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Therapeutic hypothermia in neonatal hypoxic ischemic encephalopathy

Evidence check

April 2021

Rapid evidence checks are based on a simplified review method and may not be entirely exhaustive, but aim to provide a balanced assessment of what is already known about a specific problem or issue. This brief has not been peer-reviewed and should not be a substitute for individual clinical judgement, nor is it an endorsed position of NSW Health.

Evidence check questions

1. Does the scoring system used to classify hypoxic ischaemic encephalopathy (HIE) in NSW need to be reviewed in light of emerging research?
2. Should therapeutic hypothermia (cooling) be commenced in newborns with mild HIE?
3. Should therapeutic hypothermia be commenced in newborns with diagnosis of HIE after six hours after birth?
4. Should therapeutic hypothermia be continued for >72 hours?

In brief

Hypoxic ischaemic encephalopathy (HIE) is a serious birth complication caused by impaired cerebral blood flow and oxygen delivery to the brain that affects full-term infants.[1] HIE is associated with high risk of death or early neurodevelopmental impairment.[2, 3] This is significantly decreased with the use of therapeutic hypothermia (cooling) as a standard of care.[4, 5]

Evidence from a 2013 Cochrane review of 11 randomised controlled trials (N=1,505 infants) indicates that:

- therapeutic hypothermia for 72 hours at 33.5°C is beneficial in term and late preterm newborns with HIE, reducing mortality without increasing major disability in survivors
- therapeutic hypothermia should be instituted with moderate-to-severe HIE, within six hours of birth.

No evidence was found to support therapeutic hypothermia in HIE infants born before 35 weeks.[6]

Clinical trials conducted since 2013 corroborate the Cochrane review findings.[7, 8]

Q1. Does the scoring system used to classify HIE in NSW need to be reviewed in light of emerging research?

- The modified Sarnat scoring system is a widely accepted grading system to classify HIE.[9] The current NSW policy directive on whole-body cooling in neonates suspected moderate or severe HIE recommends the use of this scoring system. No evidence was found to support a change from the Sarnat scoring system.

Table 1. Modified Sarnat scoring system for categorising encephalopathy[10]

Category	Normal	Mild encephalopathy	Moderate encephalopathy	Severe encephalopathy
Level of consciousness	Alert	Hyperalert	Lethargy	Stupor/coma
Spontaneous activity	Normal	Normal	Decreased activity	No activity
Posture	Predominantly flexed	Mild distal flexion	Arms flexed legs extended (decorticate)	Arms and legs extended (decerebrate)
Tone	Strong flexor tone in all extremities	Normal or slightly increased	Hypotonia	Flaccid
Primitive reflexes	Strong suck Complete moro	Weak suck Intact moro	Weak suck, Incomplete moro	Absent suck Absent moro
Autonomic system, any one of: **Pupils** **Heart rate** **Respirations**	 Normal 110-160bpm Regular	 Dilated Tachycardic Hyperventilation	 Constricted Bradycardia Periodic breathing	 Dilated/non-reactive Variable heart rate Apneoa

Q2. Should therapeutic hypothermia (cooling) be commenced in newborns with mild HIE?

- Infants with mild HIE are not considered for cooling in the current treatment regimens as the risk for adverse neurodevelopmental outcomes is low.[11]
- Anecdotal evidence suggests cooling therapy is increasingly offered in mild HIE. A recent survey of health practitioners in the United Kingdom indicated that they would offer therapeutic hypothermia to infants with mild HIE.[12] Further research is required to consider the safety, efficacy and long-term outcomes of therapeutic hypothermia in infants with mild HIE.[11-15]

Q3. Should therapeutic hypothermia be commenced in newborns with diagnosis of HIE after six hours after birth?

- Hypothermia initiated later than six hours (and up to 24 hours) after birth did not result in a significant reduction in death or disability compared with non-cooling.[16]

Q4. Should therapeutic hypothermia be continued for >72 hours?

- Randomised clinical trials found that longer duration cooling (120 hours), deeper cooling (32.0°C), or both, did not affect mortality rate (neonatal intensive care unit [NICU] death) [4] or reduce death or moderate or severe disability at 18 months of age [4, 17] compared with cooling at 33.5°C for 72 hours in neonates who are full-term with moderate or severe HIE.

Guidance in other jurisdictions

Guidance on the use of therapeutic hypothermia in newborns with HIE is available nationally (Queensland[18], Victoria[19-21], South Australia[22]) and internationally (New Zealand[23], Canada[24], the United Kingdom[25], the United States of America[26-28]). Generally, the guidance includes:

- Classification/Scoring systems – modified Sarnat score to classify disease
- Diagnosis – defined as the presence of intrapartum events/perinatal asphyxia, seizures and moderate to severe encephalopathy as per modified Sarnat score
- Clinical management – care occurs in a NICU and includes resuscitation, supportive care, therapeutic cooling, family involvement, continuous amplitude-integrated electroencephalography (aEEG) if available and regular neurological assessment
- Prognosis – use of magnetic resonance imaging (MRI) and formal electroencephalograph (EEG). Early prognosis of long-term outcome is difficult. Many prognostic tools are available; prognosis is best determined by using multiple modalities

Limitations

Clinical trials generally had short follow-up times and small sample sizes. There was no evidence on managing newborns at gestational age <35 weeks.

Background

The purpose of this evidence check is to inform the update of the NSW policy directive on whole-body cooling in neonates with suspected moderate or severe HIE and to support the Clinical Excellence Commission in the development of a body of work on this topic.

Methods

PubMed, Google and Google scholar were searched on 26 April 2021. Refer to Appendix 1.

Results

Table 2. Peer-reviewed sources

Source	Summary
Peer-reviewed sources	
Therapeutic hypothermia for neonatal hypoxic ischaemic encephalopathy in India (THIN study): a randomised controlled trial Aker et al. 2020[29]	• Open-label randomised controlled trial at one neonatal intensive care unit in a tertiary care centre in India. • 50 infants born at gestational age >35 weeks admitted within 5 hours after birth with predefined physiological criteria and signs of moderate/severe HIE. • The cohort was divided into two groups: standard care (n=25) or standard care plus 72 hours of hypothermia (33.5°C±0.5°C, n=25) induced by phase changing material (PCM). • Conventional MRI was available for 46 infants. It demonstrated significantly less moderate/severe abnormalities in the cooled (n=2, 9%) than in the non-cooled (n=10, 43%) infants. • There was no difference in adverse events between groups.
Hypoglycaemia and hyperglycaemia are associated with unfavourable outcome in infants with hypoxic ischaemic encephalopathy: a post hoc analysis of the CoolCap Study Basu et al. 2017[30]	• Post hoc analysis of the CoolCap Study conducted at 25 perinatal centres in the UK, the USA and New Zealand during 1999–2002. • The analysis included 234 infants at ≥36 weeks gestation with moderate-to-severe HIE who were randomised to head cooling for 72 hours starting within 6 hours of birth, or standard care with focus on death and/or severe neurodevelopmental disability at 18 months. • Two additional unfavourable outcomes hypoglycaemia (≤40mg/dL, ≤2.2mmol/L) and hyperglycaemia (>150mg/dL, >8.3mmol/L) during the first 12 hours were investigated after randomisation. • Both hypoglycaemia and hyperglycaemia were associated with unfavourable outcome at 18 months of age, **independent of HIE severity and hypothermia treatment**.
Hyperglycaemia in infants with hypoxic-ischaemic encephalopathy is associated with improved outcomes after therapeutic hypothermia:	• To investigate whether glycaemic profile is associated with multi-organ dysfunction and with response to hypothermia after perinatal HIE. • The analysis included 194 infants at ≥36 weeks' gestation with moderate-to-severe HIE who were randomised to head cooling for 72 hours starting within 6 hours of birth.

Source	Summary
Peer-reviewed sources	
a post hoc analysis of the CoolCap Study Basu et al. 2016[31]	• Early glycaemic profile in infants with moderate-to-severe HIE is associated with both the risk of multi-organ dysfunction and outcome of therapeutic hypothermia. • Hypoglycaemia, but not hyperglycaemia, was associated with more deranged multi-organ function. • In this secondary analysis of the CoolCap study, only infants with early hyperglycaemia significantly benefited from therapeutic hypothermia and had reduced risk of unfavourable outcomes (defined as death and/or severe neurodevelopmental disability at 18 months).
Hypothermia for perinatal asphyxia: trial-based quality of life at 6–7 years Campbell et al. 2018[3]	• Community study including a single parental survey 6-year to 7-year following up on surviving children from the Total Body Hypothermia for HIE (TOBY) Trial. • To assess the impact of hypothermic neural rescue at birth on health-related quality of life (HRQL) in middle childhood. • Two groups: Intensive care with cooling of the body to 33.5°C for 72 hours or intensive care alone. • Overall, 145 children (70 in the control group, 75 in the hypothermia group) whose parents consented and returned the questionnaire. • At 6–7 years, speech appeared disproportionately affected when compared with other aspects of HRQL but levels of normal emotional functioning were similar in both groups. • Non-significant differences in HRQL favouring moderate hypothermia. • Low level evidence as study used long-term survivors in a neonatal trial and was underpowered.
Effect of therapeutic hypothermia on DNA damage and neurodevelopmental outcome among term neonates with perinatal asphyxia: a randomized controlled trial Gane et al. 2013[5]	• Single blinded, randomised, controlled interventional trial, carried out at tertiary care centre in India between 2011 and 2013. • The trial was designed to investigate the effect of therapeutic hypothermia on deoxyribonucleic acid (DNA) damage and the neurodevelopmental outcome in term babies with perinatal asphyxia. DNA damage was assessed using measurement of olive tail moment (OTM), density of migrated DNA (percentage of DNA in the tail) and measurement of 8-OHdG – a biproduct of DNA oxidative damage. • Babies whose gestational age was ≥37 weeks and with any two of the following criteria: APGAR at 10 min

Source	Summary
Peer-reviewed sources	
	<5; evidence of fetal distress; assisted ventilation for at least 10 minutes after birth; and **evidence of any organ dysfunction,** were included in the study. • Two groups; newborns were randomised to therapeutic hypothermia (n=61) with cloth-covered gel packs on the side of the chest, abdomen, head and axilla to achieve target of 33–34C for 72 hours compared with normothermia (n=61). • After 72 hours, the hypothermia group showed lower olive tail moment than the control group. 8-OHdG levels increased significantly in the control group as compared to the hypothermia group. • Neurodevelopmental assessment at 12 months showed significantly low motor and mental developmental quotient in the control than hypothermia group. • Therapeutic Hypothermia reduced oxidative stress-induced DNA damage and improved neurodevelopmental outcome after 12 months.
Effect of therapeutic hypothermia on oxidative stress and outcome in term neonates with perinatal asphyxia: a randomized controlled trial Joy et al. 2013[32]	• Randomised interventional trial between 2010 and 2012 in one tertiary centre in India. • To evaluate in term babies (gestational age >37 weeks) with perinatal asphyxia, the effect of therapeutic hypothermia on oxidative stress and neurological outcome at discharge. The two measures of oxidative stress were total antioxidant status (TAS) and malondialdehyde (MDA) – a product of lipid peroxidation following free radical attack. • Two groups; newborns were randomised to therapeutic hypothermia (n=58) with cooling gel packs to a target temperature of 33–34C for 72 hours and normothermia (n=58). • Hypothermia reduced oxidative stress in term babies with perinatal asphyxia and was associated with better neurological outcome. • Babies with perinatal asphyxia who received therapeutic hypothermia had lower malondialdehyde and more total antioxidant status than the control group. • The reduction in the oxidative stress could be an important mechanism by which hypothermia works in HIE.
Pulmonary hypertension associated with hypoxic-	• Secondary analysis of two randomised trials of therapeutic hypothermia in HIE infants in the USA.

Source	Summary
Peer-reviewed sources	
ischemic encephalopathy—antecedent characteristics and comorbidities Lakshminrusimha et al. 2018[33]	• In total, 303 infants were evaluated; normothermia (n=106) versus hypothermia; 33.5° for 72 hours (n=197). • Infants were of gestational age ≥36 weeks and were admitted to the NICU at <6 hours of age, with an admitting diagnosis of acute perinatal asphyxia, neonatal depression, encephalopathy and/or fetal acidemia. • The main aim was to determine the characteristics of term infants with persistent pulmonary hypertension of the newborn (PPHN) associated with moderate or severe HIE. • The prevalence of PPHN **was not different** between infants receiving therapeutic hypothermia at 33.5°C in these two trials (44/197 = 22%) and those receiving normothermia in the induced hypothermia trial (23/106 = 22%). • Length of stay and mortality were higher in the PPHN group.
Effect of therapeutic hypothermia initiated after 6 hours of age on death or disability among newborns with hypoxic-ischemic encephalopathy Laptook et al. 2017[16]	• A randomised clinical trial conducted between 2008 and 2016 among infants at 36 weeks or later gestation with moderate or severe HIE enrolled at 6 to 24 hours after birth. • In total, 168 infants were randomly assigned to hypothermia (n=83) and non-cooling (n=85). • The main aim was to estimate the probability that hypothermia initiated at 6 to 24 hours after birth reduces the risk of death or disability at 18 months among infants with HIE. • During the intervention and rewarming, adverse events recorded in 13 hypothermia and 6 non-cooled groups and there were no group differences in organ system morbidities or need for extracorporeal membrane oxygenation. • Death or disability at 18 months of age occurred in 24.4% of hypothermic infants and 27.9% of non-cooled infants. • Hypothermia initiated at 6 to 24 hours after birth compared with non-cooling resulted in a 76% probability of any reduction in death or disability, and a 64% probability of at least 2% less death or disability at 18 to 22 months.
Multicentre study for brain/body hypothermia	• Small sample size, multicentre trial to determine blood level of high-mobility group box-1 (HMGB-1) at 24-hour

Source	Summary
Peer-reviewed sources	
for hypoxic–ischemic encephalopathy: changes in HMGB-1 Nakamura et al. 2017[34]	intervals in neonates treated with brain/body hypothermia for HIE, to evaluate the usefulness of HMGB-1 level for determining outcomes. • Fifteen neonates with HIE who underwent brain/body hypothermia (BHT (+) group) and six neonates with HIE who did not (BHT (–) group). • BHT is indicated for neonates with gestational age ≥35 weeks • Baseline HMGB-1 was significantly higher in the BHT (+) group than in the BHT (–) group. However, it significantly decreased at 24 hour intervals post intervention. • Magnetic resonance imaging (MRI) was used to determine short-term outcome. No significant differences in outcomes were detected between the two groups, nevertheless the neurological disorder (+) group had higher mean HMGB-1.

Effect of depth and duration of cooling on deaths in the NICU among neonates with hypoxic ischemic encephalopathy: a randomized clinical trial
 	
Shankaran et al. 2014[4]
	• A randomised, 2 × 2 factorial design clinical trial performed in 18 USA centres.
	• Determine if longer duration cooling (120 hours), deeper cooling (32.0°C) or both are superior to cooling at 33.5°C for 72 hours **in neonates** who are full-term with moderate or severe HIE.
	• Neonates were assigned to four hypothermia groups:
	  ○ 33.5°C for 72 hours
	  ○ 32.0°C for 72 hours
	  ○ 33.5°C for 120 hours
	  ○ 32.0°C for 120 hours
	• The adjusted risk ratio for NICU deaths for the 120 hours group versus 72 hours group was 1.37 (95% CI: 0.92-2.04) and for the 32.0°C group versus 33.5°C group was 1.24 (95% CI: 0.69-2.25).
	• Safety outcomes were similar between the 120 hours group versus 72 hours group and the 32.0°C group versus 33.5°C group, except major bleeding occurred among 1% in the 120 hours group versus 3% in the 72 hours group.
	• Among neonates who were full-term with moderate or severe HIE, longer cooling, deeper cooling or both compared with hypothermia at 33.5°C for 72 hours did not reduce NICU death.

Effect of depth and duration of cooling on death or disability at age	• Follow-up observational study to Shankaran et al 2014 to determine if cooling for 120 hours or to a

Source	Summary
Peer-reviewed sources	
18 months among neonates with hypoxic-ischemic encephalopathy Shankaran et al. 2017[17]	temperature of 32.0°C reduces death or disability at **age 18 months** in infants with HIE. • The primary outcome was death or moderate or severe disability at 18 to 22 months of age adjusted for centre and level of encephalopathy. • Among term neonates with moderate or severe HIE, cooling for longer than 72 hours, cooling to lower than 33.5°C or both did not reduce death or moderate or severe disability at 18 months of age. • The findings from this randomised controlled trial in 2014 and 2017 do not support change from the current regimen of cooling for 72 hours at 33.5°C for neonates with moderate or severe encephalopathy.

Table 2 Grey literature

Source	Summary
Grey literature sources	

Hypoxic-ischaemic encephalopathy (HIE)
Queensland Health
Published March 2016, Amended February 2018 [18]
	• Document includes:
	  ○ a checklist for therapeutic hypothermia (cooling)
	  ○ an assessment of encephalopathy severity
	  ○ A flowchart of criteria for therapeutic hypothermia
	  ○ A flowchart of HIE clinical features, investigations, and management
	• Parental considerations: involve parents in decision making, facilitate parental involvement in their baby's care, refer to local support services where required, provide written parent information on HIE, if required provide palliative and bereavement care.
	• Clinical standards for therapeutic hypothermia: care should be provided in a level 6 neonatal service which can provide mechanical ventilation, core temperature and various types of monitoring, MRI, aEEG or EEG and neurologic consultation.
	• Intrapartum events: events which may precede HIE include: a significant peripartum or intrapartum hypoxic-ischaemic event or a normal fetal heart rate pattern that changes to a sinusoidal pattern, absent baseline variability with recurrent late or variable decelerations, or bradycardia or another fetal heart rate pattern such as tachycardia with recurrent decelerations.
	• Diagnosis: suspect in babies who are depressed at birth and present with disturbed neurological function including a subnormal level of consciousness or seizures and frequently difficulty initiating and maintaining respiration and depression of tone and reflexes. 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. HIE is classified in stages: mild, moderate, and severe.
	• Clinical management: primarily supportive, with the addition of therapeutic hypothermia for neuroprotection in those babies who meet the criteria. Management includes resuscitation, observation and monitoring, supportive care (covering respiratory, cardiovascular, neurological, renal, metabolic, haematology and gastrointestinal). Infections may co-exist. Investigations include routine investigations and differential diagnosis. Care also includes allied health and neuroimaging. In moderate to severe HIE, therapeutic hypothermia provided in accordance with specific criteria and associated with significant improvement in survival.

Source	Summary
Grey literature sources	
	• Prognosis: Early prognosis of long-term outcome is difficult. Many prognostic tools are available, prognosis is best determined by using multiple modalities. • Follow up: plan discharge and follow up meetings, appropriate referrals and follow up, and considerations such as support and referral to coroner if the baby dies.

Hypoxic Ischemic Encephalopathy PPG.
South Australia Health
Published March 2013
Complete Review August 2020[22]
	• Document includes:
	  ○ Flowcharts
	  ▪ Initial Management of HIE in Referral Sites
	  ▪ Initial Management of HIE in Level 6 Neonatal Units
	  ○ Summary of practice recommendations
	  ○ Background
	• Diagnosis: Clinical seizures OR presence of signs in at least 3 of the 6 categories in the modified Sarnat staging. Assessment recorded on Encephalopathy chart
	• Principles of medical management
	  ○ cooling of neonates with moderate to severe HIE is safe and reduces the risk of death or disability at 18 to 22 months of age. Hence, infants with moderate or severe HIE should receive therapeutic hypothermia to maintain core temperature at 33-34°C.
	  ○ cooling should commence as soon as possible. There is strong evidence that cooling initiated before 6 hours of age is effective.
	  ○ Therapeutic hypothermia should be continued for 72 hours
	  ○ Resuscitation and early stabilisation are the priority
	  ○ Early consultation with a neonatologist is recommended and transfer to NICU for therapeutic hypothermia
	• Clinical management: dependant on location. See flow charts
	  ○ Passive cooling maybe recommended prior to transfer to NICU
	  ○ Therapeutic hypothermia may be considered in infants between 6 and 10 hours of age
	  ○ Support may involve intubation and ventilation, inotropes, volume replacement, renal and fluid management, aEEG and formal MRI day 4-7. Sedation may be required
	  ○ Use of tecotherm device allows for monitoring of core temperature and rewarming after 72 hours at a steady rate.
	  ○ Perform daily neurological examination

Source	Summary
Grey literature sources	
	• Prognosis – all babies receiving cooling therapy need long term follow up

Therapeutic Hypothermia in the neonate (nursing)
Royal Children's Hospital, Melbourne
Amended October 2019 [19]
	• Document includes:
	  ○ How to use Medi-Therm 111 hyer/hypothermia system
	• Key Points
	  ○ Neuroprotection in babies ≥ 35 weeks gestation and > 1.8kg with moderate to severe hypoxic ischaemic encephalopathy (HIE) is optimised by commencing therapeutic hypothermia treatment as soon as possible after resuscitation, between 1-6 hours of life.
	  ○ Whole body hypothermia must be strictly controlled and targeted to the rectal temperature range 33°C-34°C.
	  ○ Hyperthermia ≥38°C should be avoided as it adversely affects outcomes in infants with HIE.
	• Family centred Care: Explain to family the reasoning for using hypothermia and the expected length of treatment. Explain to family that their baby will feel cold for the duration of the treatment and reassure them that their baby will be kept comfortable during the treatment. Encourage bonding by allowing parents to touch their baby, do nappy changes etc.
	• Diagnosis: clinical definition using modified Sarnat Classification.
	  ○ Moderate to severe abnormal background activity on aEEG
	  ○ Consultant's discretion to commence cooling
	• Clinical Management:
	  ○ Requires continuous monitoring – observations and aEEG
	  ○ Formal EEG and MRI at 3-7 days after rewarming
	  ○ Support may include sedation, fluid restriction, close observation of skin
	• Prognosis

Encephalopathy in neonates
Safer Care Victoria
Published August 2018
Amended August 2019 [20]
	• Document includes:
	• Key Points
	  ○ Perinatal asphyxia is an important cause of neonatal encephalopathy, for which therapeutic cooling may be applicable.
	  ○ It is important to consider differential diagnoses for neonatal encephalopathy.
	  ○ Infants requiring vigorous resuscitation including an endotracheal tube and positive pressure ventilation beyond five minutes of age may require transfer to a Level 6 neonatal unit.

Source	Summary
Grey literature sources	
	○ Management includes therapeutic cooling, ventilatory support if required, fluid and blood pressure management, treatment of seizures, and other investigations for differential diagnoses. • Diagnosis: Hypoxic-ischaemic encephalopathy (HIE) is reserved for the subgroup of the term NE who have convincing evidence of peripartum or intrapartum hypoxia; ○ Apgar score of less than 5 at 5 minutes and 10 minutes ○ Fetal umbilical artery acidaemia with pH< 7.0, or base deficit ≥12 mmol/L ○ Neuroimaging evidence of acute brain injury seen on brain magnetic resonance imaging (MRI) or magnetic resonance spectroscopy (MRS) consistent with hypoxia–ischaemia ○ Presence of multisystem organ failure consistent with hypoxic–ischemic encephalopathy (HIE) ○ Exclusion of other identifiable etiologies such as trauma, coagulation disorders, infectious conditions, or genetic disorders. ○ Clinical assessment using Sarnat staging. • Clinical Management: includes resuscitation; ventilation; inotropic support fluid, electrolyte, and acid-base management; therapeutic hypothermia; seizure management. ○ MRI/MRS should be performed in infants with moderate to severe NE between days 5-14. ○ It has been suggested that cot side amplitude integrated EEG (aEEG) and/or two-channel EEG should become part of the initial evaluation and continued monitoring of infants with HIE, for seizure detection and outcome prediction. However, cot side EEG interpretation is based primarily on pattern recognition and depends on experience of the user. Caution is also raised against using the cot side aEEG or 2-channel EEG for reliable detection and treatment of neonatal seizures. Between days 4-7 a formal EEG should be done in the setting of moderate to severe NE or seizures. • Prognosis: Neurological assessment at two weeks is a good predictor of outcome. ○ Magnetic resonance imaging (MRI) and spectroscopy can provide information about cause, timing of injury and further refine the prognosis. ○ Severity of the acute encephalopathy and a standardised neurological examination (e.g. Dubowitz score - a method of clinical assessment that includes

Source	Summary
Grey literature sources	
	neurologic criteria for the infant's maturity and other physical criteria) at two weeks is predictive of outcome.

Therapeutic hypothermia for HIE: initiation in SCN
 	
Safer Care Victoria
 	
Published November 2014
Amended October 2018 [21]
	• Document includes:
	  ○ Flow chart – commencement of therapeutic hypothermia in a special care nursery in a non-tertiary hospital.
	  ○ Parent information sheet – cooling to protect babies at risk of brain damage
	• Key points:
	  ○ Therapeutic hypothermia is part of standard care for term and late preterm newborns (≥ 35 weeks) with moderate-to-severe HIE in a NICU
	  ○ Greatest neuroprotective benefit is achieved if hypothermia treatment is commenced as soon as possible after the hypoxic-ischaemic event (within six hours of birth), before the onset of seizures and secondary neuronal injury.
	  ○ Most newborns with moderate-to-severe HIE are born unexpectedly in community, non-tertiary maternity hospitals
	  ○ Hypothermia should only be commenced following referral to PIPER and discussion with neonatal consultant.
	• Diagnosis:
	  ○ Moderate or severe encephalopathy using the modified Sarnat criteria or seizures
	  ○ Evidence of perinatal hypoxia-ischemia – Apgar <5 or less at 10 minutes, ongoing active resuscitation at 10 minutes, cord pH <7.0, blood gas pH <7.0 or bases deficit ≥12 within one hour of birth.
	• Clinical management: Ensure adequate resuscitation and support for the baby, including attention to airway, breathing, circulation and glucose. Target an oxygen saturation of 91–95 per cent, an arterial pCO2 of 35–45 mmHg, a mean blood pressure of 40–50 mmHg and true blood glucose of 3–7mmol/L.
	• Prognosis: Therapeutic cooling reduces mortality and neurodevelopmental disability (cerebral palsy and cognitive impairment) at 18–24 months of age and at school age. The benefits of cooling on survival and neurodevelopment outweigh the short-term adverse effects (sinus bradycardia and thrombocytopenia).

ICU Clinical Pathway for Therapeutic Hypothermia
Treatment for neonates
	• Document includes:
	  ○ Goals and metrics
	  ○ Treatment pathway
	  ○ Guidance for the treatment of neonatal seizures

Source	Summary
Grey literature sources	

with hypoxic ischemic encephalopathy (HIE)
 	
Children's Hospital of Philadelphia
 	
Published 2018[26]
	• Key points/goals:
	  ○ Expedite arrival to tertiary facility by six hours of age
	  ○ For patients who cannot be transferred within six hours of birth, transferring facility begins passive or active cooling as soon as possible
	  ○ Standardise clinician approach to initiating therapeutic hypothermia in NICU
	• Diagnosis – Identify degree of encephalopathy using Modified Sarnat criteria & seizures, blood gas – pH ≤7 or base deficit ≥16, presence of acute perinatal event with 10 min Apgar ≤5 or active resuscitation at ≥10 minutes.
	• Clinical management: Continuous aEEG to confirm seizure activity, antiseizure meds as required, regular neurological assessment, skin care
	• Prognosis – recommend neurology follow-up, with frequency depending on presence of seizures. Recommend developmental follow-up

Hypothermia for newborns with hypoxic-ischemic encephalopathy
 	
Canadian Paediatric Society Position Statement
 	
Published June 2018
 	
Amended Nov 2020[24]
	• Document includes:
	• Key points:
	  ○ Infants ≥36 weeks GA (gestational age) with moderate-to-severe HIE who meet inclusion criteria should receive therapeutic hypothermia.
	  ○ Infants ≥35 weeks GA with moderate-to-severe HIE who meet other inclusion criteria should be considered for therapeutic hypothermia.
	  ○ Therapeutic hypothermia should not be offered for the following patients: moribund infants or infants with major congenital or genetic abnormalities for whom no further aggressive treatment is planned, infants with severe intra-uterine growth restriction or clinically significant coagulopathy, or infants with evidence of severe head trauma or intracranial bleeding.
	  ○ Community physicians caring for infants with suspected HIE for whom therapeutic hypothermia is considered should consult a neonatologist regarding initiation of passive cooling as soon as possible after birth. All infants requiring therapeutic hypothermia should be transferred to a tertiary care NICU with appropriate expertise and resources.
	  ○ Both selective head cooling and whole-body cooling is effective. Whole-body cooling is easier to set up and use, less expensive and provides access to EEG; it is

Source	Summary
Grey literature sources	
	therefore recommended for centres not currently using selective head cooling. ○ Therapeutic hypothermia should be continued for 72 hours, with a target rectal (or oesophageal) temperature of 33°C to 34°C for whole body cooling, or 34°C to 35°C for selective head cooling. Rewarming should occur over 6 to 12 hours (0.5°C every 1 to 2 hours). ○ Therapeutic hypothermia in infants younger than 35 weeks is not recommended. ○ Treatment of pain or discomfort during cooling with a low-dose opioid is recommended. ○ Treatment of seizures, despite limitations of knowledge about the side effects of antiepileptic medications, is recommended, because benefits likely outweigh the risks. • Diagnosis – ○ Cord pH ≤7.0 or base deficit ≥−16 **or** ○ pH 7.01 to 7.15 or base deficit −10 to −15.9 on cord gas or blood gas within 1 hour **and** ▪ evidence of perinatal hypoxia-ischemia – Apgar <5 or less at 10 minutes, ongoing active resuscitation at 10 minutes **and** ▪ history of acute perinatal event. ○ evidence of moderate to severe encephalopathy demonstrated by seizures or modified Sarnat scoring. • Clinical management – all infants who are depressed at birth should be assessed by careful neurological examination to see if they fulfil the above criteria. ○ Following infants should not be cooled: moribund infants or infants with major congenital or genetic abnormalities for whom no further aggressive treatment is planned; severe IUGR; clinically significant coagulopathy; severe head trauma or intracranial bleeding. ○ Evidence supporting initiating cooling after six hours of age may be beneficial is limited. Therapeutic hypothermia may still be considered after discussion with parents, always recognising the uncertainty with regards to its benefits and considering possible side effects (e.g. bleeding diathesis, hypotension, pulmonary hypertension and cardiac arrhythmias) ○ Possible side effects include sinus bradycardia, arrhythmias, anaemia, leukopenia, hypoglycaemia,

Source	Summary
Grey literature sources	
	hypokalaemia, urinary retention and coagulopathy, hypotension requiring inotropes, mild thrombocytopenia and PPHN (persistent pulmonary hypertension of the newborn). ○ MRI should be performed between day 2 and 4 • Prognosis – Long-term, multidisciplinary follow-up of survivors to assess and address neurocognitive function. ○ Cerebral palsy or severe disability occurs in more than 30% of HIE-affected newborns and is most common in infants with severe encephalopathy. ○ cognitive deficits may be prominent, even in the absence of cerebral palsy. ○ Severe visual impairment or blindness occurs in up to 25% of children after moderate or severe encephalopathy, especially in the setting of hypoglycaemia. ○ Sensorineural hearing loss, secondary to brainstem injury, affects up to 18% of survivors of moderate encephalopathy without cerebral palsy. ○ Cognitive deficits, particularly difficulties with reading, spelling and arithmetic, are seen in 30% to 50% of childhood survivors of moderate HIE. ○ Behavioural difficulties, such as hyperactivity and emotional problems, should also be considered even in survivors who do not experience motor disability. ○ Childhood epilepsy is identified in 13% of survivors.
Therapeutic hypothermia with intracorporeal temperature monitoring for hypoxic perinatal brain injury NICE Guidance Published May 2010[25]	• Document includes: ○ Intrapartum care flowchart ○ Clinical coding recommendations ○ Controlled cooling to treat babies with brain injury caused by oxygen shortage during birth (parent education) • Key points/goals: ○ Therapeutic hypothermia should be carried out in units experienced in the care of severely ill neonates, by staff who have been specifically trained. ○ Infants with a gestational age of 36 weeks or more ○ The lack of evidence for using the procedure in neonates with less severe hypoxic brain injury, and the difficulties in deciding not to use the procedure for neonates whose degree of brain injury or comorbidities

Source	Summary
Grey literature sources	

	are too severe to expect survival without severe neurological deficit.
	• Diagnosis – Hypoxic perinatal brain injury is characterised by fetal distress and is associated with acidosis. Diagnosis includes clinical examination, paired umbilical arterial and venous blood gas analysis and aEEG.
	• Clinical management
	  ○ The infant is cooled to 33°C-35°C, with the aim of preventing further neuronal loss in the days following the hypoxic injury.
	  ○ Hypothermia is usually induced by cooling the whole body with a blanket or mattress (or sometimes by cooling the head only with a purpose-made cap). Intracorporeal temperature is continuously monitored, using a rectal or nasopharyngeal thermometer, as a proxy for brain temperature.
	  ○ Treatment is started as soon as possible after diagnosis, usually within six hours of birth, and continued for approximately 72 hours. The infant is then slowly warmed to normal body temperature.
	• Prognosis: Hypoxic perinatal brain injury is caused by a decrease in the amount of oxygen supplied to an infant's brain close to the time of birth. Surviving infants may develop HIE and other organ damage, which can lead to severe, lifelong disability or death.

Hypothermia and neonatal encephalopathy
Clinical Report from Committee on Fetus and Newborn (AAP)
Published June 2014[27]
	• Document includes:
	• Key points/goals:
	  ○ Medical centres offering hypothermia should be capable of providing comprehensive clinical care, including mechanical ventilation; physiological (vital signs, temperature) and biochemical (blood gas) monitoring; neuroimaging, including MRI; seizure detection and monitoring with aEEG or EEG; neurological consultation; and a system in place for monitoring longitudinal neurodevelopmental outcome.
	  ○ Cooling infants who are born at <35 weeks gestation or those who have mild encephalopathy, cooling for longer than 72 hours, cooling at a temperature lower than that used in published clinical trials and the use of adjuvant therapies should only be performed in a research setting and with informed parental consent.
	• Diagnosis/ eligibility criteria:

Source	Summary
Grey literature sources	
	○ a pH of ≤7.0 or a base deficit of ≥16mmol/L in a sample of umbilical cord blood or blood obtained during the first hour after birth ○ history of an acute perinatal event, a 10-minute Apgar score of <5, or assisted ventilation initiated at birth and continued for at least 10 minutes ○ a neurologic examination demonstrating moderate to severe encephalopathy is essential. • Clinical management • Prognosis: therapeutic cooling led to a reduction in death or major neurodevelopmental disability to 18 months of age for 25% of treated infants overall; 32% of infants who had moderate encephalopathy and 18% of those who had severe encephalopathy.
Neonatal Encephalopathy Consensus Statement from the Newborn Clinical Network New Zealand Clinical Network Last published October 2019[23]	• Document includes: • Key points/goals: ○ This consensus statement is intended for use by secondary care practitioners involved in the care of newborns at risk of neonatal encephalopathy. • Diagnosis/eligibility criteria: ○ Moderate to severe hypoxic encephalopathy in term infants determined using a simplified Sarnat classification. ○ Cooling with mild HIE has not undergone rigorous assessment (situation is evolving) ○ Supported by aEEG findings, including abnormal baseline, discontinuity and presence of seizures. ○ >36 weeks and >1,800g • Clinical management ○ Commence before six hours of life and continue for 72 hours. ○ Monitor input and output, blood gases, electrolytes, creatinine. ○ Inotropes and volume expansion to be used cautiously. ○ aEEG monitoring with prompt treatment of seizures. ○ Opiate infusion is indicated to provide comfort during cooling. ○ Serial clinical neurological assessments ○ Supportive care • Prognosis/follow up ○ MRI at 48-96 hours will show acute changes but may not be possible due to cooling.

Source	Summary
Grey literature sources	
	○ Convalescent formal EEG performed at approximately 7 days will provide useful prognostic information. ○ Infants who have had moderate to severe neonatal encephalopathy should undergo a structured follow-up process, which should be discussed with parents, preferably at a discharge planning meeting. ○ For all infants who are cooled, follow up should be performed and a neurological examination should be done at (a minimum of) 12 months of age, either by the paediatrician who provided care in the neonatal period or the paediatrician providing care at 12 months of age. ○ Dependent on the clinical state and consultant decision these infants should have a psychometric assessment at 18-24 months of age, in the Child Development Unit.
Therapeutic hypothermia in neonates – recommendations of the neonatal encephalopathy task force Academic Medical Center Patient Safety Organization (AMC PSO) 2016[28]	• Document includes: ○ Eligibility criteria flowchart ▪ Indicated ▪ Should be considered • Key points/goals: ○ Potentially eligible neonates should be examined as soon as possible. ○ If unsure of eligibility for therapeutic cooling repeat the examination within the first hour to evaluate the evolution of neonatal encephalopathy • Diagnosis/eligibility criteria: ○ ≥34 weeks and ○ concern for encephalopathy or seizures and one of the following: sentinel event before delivery, such as uterine rupture, profound bradycardia or cord prolapse; prolonged resuscitation; acidosis – pH <7.1 from cord gas or blood gas within 60 minutes of birth; abnormal base excess - ≤10mEq/L from cord gas or blood gas within 60 minutes of birth. ○ Exclusion: <34 weeks; <1750g; severe congenital abnormalities/genetic syndromes; established metabolic disorders; major intracranial haemorrhage; overwhelming sepsis; uncorrectable, clinically relevant coagulopathy • Clinical management ○ Passive cooling and supportive care if waiting for transfer to NICU.

Source	Summary
Grey literature sources	
	○ NICU – cool to 33.5 °C ± 1 °C, vascular access, neurological consult/exam, aEEG or formal EEG, fluid and acidosis management, adequate sedation • Prognosis/follow up – MRI as soon as clinically stable.

Appendix

PubMed search terms: (Neonatal Hypoxic Ischemic Encephalopathy AND ((clinical trial [Filter]) AND (2013:2021[pdat]))) AND (therapeutic hypothermia AND ((clinical trial [Filter]) AND (2013:2021[pdat]))) Filters: Clinical Trial

(("infant, newborn"[MeSH Terms] OR ("infant"[All Fields] AND "newborn"[All Fields]) OR "newborn infant"[All Fields] OR "neonatal"[All Fields] OR "neonate"[All Fields] OR "neonates"[All Fields] OR "neonatality"[All Fields] OR "neonatal"[All Fields] OR "neonate s"[All Fields]) AND ("hypoxic ischaemic encephalopathy"[All Fields] OR "hypoxia ischemia, brain"[MeSH Terms] OR ("hypoxia ischemia"[All Fields] AND "brain"[All Fields]) OR "brain hypoxia-ischemia"[All Fields] OR ("hypoxic"[All Fields] AND "ischemic"[All Fields] AND "encephalopathy"[All Fields]) OR "hypoxic ischemic encephalopathy"[All Fields]) AND ("clinical trial"[Publication Type] AND 2013/01/01:2021/12/31[Date - Publication]) AND (("hypothermia, induced"[MeSH Terms] OR ("hypothermia"[All Fields] AND "induced"[All Fields]) OR "induced hypothermia"[All Fields] OR ("therapeutic"[All Fields] AND "hypothermia"[All Fields]) OR "therapeutic hypothermia"[All Fields]) AND ("clinical trial"[Publication Type] AND 2013/01/01:2021/12/31[Date - Publication]))) AND (clinical trial [Filter])

Grey literature

National and international guidelines, government reports and other relevant documents were searched. Google and Google scholar were searched, as well as organisational websites (such as AAP and NICE). Terms such as ‘neonatal hypoxic ischemic encephalopathy’ ‘therapeutic cooling’ and ‘hypoxic ischemic encephalopathy’ were used.

Inclusion and exclusion criteria

Inclusion	Exclusion

Population
• Newborns ≥32 weeks, with a potential diagnosis of neonatal HIE, born in hospital.
 	
Intervention
	• Newborns born outside of a hospital, care during transport/retrieval
	• Newborns <32 weeks gestation
	• Major congenital abnormalities, including:
	  ○ suspected neuromuscular disorders
	  ○ suspected chromosomal abnormalities
	  ○ life-threatening abnormalities of the cardiovascular or respiratory systems
	• Uncontrolled pulmonary hypertension
	• Critical bleeding or coagulopathy
	• Moribund or “in extremis”

Inclusion	Exclusion
• Therapeutic cooling (whole body or selective head cooling), including active and passive methods initiated after birth before 12 hours of life **Outcomes** • Death and long-term neurodevelopmental disability, adverse effects of cooling, early indicators of neurodevelopmental outcome **Setting** • Studies from clinical trials and clinical registries • English language **Timeframe** • Published 2013 to current	• Standard care • Combined drug treatment with therapeutic cooling • Observational studies, retrospective cohort studies with historical controls

References

1. Allen KA, Brandon DH. Hypoxic ischemic encephalopathy: pathophysiology and experimental treatments. Newborn and Infant Nursing Reviews. 2011 2011/09/01/;11(3):125-33. Available from: https://www.sciencedirect.com/science/article/pii/S1527336911001000 DOI: https://doi.org/10.1053/j.nainr.2011.07.004
2. Tagin MA, Woolcott CG, Vincer MJ, et al. Hypothermia for neonatal HIE: an updated systematic review and meta-analysis. Arch Pediatr Adolesc Med. 2012;166(6):558-66. Available from: https://pubmed.ncbi.nlm.nih.gov/22312166/ DOI: 10.1001/archpediatrics.2011.1772
3. Campbell H, Eddama O, Azzopardi D, et al. Hypothermia for perinatal asphyxia: trial-based quality of life at 6-7 years. Arch Dis Child Fetal Neonatal Ed. 2017;103(7):654-9. Available from: https://adc.bmj.com/content/103/7/654 DOI: 10.1136/archdischild-2017-313733
4. Shankaran S, Laptook AR, Pappas A, et al. Effect of depth and duration of cooling on deaths in the NICU among neonates with hypoxic ischemic encephalopathy: a randomized clinical trial. JAMA. 2014;312(24):2629-39. Available from: https://jamanetwork.com/journals/jama/fullarticle/2084890 DOI: 10.1001/jama.2014.16058
5. Gane BD, Bhat V, Rao R, et al. Effect of therapeutic hypothermia on DNA damage and neurodevelopmental outcome among term neonates with perinatal asphyxia: a randomized controlled rrial. Journal of Tropical Pediatrics. 2014;60(2):134-40. Available from: https://academic.oup.com/tropej/article/60/2/134/1659395 DOI: 10.1093/tropej/fmt098
6. Jacobs SE, Berg M, Hunt R, et al. Cooling for newborns with with hypoxic ischaemic encephalopathy. Cochrane Database of Systematic Reviews. 2013. Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD003311.pub3/full DOI: https://doi.org/10.1002/14651858.CD003311.pub3
7. Abate BB, Bimerew M, Gebremichael B, et al. Effects of therapeutic hypothermia on death among asphyxiated neonates with hypoxic-ischemic encephalopathy: a systematic review and meta-analysis of randomized control trials. PLoS ONE. 2021 2021/02/25;16(2). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7906350/ DOI: 10.1371/journal.pone.0247229
8. Rao R, Trivedi S, Vesoulis Z, et al. Safety and short-term outcomes of therapeutic hypothermia in preterm neonates 34-35 weeks gestational age with hypoxic-ischemic encephalopathy. J Pediatr. 2017 Apr;183:37-42. Available from: https://pubmed.ncbi.nlm.nih.gov/27979578/ DOI: 10.1016/j.jpeds.2016.11.019
9. Wachtel EV, Hendricks-Muñoz KD. Current management of the infant who presents with neonatal encephalopathy. Current Problems in Pediatric and Adolescent Health Care. 2011;41(5):132-53. Available from: https://www.sciencedirect.com/science/article/pii/S1538544210002348 DOI: 10.1016/j.cppeds.2010.12.002
10. Chalak LF, Nguyen KA, Prempunpong C, et al. Prospective research in infants with mild encephalopathy identified in the first six hours of life: neurodevelopmental outcomes at 18-22 months. Pediatr Res. 2018 Dec;84(6):861-8. Available from: https://www.ncbi.nlm.nih.gov/pubmed/30250303 DOI: 10.1038/s41390-018-0174-x
11. El-Dib M, Inder TE, Chalak LF, et al. Should therapeutic hypothermia be offered to babies with mild neonatal encephalopathy in the first 6 h after birth? Pediatr Res. 2019 Mar;85(4):442-8. Available from: https://www.nature.com/articles/s41390-019-0291-1.pdf DOI: 10.1038/s41390-019-0291-1
12. Oliveira V, Singhvi DP, Montaldo P, et al. Therapeutic hypothermia in mild neonatal encephalopathy: a national survey of practice in the UK. Arch Dis Child Fetal Neonatal Ed. 2018 Jul;103(4):F388-f90. Available from: https://spiral.imperial.ac.uk:8443/bitstream/10044/1/51194/9/MildHIE_UKSurvey_Revised_Clean.pdf DOI: 10.1136/archdischild-2017-313320

13. Kumar V, Singla M, Thayyil S. Cooling in mild encephalopathy: costs and perils of therapeutic creep. Seminars in fetal & neonatal medicine. 2021 2021/04/09:101244. Available from: https://www.ncbi.nlm.nih.gov/pubmed/33849797 DOI: 10.1016/j.siny.2021.101244
14. Prempunpong C, Chalak LF, Garfinkle J, et al. Prospective research on infants with mild encephalopathy: the PRIME study. Journal of Perinatology. 2018 Jan 2018

2020-08-25;38(1):80-5. Available from: https://www.nature.com/articles/jp2017164 DOI: 10.1038/jp.2017.164
15. Kariholu U, Montaldo P, Markati T, et al. Therapeutic hypothermia for mild neonatal encephalopathy: a systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed. 2020 Mar;105(2):225-8. Available from: https://spiral.imperial.ac.uk:8443/bitstream/10044/1/66596/2/Mild%20HIE%20SR%20Accepted%20Version%2029.11.2018.pdf DOI: 10.1136/archdischild-2018-315711
16. Laptook AR, Shankaran S, Tyson JE, et al. Effect of therapeutic hypothermia initiated after 6 hours of age on death or disability among newborns with hypoxic-ischemic encephalopathy: a randomized clinical trial. JAMA. 2017 Oct 24;318(16):1550-60. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29067428 DOI: 10.1001/jama.2017.14972
17. Shankaran S, Pappas A, McDonald SA, et al. Effect of depth and duration of cooling on death or disability at age 18 months among neonates With hypoxic-ischemic encephalopathy: a randomized clinical trial. JAMA. 2017;318(1):57-76. Available from: https://jamanetwork.com/journals/jama/fullarticle/2635631 DOI: 10.1001/jama.2017.7218
18. Clinical Excellence Queensland. Queensland Clinical Guidelines: Hypoxic-ischaemic encephalopathy (HIE) [Internet]. Queensland: Clinical Excellence Queensland; 2018 [cited April 2021]. Available from: https://www.health.qld.gov.au/__data/assets/pdf_file/0014/140162/g-hie.pdf
19. The Royal Children's Hospital Melbourne. Therapeutic hypothermia in the neonate Melbourne: The Royal Children's Hospital; 2019 [cited April 2021]. Available from: https://www.rch.org.au/rchcpg/hospital_clinical_guideline_index/Therapeutic_hypothermia_in_the_neonate/
20. Safer Care Victoria. Encephalopathy in neonates [Internet]. Victoria: Safer Care; 2019 [cited April 2021]. Available from: https://www.bettersafercare.vic.gov.au/clinical-guidance/neonatal/encephalopathy-in-neonates
21. Safer Care Victoria. Therapeutic hypothermia for hypoxic ischaemic encephalopathy: initiation in special care nurseries [Internet]. Victoria: Safer Care; 2018 [cited April 2021]. Available from: https://www.bettersafercare.vic.gov.au/clinical-guidance/neonatal/therapeutic-hypothermia-for-hypoxic-ischaemic-encephalopathy-initiation-in-special-care-nurseries#
22. SA Maternal Neonatal and Gynaecology Community of Practice. Hypoxic ischaemic encephalopathy (including neonatal hypothermic neuroprotection) [Internet]. South Australia: SA Health; 2020 [cited April 2021]. Available from: https://www.sahealth.sa.gov.au/wps/wcm/connect/public+content/sa+health+internet/resources/policies/hypoxic+ischaemic+encephalopathy+including+neonatal+hypothermic+neuroprotection+-+sa+perinatal+practice+guidelines
23. Newborn Clinical Network. Neonatal Encephalopathy Consensus Statement from the Newborn Clinical Network [Internet]. New Zealand: Newborn Clinical Network; 2019 [cited April 2021]. Available from: https://www.starship.org.nz/guidelines/neonatal-encephalopathy-consensus-statement-from-the-newborn-clinical/
24. Lemrye B, Chau V. Hypothermia for newborns with hypoxic-ischemic encephalopathy. Paediatrics & Child Health. 2018:285–91 Available from: https://academic.oup.com/pch/article/23/4/285/5036427 DOI: 10.1093/pch/pxy028
25. National Institute for Health and Care Excellence (NICE). Therapeutic hypothermia with intracorporeal temperature monitoring for hypoxic perinatal brain injury 2018 [Internet]. United

Kingdom: NICE; 2018 [cited April 2021]. Available from: https://www.nice.org.uk/guidance/ipg347/resources/therapeutic-hypothermia-with-intracorporeal-temperature-monitoring-for-hypoxic-perinatal-brain-injury-pdf-1899867578267077

26. Flibotte J, Dysart K, Stoller J, et al. Clinical pathway for therapeutic hypothermia treatment for neonates with hypoxic ischemic encephalopathy (HIE). Philadelphia: Children's Hospital of Philadelphia; 2021 [cited April 2021]. Available from: https://www.chop.edu/clinical-pathway/therapeutic-hypothermia-hypoxic-ischemic-encephalopathy-hie-clinical-pathway
27. American Academy of Pediatrics. Hypothermia and neonatal encephalopathy Paediatrics. 2014;133:1146-50. Available from: https://publications.aap.org/pediatrics/article/133/6/1146/76110/Hypothermia-and-Neonatal-Encephalopathy?autologincheck=redirected DOI: https://doi.org/10.1542/peds.2014-0899
28. Academic Medical Centre Patient Safety Organization. Therapeutic hypothermia in neonates: recommendations of the Neonatal Encephalopathy Task Force 2016 [Internet]. Boston, MA: Academic Medical Centre; 2016 [cited April 2021]. Available from: file:///C:/Users/60129051/Downloads/crico_neonates.pdf
29. Aker K SR, Eikenes L, Martinez-Biarge M, Nakken I. Håberg AK, Gibikote S, Thomas N,. Therapeutic hypothermia for neonatal hypoxic-ischaemic encephalopathy in India (THIN study): a randomised controlled trial. Arch Dis Child Fetal Neonatal Ed. 2020 Jul;105(4):405-11. Available from: https://pubmed.ncbi.nlm.nih.gov/31662328/ DOI: 10.1136/archdischild-2019-317311
30. Basu SK, Salemi JL, Gunn AJ, et al. Hyperglycaemia in infants with hypoxic–ischaemic encephalopathy is associated with improved outcomes after therapeutic hypothermia: a post hoc analysis of the CoolCap Study. Arch Dis Child Fetal Neonatal Ed. 2017;102(4):F299-F306. Available from: https://fn.bmj.com/content/fetalneonatal/102/4/F299.full.pdf DOI: 10.1136/archdischild-2016-311385
31. Basu SK KJ, Guffey D, Minard CG, Guillet R, Gunn AJ. Hypoglycaemia and hyperglycaemia are associated with unfavourable outcome in infants with hypoxic ischaemic encephalopathy: a post hoc analysis of the CoolCap Study. Arch Dis Child Fetal Neonatal Ed. 2016;101:F149-F55. Available from: https://fn.bmj.com/content/101/2/F149.info DOI: 10.1136/archdischild-2015-308733
32. Joy R, Pournami F, Bethou A, et al. Effect of therapeutic hypothermia on oxidative stress and outcome in term neonates with perinatal asphyxia: a randomized controlled trial. 2013;59(1):17-22. Available from: https://academic.oup.com/tropej/article/59/1/17/1733831 DOI: doi:10.1093/tropej/fms036
33. Lakshminrusimha S, Shankaran S, Laptook A, et al. Pulmonary hypertension associated with hypoxic ischemic encephalopathy - antecedent characteristics and comorbidities. Journal of Pediatrics. 2018 (196):45-51. Available from: https://pubmed.ncbi.nlm.nih.gov/29502880/ DOI: 10.1016/j.jpeds.2017.12.055
34. Nakamura T, Asanuma H, Kusuda S, et al. Multicenter study for brain/body hypothermia for hypoxic–ischemic encephalopathy: changes in HMGB-1. Paediatrics International. 2017 (59):1074-109. Available from: https://onlinelibrary.wiley.com/doi/10.1111/ped.13377 DOI: 10.1111/ped.13377

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