clinical practice

Maternity and Neonatal **Clinical Guideline**

Hypoxic-ischaemic encephalopathy (HIE)

Queensland Government

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Endorsed by:	Queensland Clinical Guidelines Steering Committee Statewide Maternity and Neonatal Clinical Network (Queensland)
Contact:	Email: Guidelines@health.qld.gov.au URL: www.health.qld.gov.au/qcg

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- Advising consumers of their choices in an environment that is culturally appropriate and which enables comfortable and confidential discussion. This includes the use of interpreter services where necessary
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Checklist for therapeutic hypothermia (cooling)

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 the need for transfer and therapeutic hypothermia with a neonatologist.

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 < 7.00 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 of relative contraindications (e.g. uncontrolled pulmonary hypertension, critical bleeding or coagulopathy, major congenital abnormalities
  - ❑ Not moribund and with plans for full care

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.
Shankaran S, Laptook AR, Ehrenkranz RA, Tyson JE, McDonald SA, Donovan ER, et al. Whole-body hypothermia for neonates with hypoxic -ischaemic encephalopathy. N Engl J Med 2005:353(15);1574-84

Abbreviations: **≥**: greater than or equal to; **<**: less than; **≤**: less than or equal to; **aEEG:** Amplitude-integrated electroencephalograph; **EEG**: Electroencephalograph

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Assessment of encephalopathy severity

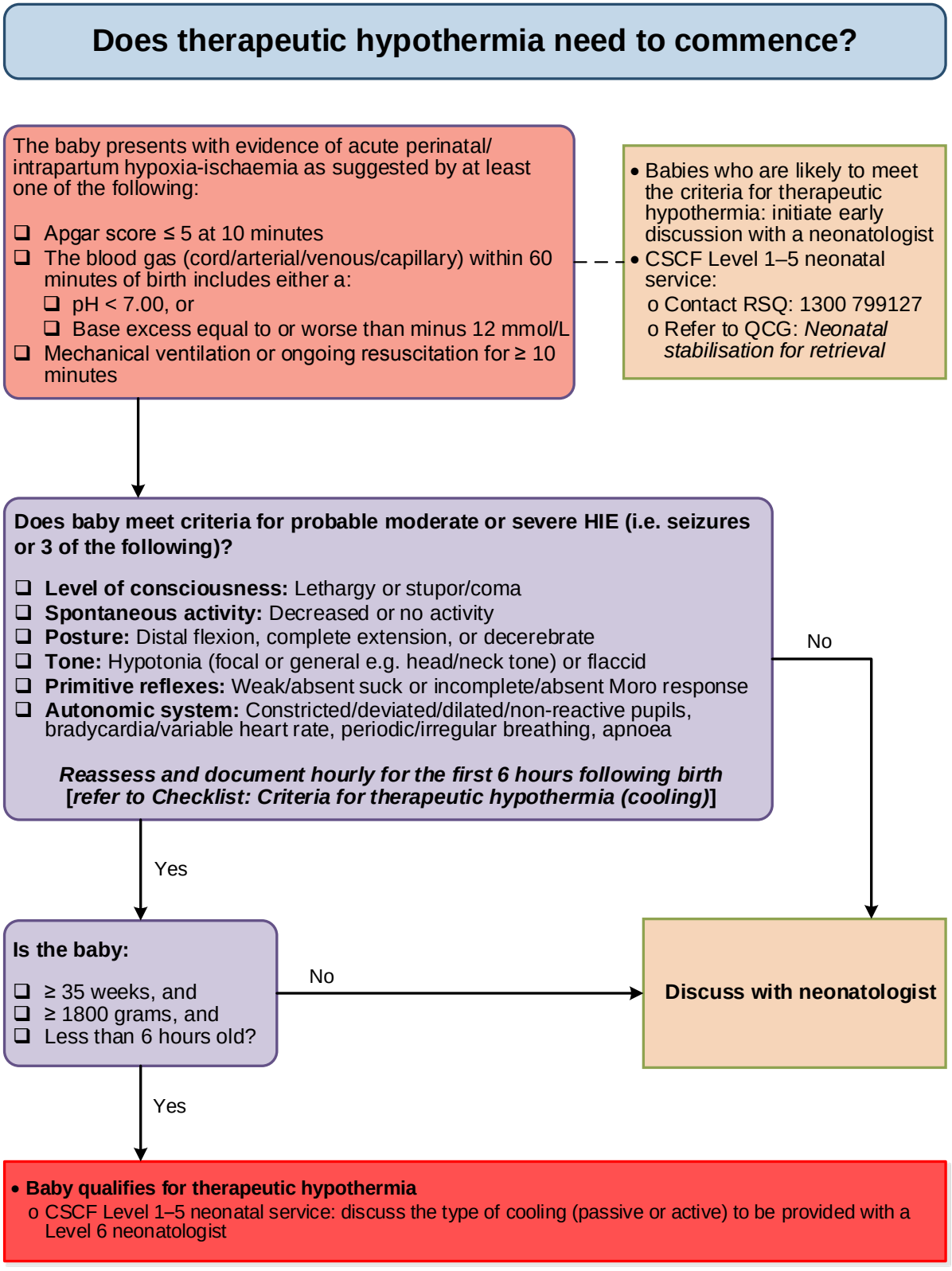
Assess baby's signs against each criterion and record the encephalopathy severity as normal **(n)**, mild **(mild)**, moderate **(mod)** or severe **(s)** each hour during the first 6 hours of life. If criterion is not assessable record as not applicable **(N/A)**.

Modified Sarnat Criteria

Assessment Criteria	**Encephalopathy severity** Record severity each hour				**Hours from birth** Record actual time of assessment and severity for each sign (**n/mild/mod/s or N/A**) each hour					
	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 activity	No activity						
Posture	Normal	Normal	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 suck	Weak suck	Absent						
Moro reflex	Strong	Strong, low threshold	Incomplete Moro	Absent						
Autonomic system	Pupils equal and reacting to light; normal heart rate and respirations	Pupils equal and reacting to light; normal heart rate and respirations	Pupils constricted; bradycardia or periodic/irregular breathing	Pupils deviated/ dilated/ non-reactive; variable heart rate or apnoea						

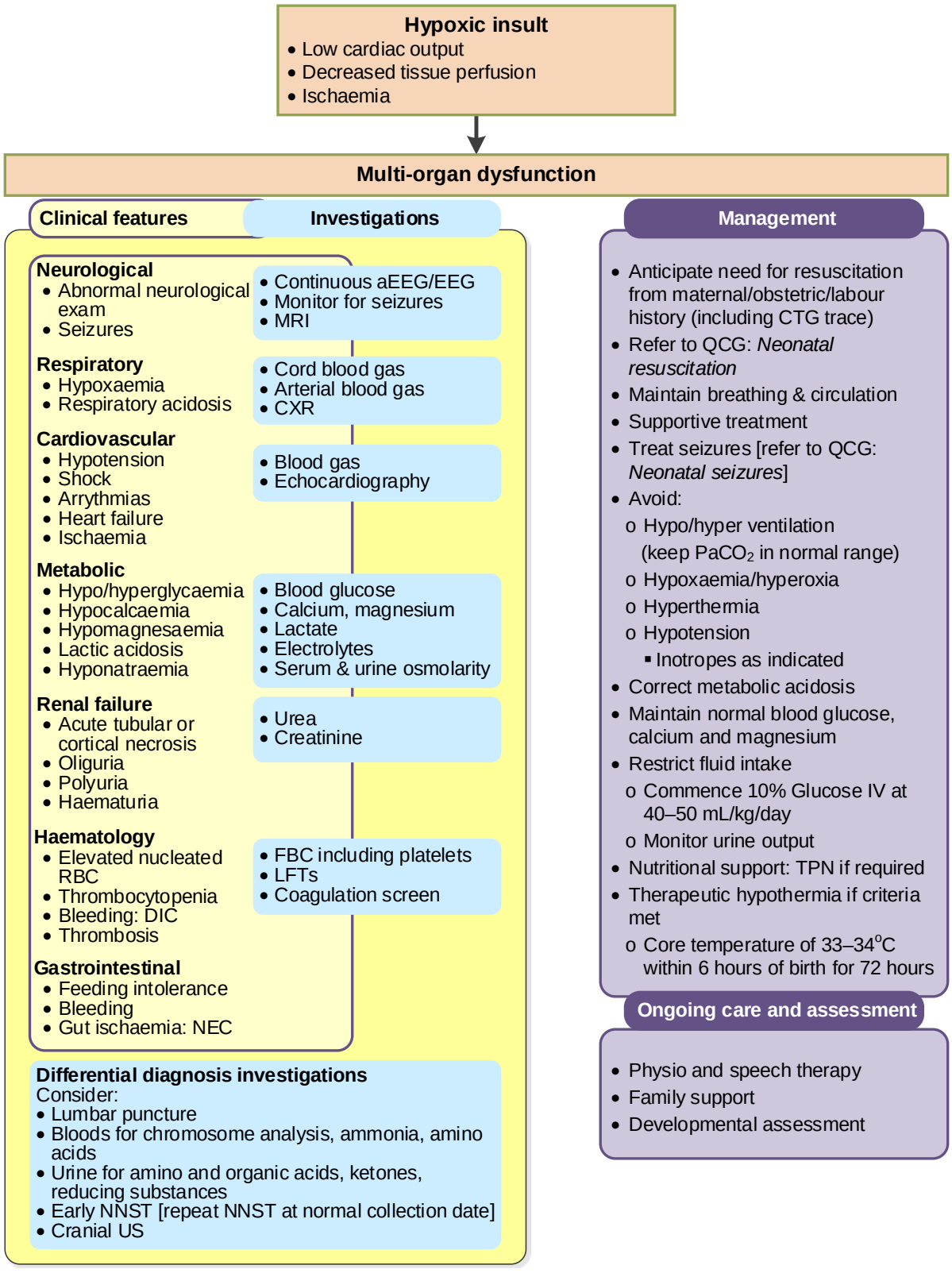
*Assess tone in both limbs and trunk/neck. Presence of hypotonia in either meets the criteria.

Flowchart: Criteria for therapeutic hypothermia (cooling)



Abbreviations: aEEG: Amplitude-integrated electroencephalograph; **CSCF**: Clinical Services Capability Framework; **EEG**: Electroencephalograph; **QCG**: Queensland Clinical Guidelines; **RSQ**: Retrieval Services Queensland; **≥:** greater than or equal to; **≤**: less than or equal to

Flowchart: HIE clinical features, investigations and management



Abbreviations: **aEEG** Amplitude-integrated electroencephalograph; **CTG** Cardiotocograph; **CXR** Chest x-ray; **DIC** Disseminated intravascular coagulation; **EEG** Electroencephalograph; **FBC** Full blood count; **IV** Intravenous; **LFTs** Liver function tests; **MRI** Magnetic resonance imaging; **NEC** Necrotising enterocolitis; **NNST** Newborn screening test; **$PaCO_2$** Partial pressure of carbon dioxide; **QCG** Queensland Clinical Guideline; **RBC** Red blood cells; **TPN** Total parental nutrition; **US** ultrasound

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Abbreviations

aEEG	Amplitude-integrated electroencephalograph
APTT	Activated partial thromboplastin time
BP	Blood pressure
CUS	Cranial ultrasound
EEG	Electroencephalograph
FBC	Full blood count
HIE	Hypoxic-ischaemic encephalopathy
HR	Heart rate
INR	International normalise ratio for blood clotting
ISC	Infant Servo Control
MRI	Magnetic resonance imaging
NICU	Neonatal intensive care unit
NNST	Newborn screening test
RSQ	Retrieval Services Queensland
SpO_2	Peripheral capillary oxygen saturation

Definition of terms

Shared decision making	Definition adapted for the newborn and family: Shared decision making involves the integration of a family's values, goals and concerns with the best available evidence about benefits, risks and uncertainties of treatment, in order to achieve appropriate health care decisions for the baby. It involves clinicians and parents (and carers) making decisions about the baby's management together. In partnership with their clinician, parents (and carers) are encouraged to consider available screening, treatment, or management options and the likely benefits and harms of each, to communicate their preferences, and help select the course of action that best fits these.[1]

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1 Introduction

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. It is a condition which can cause significant mortality and long-term morbidity.[2] HIE can be a clinical consequence of perinatal, birth and/or neonatal asphyxia.

1.1 Incidence

In Queensland, from 2007–2012, the incidence of "Intrauterine hypoxia and birth asphyxia" was 4–6 per 1000 live preterm and term births.[3] In developed countries, noting differences in definitions between studies and countries, the incidence of[4]:

- Intrapartum hypoxia-ischaemia is 3.7 (range 2.9–8.3) per 1000 term births, and
- HIE is 2.5 per 1000 live term births

1.2 Parental considerations

Parents of babies with HIE usually experience acute distress due to the seriousness of their baby's condition. It is difficult to offer an early accurate prognosis in the first few days after birth, therefore, regular discussions and meetings with the parents, neonatologist, other medical teams, and nursing staff will be required:

- Involve parents in shared decision making:
  - Discuss HIE and treatment options
  - Refer to Appendix A: Parental discussion points
- Facilitate parental involvement in their baby's care:
  - Explain tests and procedures, comfort measures, pain management, equipment
  - Dependent upon the baby's condition, assist the parents to provide care measures
- Refer to local support services where required (e.g. social work)
- Provide written parent information on HIE
- If required, provide palliative and bereavement care

1.3 Clinical standards for therapeutic hypothermia

Where active therapeutic hypothermia is indicated [refer to Section 4.5 Therapeutic hypothermia] provide care in a Level 6 neonatal service (as defined by the Clinical Services Capability Framework[5]) which is capable of providing comprehensive clinical care including[6]:

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

2 Intrapartum events

An absence of an intrapartum sentinel event does not exclude the diagnosis of HIE. Events which may precede HIE include:

- A significant peripartum or intrapartum hypoxic-ischaemic event (e.g. uterine rupture, placental abruption, cord prolapse, amniotic fluid embolism, fetal exsanguination from a vasa praevia or massive feto-maternal haemorrhage[7])
- A normal fetal heart rate pattern that changed to[7]:
  - Sinusoidal pattern
  - Absent baseline variability with recurrent late or variable decelerations, or bradycardia
  - Another fetal heart rate pattern such as tachycardia with recurrent decelerations or persistent minimal variability with recurrent decelerations [refer to Queensland Clinical Guideline *Intrapartum fetal surveillance*[8]]

3 Diagnosis

Suspect neonatal encephalopathy in the baby who is depressed at birth and who, in the earliest hours of life, presents with disturbed neurological function including[7]:

- A subnormal level of consciousness or seizures
- And frequently:
  - Difficulty initiating and maintaining respiration
  - Depression of tone and reflexes

3.1 Differential diagnosis

Use the term neonatal encephalopathy, rather than HIE, until there is comprehensive evidence of a hypoxic and/or ischaemic injury during the perinatal and/or intrapartum period.[5]

Table 1. Differential diagnosis

Aspect	Consideration
Differential diagnosis	• Metabolic abnormalities, congenital abnormalities, meningitis, hypoglycaemia, hyperbilirubinaemia[9], chronic placental insufficiency • Other causes of seizures/encephalopathy in neonates include intracranial haemorrhage, perinatal stroke, drug withdrawal
Investigations	• Refer to Section 4.3.2 Investigations

3.2 Diagnostic criteria

To determine the probability of HIE in the baby who has neonatal encephalopathy, assess for features suggestive of a hypoxic and/or ischaemic injury during the perinatal and/or intrapartum period:

- Fetal umbilical artery acidaemia: pH less than 7.00 and/or base excess worse than or equal to minus 12 mmol/L
- Apgar score of less than or equal to 5 at 5 and 10 minutes[7]
- Examination consistent with mild, moderate or severe encephalopathy [refer to Section 3.3 Clinical staging and/or Checklist for therapeutic hypothermia (cooling)
- Onset of multisystem organ failure which may include a combination of renal injury, hepatic injury, hematologic abnormalities, cardiac dysfunction, metabolic derangements, and gastrointestinal injury[7]

3.3 Clinical staging

HIE is classified in stages, which if applied consistently provide useful information about the magnitude of injury and prognosis. Refer to Table 2 for HIE staging criteria. Sarnat and Sarnat described the original HIE clinical staging system.[10] It is important to note this was originally described when the babies were 24 hours old and at a time when no early therapeutic intervention was available [refer to Appendix B: Sarnat and Sarnat staging system]

Undertake assessment of HIE stage as soon as possible after the baby is stabilised. In those babies who are high risk, perform frequent (i.e. minimum hourly) assessment of neurological status within the first 6 hours of birth [refer to Checklist for therapeutic hypothermia (cooling)
A baby may deteriorate and move from Stage 1 to Stage 2. If the baby meets the criteria for therapeutic hypothermia within the first 6 hours of birth, then the baby may still benefit from therapeutic hypothermia even though the baby was not eligible at birth. Therapeutic interventions will require the baby to be transferred to a Level 6 neonatal service.

Table 2. Modified HIE staging criteria

Stage of HIE	Features[2]
Mild (Stage 1)	• Muscle tone may be increased slightly 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 3–4 days of life, the central nervous system examination findings become normal
Moderate (Stage 2)	• The baby is lethargic, with significant hypotonia and diminished deep tendon reflexes • The grasping, Moro, and sucking reflexes may be sluggish or absent • The baby may experience occasional periods of apnoea • Seizures may occur within the first 24 hours of life • Full recovery within 1–2 weeks is possible and is associated with a better long-term outcome • An initial period of well-being or mild HIE may be followed by sudden deterioration, suggesting ongoing brain cell dysfunction, injury, and death: o During this period, seizure intensity might increase
Severe (Stage 3)	• Stupor or coma is typical: o The baby may not respond to any physical stimulus • Breathing may be irregular and the baby often requires ventilator support • Generalised hypotonia and depressed deep tendon reflexes are common • Neonatal reflexes (e.g. sucking, swallowing, grasping, Moro) are absent • Disturbances of ocular motion (e.g. skewed deviation of the eyes, nystagmus, bobbing, and loss of "doll's eye" i.e. conjugate movements) 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 subside and the EEG becomes isoelectric or shows a burst suppression pattern ▪ At that time, wakefulness may deteriorate further, and the fontanelle may bulge, suggesting increasing cerebral oedema • Irregularities of heart rate (HR) and blood pressure (BP) are common during the period of reperfusion injury, as is death from cardiorespiratory failure
Clinical interpretation	• In Stage 1, the baby will usually require minimal support with a normal neurological examination within 3–4 days • In Stage 2 and 3, the baby will be significantly more unwell and the level of support required is dependent on the degree of organ compromise

4 Clinical management

Clinical management is primarily supportive, with the addition of therapeutic hypothermia for neuroprotection in those babies who meet the criteria [refer to Section 4.5 Therapeutic hypothermia]. Consider if the baby requires transfer to a Level 6 neonatal service. Prompt contact with Retrieval Services Queensland (RSQ) is advised [refer to Section 4.5.4 Babies born in Level 1 to 5 neonatal facilities].

4.1 Resuscitation

Table 3. Initial care

Aspect	Considerations
Resuscitation	• Babies with hypoxic ischaemic encephalopathy 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 therapeutic hypothermia o Monitor temperature to avoid hyperthermia[11] (greater than 37.5 ^{o}C[12]) • Refer to the Queensland Clinical Guideline: *Neonatal resuscitation*[13] • Measure cord blood gases • Ensure a capillary, venous or arterial blood gas is taken within the first hour following birth

4.2 Observation and monitoring

Table 4. Observation and monitoring

Aspect	Considerations
Observation	• As the criteria for therapeutic hypothermia may be met within the first 6 hours following birth, undertake serial clinical assessments for level of encephalopathy, on all babies who meet any of the following: 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 7.00 and/or base excess worse than or equal to minus 12 mmol/L (cord gas or gas measured within an hour of birth) • Commence continuous monitoring (HR, respiration rate and SpO_2) and hourly (or more frequent) documented observations (including temperature, BP and HIE staging criteria) [refer to Table 2. Modified HIE staging criteria] • Avoid hyperthermia[11] (greater than 37.5 ^{o}C[12]) • Transfer to Level 6 neonatal service may be required

4.3 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) [refer to Table 5. Supportive care].

Table 5. Supportive care

Aspect	Consideration
Respiratory	• Ventilatory support as required; beware of: o Hyperoxia in the first 6 hours of life as it is a risk factor for adverse outcomes in babies with HIE treated with therapeutic hypothermia[14] o Over-ventilation and consequent hypocapnia that may lead to severe brain hypoperfusion, cellular alkalosis and worse neurodevelopmental outcomes
Cardiovascular	• Hypotension, shock, cardiomegaly, arrhythmias, heart failure or ischaemia may occur • Maintain mean arterial pressure above 35–40 mmHg for term babies • Inotropes may be required if hypotensive • Exercise caution before giving fluid boluses in the absence of suspected hypovolaemia [refer to Renal row below] • Avoid iatrogenic hypertension • Consider echocardiography (ECHO) as it may identify hypovolaemia, poor myocardial contractility and low flow states
Neurological	• Refer to Table 4. Observation and monitoring • In moderate to severe HIE: o Commence continuous aEEG (if available) for 96 hours (or EEG, ideally accompanied by video) in order to confirm clinical seizures and detect subclinical seizures and provide prognostic value • For management of seizures, refer to the Queensland Clinical Guideline: *Neonatal seizures*[15]
Renal	• Oliguria, haematuria, proteinuria, myoglobinuria, polyuria or renal failure may occur • Investigations: urea, creatinine • Commence IV 10% glucose at 40–50 mL/kg/day • Monitor fluid balance • Consider avoiding nephrotoxic drugs o Monitor levels of gentamicin: longer dosing intervals (e.g. 36 hours) may be required in babies receiving hypothermia[16,17] • If oliguria/anuria present consider: o Circulating blood volume, if hypovolaemia likely, an IV 0.9% sodium chloride bolus may be required o Urinary catheterisation o Dopamine or other inotrope infusion [refer to local drug protocols] o Withholding the subsequent dose of aminoglycoside (gentamicin) if prescribed
Metabolic	• Hypo/hyperglycaemia, hypocalcaemia, hyponatraemia, hypomagnesaemia, lactic acidosis may occur • Investigations include blood glucose, calcium, magnesium, serum lactate, electrolytes, serum and urine osmolarity • Maintain blood glucose levels within normal physiological ranges o Perform an early blood glucose level o Refer to Queensland Clinical Guideline: *Newborn hypoglycaemia*[18]
Haematology	• Thrombocytopenia, thrombosis, elevated nucleated red blood cells may be present: collect a full blood count • Disseminated intravascular coagulopathy (DIC) is a significant risk after hypoxic injury to the liver[2] • Monitor liver function tests (LFTs)[19] • If there is bleeding, thrombocytopenia or petechiae o Perform a coagulation profile o Consider fresh frozen plasma (FFP), or other component therapy as required, and a second dose of Vitamin K
Gastrointestinal	• The baby is at risk for necrotising enterocolitis • Do not feed if receiving therapeutic hypothermia • Cautiously reintroduce feeds following rewarming: breast milk is ideal

4.3.1 Infection

Table 6. Infection

Aspect	Consideration
Infection	• May co-exist with HIE[20-22] • Investigations include a septic work-up • Start antibiotics penicillin and gentamicin as per local policy • Refer to Queensland Clinical Guideline: *Early onset Group B streptococcal disease*[23]

4.3.2 Investigations

Table 7. Investigations summarised

Aspect	Consideration
Routine investigations	• Blood gases, electrolytes, glucose and lactate (all obtainable from blood gas sample) • FBC including platelets • INR and APTT clotting studies • Liver and renal function: day 1–2 • Septic work-up • The above may need to be repeated (e.g. daily or more often) if abnormal or if there is ongoing moderate or severe encephalopathy or signs of dysfunction of other organs (e.g. oliguria)
Differential diagnosis	• To exclude other causes of neonatal encephalopathy consider: o Lumbar puncture o Blood for chromosome analysis, ammonia, amino acids o Urine for amino and organic acids, ketones, reducing substances o Early newborn screening test (NNST) if metabolic/genetic disorders suspected. Repeat NNST when it would normally have been collected o Cranial ultrasound (CUS)

4.3.3 Allied health, physiotherapy and speech therapy

Table 8. Allied health

Aspect	Consideration
Allied health, physiotherapy and speech therapy	• Role in providing neurodevelopmental input and education for parents • Initial and ongoing neurological examination of the baby, including assessment of tone, movement, behaviour and oromotor responses, are valuable in order to track progress

4.4 Neuroimaging

Table 9. Neuroimaging

Aspect	Consideration
Neuroimaging	• Is unable to determine aetiology of HIE[7] but may be essential to rule out alternative diagnoses (e.g. brain malformation, intracranial haemorrhage, tumour) • CUS: o Perform on day 1 to exclude neurosurgical cause for HIE or structural brain abnormality o CUS (and computed tomography) lack sensitivity in newborn babies for evaluating the nature and extent of the injury[7] • MRI, including magnetic resonance spectroscopy[7]: o Routinely perform at 7 (5–10) days of life to better define and assess the extent of the injury which will aid likely prognosis o Patterns of brain injury consistent with HIE include deep nuclear gray matter or watershed cortical injury

4.5 Therapeutic hypothermia

In moderate to severe HIE, therapeutic hypothermia provided in accordance with specific criteria [refer to Table 10. Criteria for therapeutic hypothermia] is associated with statistically significant improvement in survival[24] with normal neurological function[25] and a reduction in:

- Major disability[24, 25]
- Neurodevelopmental disability[24], including cerebral palsy[24, 25]
- Developmental delay[24, 25]
- Blindness[25]
- Risk of death at 18 months[25]

Commence therapeutic hypothermia within 6 hours of birth where the criteria outlined in Table 10 are met.

Table 10. Criteria for therapeutic hypothermia

Aspect	Consideration
Inclusion criteria[24]	• 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 o Needing mechanical ventilation or ongoing resuscitation at 10 minutes o pH less than 7.00 or a base excess worse than or equal to minus 12 mmol/L on cord/arterial/venous/capillary blood gas obtained within 60 minutes of birth • Evidence of moderate or severe encephalopathy [refer toChecklist for therapeutic hypothermia (cooling)] • Greater than or equal to 35 weeks gestational age • Birth weight greater than or equal to 1800 g • Able to begin cooling before 6 hours of birth
Relative contraindications	• Major congenital abnormalities identified[24] including: o Suspected neuromuscular disorders o Suspected chromosomal abnormalities o Life threatening abnormalities of the cardiovascular or respiratory systems • Uncontrolled pulmonary hypertension • Critical bleeding or coagulopathy[26, 27] • So severely affected that there is little hope for normal outcome[24,28] i.e. moribund or “in extremis” (e.g. very low BP or severe acidosis unresponsive to treatment)

4.5.1 Babies not meeting critera

Babies not meeting the standard criteria for therapeutic hypothermia have not been studied in randomised controlled trials and therefore evidence of benefit or harm is limited in this group. Cooling babies with intracranial haemorrhage has not proven to be beneficial.[26]

The use of therapeutic hypothermia in babies who do not meet the standard critieria requires cautious consideration on a case-by-case basis in consultation with the NeoRESQ Neonatal Clinical Coordinator/Neonatologist from a unit which specialises in therapeutic hypothermia.

4.5.2 Assessment and monitoring

Table 11. Assessment and monitoring

Aspect	Considerations
Initial stabilisation	• Assess and stabilise baby prior to commencing therapeutic hypothermia • Commence passive cooling o Nurse baby wearing only a nappy and 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) o Hypothermia makes vascular access more difficult o Collect blood samples as per neonatologist's request [refer to Table 7] • Insert nasogastric tube
Observation and monitoring	• Commence continuous monitoring with hourly documentation o Cardio-respiratory and oxygen saturation o If invasive BP monitoring is not available, document 10 minutely manual BP • Temperature: o Active cooling–continuous core monitoring o Passive cooling–intermittent axilla tempreture if rectal probe unavailable • Observe for seizure activity [refer to Queensland Clinical Guideline: *Neonatal seizures*[15]] • Monitor urine output • Daily neurological examinations as HIE may evolve over 1–4 days

4.5.3 Cooling and rewarming clinical management

Refer to Appendix C: Therapeutic hypothermia: cooling and rewarming

4.5.4 Babies born in Level 1 to 5 neonatal facilities

Table 12. Babies born in Level 1 to 5 neonatal facilities

Aspect	Considerations
Resuscitation	• Attention to airway, breathing and circulation takes priority over cooling • Refer to Queensland Clinical Guideline: *Neonatal resuscitation*[29]
Identify eligibility	• Consider all babies who meet the eligibility criteria for therapeutic hypothermia [refer to Table 10. Criteria for therapeutic hypothermia] • Be proactive in identifying if a baby may be a candidate for therapeutic hypothermia if the blood gas pH is less than 7.00 at birth
Inter-hospital transfer	• Contact RSQ to arrange: o Consultation and decision by neonatologist with regard to the commencement of therapeutic hypothermia o Organise retrieval and a neonatal intensive care unit (NICU) bed • Refer to Queensland Clinical Guideline: *Neonatal stabilisation for retrieval*[29]
Therapeutic hypothermia and temperature monitoring	• Where therapeutic hypothermia is deemed appropriate by the neonatologist, target a temperature of between 33.0 °C and 34.0 °C • The required core temperature can usually be achieved by turning the heater off (passive cooling) • Refer to Appendix D: Flowchart: Passive coolingAny baby who is being cooled passively requires temperature monitoring: o In passive cooling, if continuous temperature monitoring is not available by a rectal probe, measure axilla temperature every 20 minutes o Document temperature every 30 minutes (rectal) or 20 minutes (axilla) • If the target temperature is not achieved after 2 hours, or the baby's temperature is not dropping by at least 0.5 ^{o}C each 30 minutes towards target temperature, further consultation with a neonatologist is required o Active cooling may be indicated • Turn the heater on if the baby's temperature is less than 33.5 °C and continue to closely monitor the temperature • Refer to Appendix C: Therapeutic hypothermia: cooling and rewarming

5 Prognosis

Early prognosis of long term outcome is difficult. Older prognostic studies such as Sarnat and Sarnat[10] do not take into consideration the benefits of therapeutic hypothermia. The 2013 Cochrane review included outcomes for babies with moderate or severe HIE who were cooled according to strict protocols.[24] 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.[24] Outcomes following treatment with whole body therapeutic hypothermia included[24]:

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

Current outcomes may differ as therapeutic hypothermia has become standard treatment for most babies with moderate or severe HIE and also as utilisation of therapeutic hypothermia has sometimes occurred outside the established inclusion criteria.[26]

5.1 Prognostic tools

Most prognostic tools were developed in the pre-therapeutic hypothermia era. Prognostic tool accuracy is improved if employed by skilled practitioners. Prognosis is best determined by using multiple modalities (clinical assessment and neurological examination, EEG and/or aEEG, MRI, Dubowitz and General Movements assessment), each within its optimal window, rather than any single method. Refer to Table 13 Predictors of outcome after HIE: comparison between cooled and non-cooled babies.[30]

Table 13. Predictors of outcome after HIE: comparison between cooled and non-cooled babies

Outcome parameter[30]	Pre cooling era[30]	Therapeutic hypothermia era[30]
Apgar score	• Score ≤ 4 at 5 minutes associated with neonatal seizures and poor neurodevelopmental outcome at 12 months [N=15][31] • Score ≤ 4 at 10 minutes associated with death or moderate/severe disability at 18–22 months [N=52][32]	• Score at 5 minutes not shown to be useful in cooled newborns[32] • Score ≤ 2 at 10 minutes associated with death or moderate/severe disability at 18–22 months [N=24][32] • Score 0 at 10 minutes associated with death or severe disability at 18–22 months [N=12][33]
Umbilical cord pH or arterial pH within 1 hour of birth	• Arterial cord pH < 7.00 associated with development of different degrees of CP [N=157][34]	• Lower arterial neonatal pH within first hour after birth associated with death or injury (seen on MRI) in second week after birth [N=109][35]
Base deficit	• Base deficit equal to or worse than 6.2 within 4 hours of birth plus need for resuscitation at birth: strong predictor of severe disability [N=204][36]	• N/A
Lactate	• Lactate levels 11.09 (± 4.6) mmol/L within the first hour after birth associated with associated with moderate to severe encephalopathy [N=65][36]	• Lactate levels ≥ 4.4 mmol/L highly predictive of degree of encephalopathy when combined with raised LDH, CK, and uric acid levels[37] • Lactate level alone: a poor predictor of good outcome[37] [N=94]
Sarnat score I–III	• Stages II and III 48 hours after birth associated with poor neurodevelopmental outcome at 12 months [N=28][31] • Stages II and III at 6 hours after birth associated with death or disability at 18–22 months [N=101][38]	• Stages II and III at 24 hours after birth associated with death or disability at 18–22 months [N=103][38]
Neurological examination	• Abnormal neurological examination on day 17 associated with abnormal neonatal MRI and poor neurodevelopmental outcome at 24 months[34] • Normal examination at any time associated with good outcome [N=157][34]	• Abnormal neurobehavioral assessment on/after day 12 has a good correlation with injury seen on MRI (median day 8) [N=68][39]; [N=45][40]
Abnormal aEEG (voltage criteria: upper margin > 10 mV, lower margin < 5 mV)	• Abnormal aEEG by 6 hours after birth can predict death or disability at 18–22 months[41] • Development of SWC is a good outcome predictor, if onset within 36 hours after birth [N=21][41]	• Abnormal aEEG by 48 hours after birth can predict death or disability at 18–22 months[42] • Development of SWC delayed due to hypothermia, but good outcome predictor if onset within 60 hours after birth [N=34][42]
Conventional MRI at day 8	• Major neonatal MRI abnormalities predict death or severe disability at 18 months [N=67][43,44,45,46]	• Major neonatal MRI abnormalities predict death or severe disability at 18 months [N=64][47]
MRI: T1- and T2-weighted and diffusion abnormalities	• All T1- and T2-weighted and diffusion MRI abnormalities predictive of death and major sensorineural disability at 2 years of age[48]	• All T1- and T2-weighted and diffusion MRI abnormalities predictive of death and major sensorineural disability at 2 years of age[48]

CK: creatine kinase; CP: cerebral palsy; LDH: lactate dehydrogenase; N/A: not applicable; SWC: sleep-wake cycling
Severe disability defined as: severe CP, severe developmental delay, sensorineural deafness, or cortical blindness.

6 Follow-up

- Plan a discharge and follow-up meeting with the parents
  - Discuss what happened to their baby, treatments and ongoing follow-up when the parents are ready to take their baby home (or shortly post-discharge) and when able to better take in information and ask questions
- Ensure all babies with moderate to severe HIE, and all babies who have received therapeutic hypothermia have a neurodevelopmental review by health professionals skilled in infant neuromotor and behavioural development (e.g. medical, allied health) and appropriate referrals are made prior to discharge
- Enrol babies with moderate to severe HIE into a standardised follow-up program from birth to 2 years of age which can provide assessment, appropriate follow-up and data collection on outcomes
- 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
- If the baby dies:
  - Discuss the purpose and/or value of an autopsy with the parent(s)
  - Suggest and refer parents to adequate support personnel for emotional/psychological support
  - Discuss and refer to the Coroner as required

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Appendix A: Parental discussion points

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	Suggested advice to parent(s)
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 also from subsequent secondary changes within the brain • These secondary changes are known to increase the amount of brain injury that occurs. Within 6 hours from injury 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 • 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 if started within 6 hours of birth
Cooling	• Your baby will continue to receive standard intensive care support • Your baby's temperature will be slowly lowered and kept between 33 and34 °C for 72 hours. Cooling will be achieved by exposing your baby to the ambient air temperature and with the use of cool gel packs if required • Your baby's temperature and other vital signs will be closely monitored throughout the process. If your baby shows any signs of discomfort during cooling he/she will be prescribed 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: Sarnat and Sarnat staging system

The staging system proposed by Sarnat and Sarnat[10] is often useful in classifying the degree of encephalopathy. Stages 1, 2, and 3 correlate with the descriptions of mild, moderate, and severe encephalopathy described by Zanelli et al.[2]

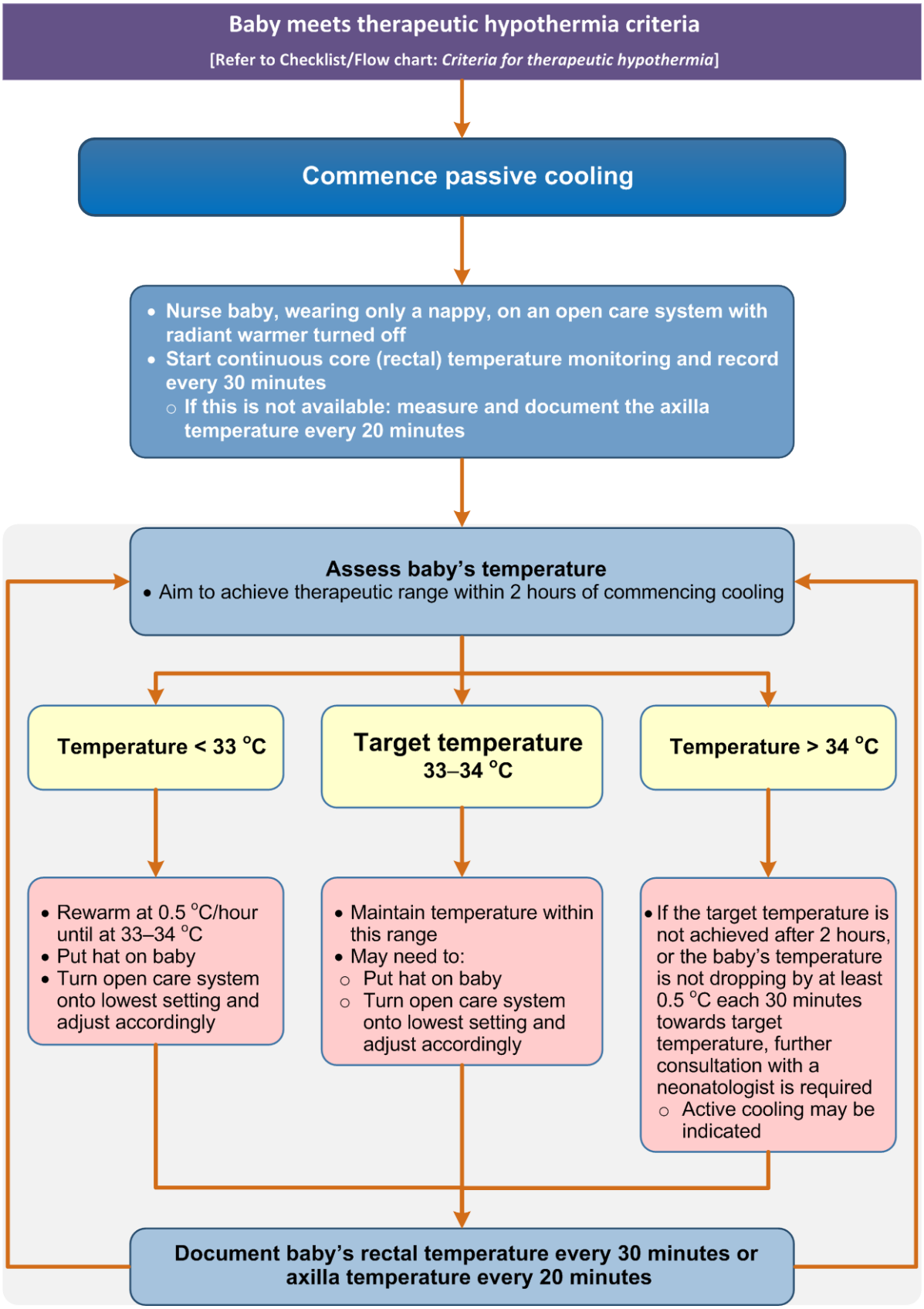
	Stage 1	**Stage 2**	**Stage 3**
Level of consciousness	Hyperalert	Lethargic or obtund	Stuporous
Neuromuscular control			
Muscle tone	Normal	Mild hypotonia	Flaccid
Posture	Mild distal flexion	Strong distal flexion	Intermittent decerebration
Stretch reflexes	Overactive	Overactive	Decreased or absent
Segmental 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)
Electroencephalo-gram 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

Appendix C: Therapeutic hypothermia: cooling and rewarming

Cooling	
Aspect	**Considerations**
Clinical standard	• Commence cooling within 6 hours of birth before secondary reperfusion injury begins • Cooling is continued for 72 hours • Achieve core temperature between 33.0 and 34.0 °C[24, 28, 49] by 2 hours from commencement
Clinical practice	• 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 • Refer to Appendix D: Flowchart: Passive coolingActive cooling: use a cooling and rewarming bed if available • If the baby is ventilated maintain the humidifier temperature at the temperature recommended by the manufacturer
Active cooling option 1:	• The preferred method: initiate servo-controlled cooling and rewarming mattress as programmed or as per manufacturer instructions
Active cooling option 2: Manual cooling	• Apply the cool pack to the back of the 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 between 33 and 34 °C • The cool pack temperature guide is 10 °C (acquire from the fridge, never the freezer) • Cover cool packs with a cotton/other appropriate cover • Observe skin in contact with cool packs every 15 minutes and document this observation o Subcutaneous fat necrosis can occur from tissue exposure to excessively cold temperatures
Ceasing cooling prior to 72 hours	• Indications to consider ceasing cooling prior to 72 hours include: o Life threatening coagulopathy o Uncontrolled pulmonary hypertension o A cardiac arrhythmia requiring treatment (excluding sinus bradycardia) o Deterioration in condition which leads to redirected/palliative care based on discussions with parents and the treating team
Sedation/pain relief	• If the baby shows any signs of distress or there is excessive shivering causing difficulties maintaining the desired baby temperature, consider: o Low dose morphine and/or midazolam o Paracetamol: ▪ Preferably administer per rectum ▪ The presence of the rectal thermistor sensor does not inhibit administration ▪ May also be administered intravenously • Metabolism of most drugs, including analgesics and sedatives, is altered by hypothermia and NICU-specific guidelines or consultation with a neonatal pharmacist is advised
Feeding	• Withhold enteral feeds due to the risk of gut compromise and/or necrotising enterocolitis
Risks	• Therapeutic hypothermia does not appear to affect the incidence or severity of most typical multi-organ system complications found in asphyxiated babies[21] • Risks may include[24]: o Subcutaneous fat necrosis o Thrombocytopaenia o Sinus bradycardia: transient and reversible with warming • Due to the potential for accumulation and toxicity, carefully administer all pharmacological agents according to clinical need[50]

Rewarming	
Aspect	**Considerations**
Principles of rewarming	• After 72 hours of cooling, rewarm baby at a rate not exceeding 0.5 °C every 2 hours • The target rectal temperature is 37 °C • Babies will take 12–16 hours to rewarm • Rectal probe measurements may cease after the baby has maintained the target rectal temperature of 37 °C for at least 6 hours • Prevent rebound hyperthermia which is detrimental in moderate to severe HIE • Ensure aEEG is continued for total of 96 hours (or EEG, ideally accompanied by video) as the rewarming period is a high risk interval for recurrence of seizures
Rewarming option 1: Cooling and warming mattress	• Rewarm baby on the proprietary servo-controlled cooling and rewarming mattress as programmed or as per manufacturer instructions • Document, every 30 minutes, rewarming times, increments and temperatures • Upon reaching a rectal temperature of 37 °C: o Attach a skin temperature probe to the baby, connect to open care system and set skin Infant Servo Control (ISC) mode to desired temperature o Connect rectal temperature probe to the relevant monitoring system for ongoing continuous display
Rewarming option 2: Manual rewarming	• Nurse the baby on ISC mode o The lowest setting that can be achieved on some ISC systems is 34.5 °C, therefore carefully manage manual heater increases prior to reaching 34.5 °C o Increase the desired set temperature by 0.1 °C every 20 minutes ▪ Over the two hour period, this regimen provides for five 0.1 °C increases with one 20 minute period at the end of the two hour time frame of no temperature increase before resuming further temperature increases • Document, every 20 minutes, rewarming times, increments and temperatures o A specialised observation form for this purpose is suggested

Appendix D: Flowchart: Passive cooling



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

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Working Party Clinical Lead

Dr Lucy Cooke, Clinical Director, Neonatal Critical Care Unit, Mater Health Services

QCG Progam Officer

Ms Lyndel Gray, Clinical Nurse Consultant

Working Party Members

Miss Tracey Bulow, Advanced Practice Physiotherapist, Neonatal Critical Care Unit, Mater Health Services
Mrs Sara Carter, A/Educator, Women and Newborn Services, Royal Brisbane and Women's Hospital
Dr Mark Davies, Neonatologist, Grantley Stable Neonatal Unit, Royal Brisbane and Women's Hospital
Dr Paul Devenish-Meares, Obstetrician, Mater Health Services
Dr John Gavranich, Clinical Director, Coordinated Care Stream, Ipswich Hospital
Ms Leah Hardiman, Consumer, President, Maternity Choices Australia
Dr Timothy Hong, Neonatologist, Newborn Care Unit, Gold Coast University Hospital
Ms Karen Hose, Neonatal Nurse Practitioner, Women's and Newborn Services, Royal Brisbane and Women's Hospital
Dr Arif Huq, Staff Specialist, Paediatrics and Neonatology, Bundaberg Hospital
Dr Luke Jardine, Neonatologist, Neonatal Critical Care Unit, Mater Health Services
Mrs Kathryn Kielly, Midwife, Logan Hospital; and Consumer, Hope for HIE
Dr Pieter Koorts, A/Director, Grantley Stable Neonatal Unit, Royal Brisbane and Women's Hospital
Miss Christine Latimer, Clinical Facilitator, Neonatal Unit, The Townsville Hospital
Associate Professor Helen Liley, Senior Staff Specialist, Neonatal Critical Care Unit, Mater Health Services
Mrs Hayley McGillivray, Clinical Nurse, Special Care Nursery, Hervey Bay Hospital
Ms Naoni Ngenda, Physiotherapist, Grantley Stable Neonatal Unit, Royal Brisbane and Women's Hospital
Ms Alecia Staines, Consumer, Maternity Choices Australia
Ms Cathy van den Berg, Nurse Unit Manager, Newborn Care Unit, Gold Coast University Hospital

Queensland Clinical Guidelines Team

Associate Professor Rebecca Kimble, Director
Ms Jacinta Lee, Manager
Ms Lyndel Gray, Clinical Nurse Consultant
Dr Brent Knack, Program Officer
Ms Stephanie Sutherns, Clinical Nurse Consultant
Steering Committee, Queensland Clinical Guidelines

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