Policy

Clinical Guideline

South Australian Perinatal Practice Guidelines – Hypoxic Ischaemic Encephalopathy including Neonatal Hypothermic Neuroprotection

Policy developed by: SA Maternal & Neonatal Clinical Network
Approved SA Health Safety & Quality Strategic Governance Committee on:
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Summary Guidelines for the management of the neonate with hypoxic ischaemic encephalopathy including neonatal hypothermic neuroprotection

Keywords hie, hypoxic ischaemic encephalopathy, neonatal hypothermic neuroprotection, perinatal asphyxia, hypercarbia, neonatal encephalopathy, Perinatal Practice Guidelines, clinical guideline

Policy history
Is this a new policy? **Y**
Does this policy amend or update an existing policy? **N**
Does this policy replace an existing policy? **N**
If so, which policies?

Applies to
All SA Health Portfolio
All Department for Health and Ageing Divisions
All Health Networks
CALHN, SALHN, NALHN, CHSALHN, WCHN, SAAS
Other

Staff impact All Clinical, Medical, Nursing, Allied Health, Emergency, Dental, Mental Health, Pathology

PDS reference CG118

Version control and change history

Version	Date from	Date to	Amendment
1.0	23/09/2013	Current	Original version

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South Australian Perinatal Practice Guidelines

hypoxic ischaemic encephalopathy including neonatal hypothermic neuroprotection

Note

This guideline provides advice of a general nature. This statewide guideline has been prepared to promote and facilitate standardisation and consistency of practice, using a multidisciplinary approach. The guideline is based on a review of published evidence and expert opinion.

Information in this statewide guideline is current at the time of publication.

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Health practitioners in the South Australian public health sector are expected to review specific details of each patient and professionally assess the applicability of the relevant guideline to that clinical situation.

If for good clinical reasons, a decision is made to depart from the guideline, the responsible clinician must document in the patient's medical record, the decision made, by whom, and detailed reasons for the departure from the guideline.

This statewide guideline does not address all the elements of clinical practice and assumes that the individual clinicians are responsible for discussing care with consumers in an environment that is culturally appropriate and which enables respectful confidential discussion. This includes:

- The use of interpreter services where necessary,
- Advising consumers of their choice and ensuring informed consent is obtained,
- Providing care within scope of practice, meeting all legislative requirements and maintaining standards of professional conduct, and
- Documenting all care in accordance with mandatory and local requirements

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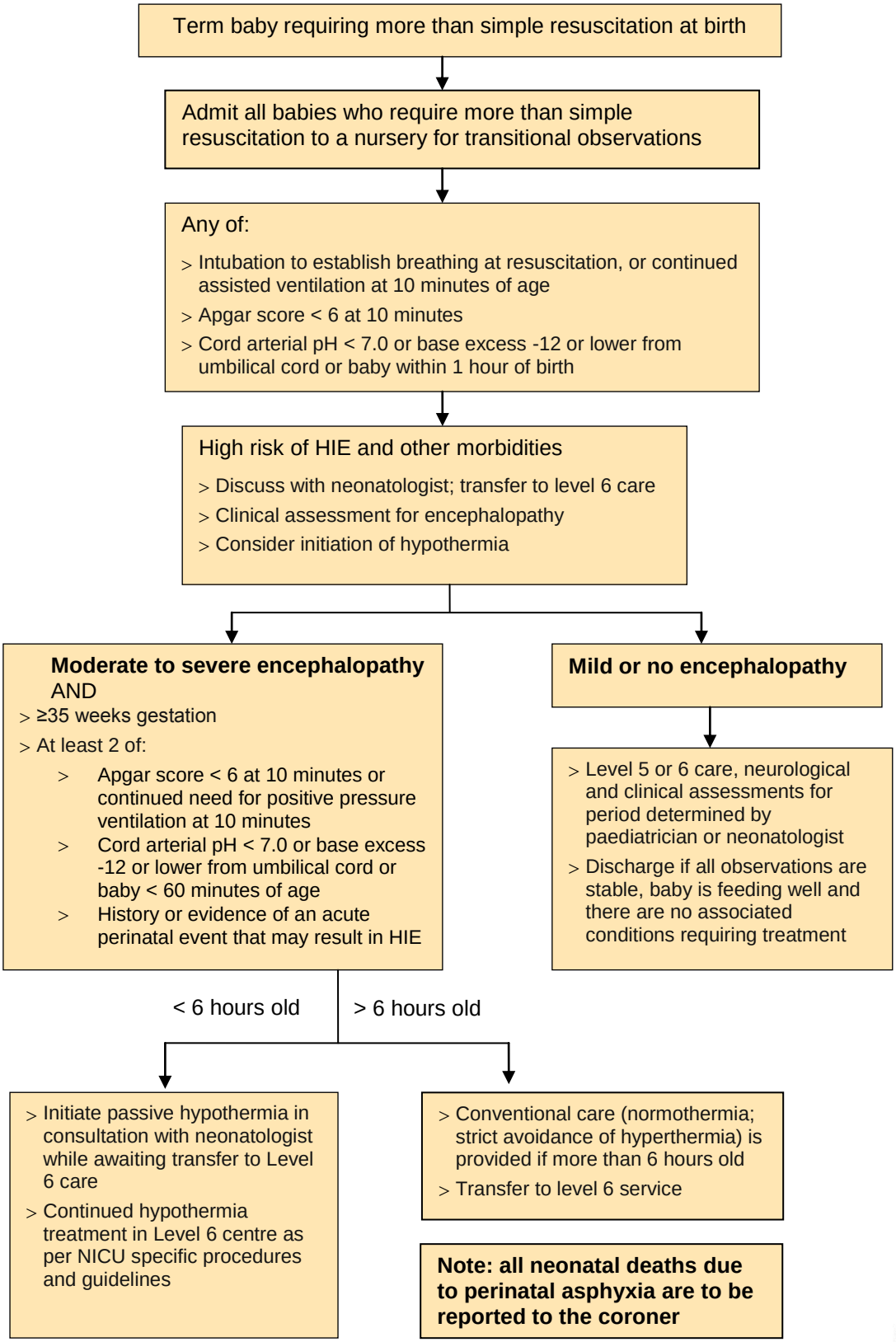
Flow chart for management of perinatal asphyxia, HIE and hypothermic neuroprotection



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Background

- **Neonatal encephalopathy** describes central nervous system dysfunction in the newborn period without implying the specific pathophysiology[1,2]
- The differential diagnosis of neonatal encephalopathy includes:
    - Hypoxic-ischaemic encephalopathy (HIE)
    - Infection
    - Perinatal stroke
    - Intracranial haemorrhage
    - Congenital brain malformations
    - Inborn errors of metabolism
    - Genetic syndromes
    - Neuromuscular disorders
    - Drug effects

This guideline will focus on the management of Hypoxic Ischaemic Encephalopathy (HIE) and not the other causes of neonatal encephalopathy

The differential diagnosis of neonatal encephalopathy should be considered in all cases of HIE

Hypoxic ischaemic encephalopathy

- Hypoxic-ischaemic encephalopathy refers to the acute clinical syndrome seen in babies following an acute severe hypoxic-ischaemic (asphyxial) event which is typically perinatal in timing. Such asphyxial events are usually noted clinically because of a sentinel obstetric event (e.g. placental abruption, cord accident, uterine rupture, amniotic fluid embolism etc.) and / or because of the development of adverse features on fetal heart rate monitoring (typically an acute sustained bradycardia or the development of reduced variability with deep variable or late decelerations)
- In developed countries, HIE occurs in 1 to 2 per 1,000 deliveries at term[3]
- Globally, 10 – 60% of affected babies die and at least 25% of survivors have long term neurodevelopmental sequelae[4]
- Studies have shown that following a reversible global hypoxic-ischaemic insult, neuronal death occurs in two phases[5,6,7]
    - **primary neuronal death** related to cellular hypoxia (primary energy failure)
    - **secondary or delayed neuronal death** related to apoptotic processes (secondary energy failure) occurring after a latent period where oxidative metabolism has normalised
- The delayed phase is associated with encephalopathy and increased seizure activity; it accounts for a significant proportion of the final cell loss even after very severe insults[8]
- These studies have shown that normal cerebral oxidative metabolism returns soon after the episode of injury, but thereafter there is a progression to secondary energy failure, the

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degree of which predicts outcome (mortality and neurodevelopmental outcome at both one and four years of age). [9,10] This latent phase presents a therapeutic window of opportunity.

- The Sarnat and Sarnat[11] classification process identifies 3 levels or grades of severity of HIE; these grades, their clinical characteristics and their prognostic significance are as follows:-

    - Grade 1 (mild) HIE, characterised by hyperalertness, active tendon reflexes, mydriasis, jitteriness but no seizures; the majority of such babies have a normal outcome
    - Grade 2 (moderate) HIE, characterised by lethargy, poor feeding, hypotonia, decreased primitive reflexes, miosis and seizures; such babies have a 25-45 % risk of death or significant disability
    - Grade 3 (severe) HIE, characterised by stupor / coma, irregular respirations, marked hypotonia with intermittent decorticate posturing and with absent primitive reflexes; such babies have a > 90 % risk of death or significant disability

Neonatal hypothermic neuroprotection

Introduction

- The following guideline is an approach to patient selection and management with neonatal hypothermic neuroprotection. Because many babies who would benefit from hypothermic neuroprotection are born outside of a tertiary (Level 6) unit, this guideline encourages early consultation regarding the possible initiation of hypothermic neuroprotection in outborn settings, pending retrieval to a tertiary (Level 6) service at the Flinders Medical Centre (FMC) or Women's and Children's Hospital (WCH)

Therapeutic hypothermia

- Evidence from a systematic review of 11 randomised controlled trials involving 1505 neonates demonstrates that therapeutic hypothermia is safe and beneficial in term and late preterm newborns (≥ 35 weeks gestation) with hypoxic ischaemic encephalopathy.[8] Therapeutic hypothermia reduces combined death or major neurodevelopmental disability to 18 months of age (RR 0.75, 95% CI 0.68 to 0.83, NNT 7, 95% CI 5 to 10), mortality (RR 0.75, 95% CI 0.64 to 0.88, NNT 11, 95% CI 8 to 25), and neurodevelopmental disability in survivors (RR 0.77, 95% CI 0.63 to 0.94, NNTB 8, 95% CI 5 to 14).[8] These benefits have been shown to exist whether hypothermia is commenced at the birth hospital or a tertiary centre, without any increase in adverse effects.[12] In a follow up study of childhood outcomes following hypothermia for Neonatal Encephalopathy, hypothermia resulted in fewer deaths without an increase in the rate of severe disability in children at 6-7 years of age[13]
- Thus, current evidence supports hypothermia being instituted in term and late preterm newborns with moderate to severe hypoxic ischaemic encephalopathy if identified before 6 hours of age[8]
- Therapeutic hypothermia aims to lower the temperature of the vulnerable brain structures, particularly the basal ganglia, to a temperature of 33-34°C[8]

General principles of hypothermic neuroprotection

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- **In outborn settings, early consultation is strongly recommended where a baby is at risk of HIE or has an encephalopathy of any presumed cause, in order that therapy can be initiated in a timely manner**
- Hypothermic neuroprotection is an adjunct therapy and should only be considered once the neonate has been resuscitated and stabilised
- Hypothermia makes vascular access more difficult; hence early attention to vascular access (arterial and venous) in neonates who are likely to be cooled is prudent
- Cooling should be initiated as early as practicable, but within 6 hours of birth
- The target temperature for hypothermic neuroprotection is a core temperature of 33-34°C (measured with an oesophageal or deep rectal probe); this is maintained for 72 hours, with subsequent rewarming over the next 6-12 hours
- Hypothermic neuroprotection should only be managed in a Level 6 facility, though the process may be initiated in an outborn and/or retrieval setting
- Inadvertent hyperthermia in the context of HIE accentuates injury; accordingly, hyperthermia in this setting is to be avoided
- Sedation should be considered if the neonate is shivering or appears uncomfortable; note also that sedation may reduce the need for active cooling (it may also require provision of respiratory support)

General principles of supportive therapy in babies with suspected perinatal asphyxia at risk of HIE

Resuscitation

- Appropriate and timely resuscitation is required to prevent ongoing hypoxia, hypercarbia and acidosis. This may prevent or reduce the clinical severity of HIE (link to neonatal resuscitation)
- Cord blood gases should be measured if possible in every resuscitated neonate as the most objective way to assess the baby's condition just before birth[14] (ARC: neonatal guidelines for further information see website www.resus.org.au/policy/guidelines)
    - Collect umbilical cord ABG from a clamped cord (ideally arterial) as soon as possible after delivery
    - Blood samples taken for acid base status remain stable in a plastic syringe for up to 30 minutes before analysis[15]
    - A blood gas collected within 1 hour of birth can also be used as a guide to intrapartum hypoxic-ischaemic stress

Admission to a nursery

- Babies who require more than simple resuscitation should receive monitoring and a medical review in a nursery setting
- Paediatrician or neonatologist advice should be requested
- Perinatal asphyxia may result in morbidities other than HIE. Monitor for respiratory distress, hypotension due to myocardial ischaemia, renal failure, hypoglycaemia, gut compromise, liver damage, and vascular endothelial injury causing DIC and bleeding
- Consideration should be given also to treatable causes of asphyxia such as anaemia,

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hypovolaemia and sepsis, and to conditions that may mimic asphyxia, in particular sepsis

> Avoid hyperthermia; use caution if care is in an incubator, or if oxygen is being delivered in a head box. Intranasal oxygen with flow adjusted to achieve desired saturation targets is probably a better strategy than head box for oxygen administration in this setting

Inter hospital transfer

> Any neonate recognised to be at high risk of HIE, or where HIE is considered a possible diagnosis must be considered for therapeutic hypothermia and transfer to a Level 6 neonatal unit

> Early consultation with a Neonatologist is recommended. Management and discussions can be facilitated by calling MedSTAR - call 13STAR (13 78 27), select “option 1”

Stabilisation of babies post-resuscitation and initial management where there is a risk of or diagnosed HIE

Immediate requirements for airway, ventilation and circulatory support are assessed and managed

> Intubate and ventilate if there are ineffective spontaneous breaths, desaturation despite oxygen, respiratory failure on blood gases, obtundation, or early seizures

> Volume replacement is considered where there is poor perfusion, hypotension or suspected blood loss

Assess and manage immediate abnormalities of plasma glucose and acid-base

> Correct PGLs of < 3.5 with a 10 % glucose bolus and subsequent 10 % glucose infusion.

> Cerebral glucose utilisation may be increased with seizures

> If correction of metabolic acidosis with bicarbonate is considered necessary, do this slowly

Respiratory

> Monitor oxygen saturations with a pre-ductal target of 90 – 95 %

> In ventilated babies maintain pCO_2 at 35-45 where possible. Many babies with HIE will spontaneously hyperventilate

Cardiac

> Attach cardiac monitoring

> Monitor non-invasive blood pressure where arterial access is not available. Normal mean arterial BP should be > 40. Pending arterial line placement,15 minutely Doppler measurement must be recorded

> A baseline bradycardia (80 – 100) is usual with hypothermia, therefore adjust the low alarm to 80 bpm

> Hypotension is a common consequence of myocardial ischaemia

> If hypovolaemia is suspected give 10–20 mL/kg of sodium chloride 0.9 %.Inotrope therapy may also be necessary

Fluids and electrolytes

> Insert a nasogastric tube and keep this on free drainage. Do not feed because of risks of gu

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ischaemia and airway compromise

- Insert an IV
- Restrict fluids to 30-40 mL/kg/day
- Monitor PGLs and maintain these >3.5 mmol/L
- Fluid restriction is essential because of the risk of inappropriate anti diuretic hormone secretion and renal failure
- The prescribed infusion rate gives approx. 3 mg/kg/min of 10 % glucose. Higher glucose concentrations may be required to avoid hypoglycaemia
- Monitor urine output via weighed nappies
- Take baseline electrolytes and ionised calcium

Neurological

- A doctor should perform a neurological examination to determine the presence and severity of HIE based on the clinical criteria in the Table 1 below, and this should be repeated periodically (4-6 hourly)
- Treat all clinically evident seizures with phenobarbitone. Commence at 20 mg/kg/dose repeated up to 60 mg/kg (total) over the first 24 hours
- Seizures due to HIE are often refractory to treatment
- Further management of seizures is to be discussed with the Neonatal Consultant responsible. Treatment with phenytoin (Dilantin®) or a benzodiazepine may be considered
- Seizures may interfere with ventilation and circulation, and may cause hypermetabolic cell death

Sepsis

- Take a blood culture and commence penicillin and gentamicin if there is a possibility of sepsis

Skin integrity

- The sedated or obtunded infant is prone to problems with skin integrity. Change position to reduce pressure
- Make sure that no ice packs are used and that the infant is not lying on wet sheets

Hypothermic neuroprotection

- Institute hypothermia if less than 6 hours old according to the following protocol
- For babies who are not being treated with hypothermia because they have a mild encephalopathy, or have moderate / severe encephalopathy but are > 6 hours old, it is essential to avoid hyperthermia

Inclusion criteria for neonatal hypothermic neuroprotection

Term or near term (≥ 35 weeks gestation) neonates with a perinatal event, need for resuscitation and acidosis as defined below; consider early transfer to a level 6 service even in the absence of obvious encephalopathy

Call MedSTAR Kids – 13STAR (13 78 27) and select “option 1”

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For hypothermia treatment, baby must meet **all** of the following criteria:

- Greater than or equal to (≥) 35 weeks gestation
- Less than 6 hours of age
- Evidence of asphyxia as defined by the presence of at least 2 of the following:-
  - Apgar score < 6 at 10 minutes or continued need for positive pressure ventilation at 10 minutes
  - History or evidence of an acute perinatal event that may result in HIE (cord prolapse, placental abruption, ruptured uterus, ruptured vasa praevia, severe fetal bradycardia etc)
  - pH less than 7.00 **OR** base excess < -12 mmol/L on cord or early neonatal blood gas analysis (< 60 minutes of age)
- The presence of moderate / severe encephalopathy, based on the modified Sarnat classification is defined as:

  Clinical seizures **OR** presence of signs in **at least 3 of the following 6** categories:

Table 1: Criteria for defining moderate and severe encephalopathy[11]

Clinical category		Moderate encephalopathy	Severe encephalopathy
1. Level of consciousness		Lethargy	Stupor / coma / obtunded
2. Spontaneous activity		Decreased	No activity
3. Posture		Arms flexed, legs extended (decorticate)	Arms and legs extended (decerebrate)
4. Tone		Hypotonia	Flaccid
5. Primitive reflexes		Weak suck, gag and Moro	Absent suck / gag and Moro
6. Autonomic	**Pupils**	Constricted	Dilated / deviated / non-reactive
	Heart Rate	Bradycardic	Variable
	Respiration	Periodic breathing	Apnoea

Exclusion Criteria

- Major congenital abnormality
- Clinical coagulopathy or thrombocytopenia which has not responded to appropriate therapy
- Neonate unlikely to survive / in extremis

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Establishing hypothermia

Level 6 setting

Preliminary steps

> Discussion with parents regarding planned strategy (see Appendix 1)
> Neonate to be nursed in an open cot with radiant warmer
> Neonate needs to be clinically stable
> Venous and arterial catheters should be inserted
> Blood samples prior to cooling
> Continuous cardiorespiratory monitoring (including heart rate, respiratory rate, electrocardiograph, oxygen saturation, invasive blood pressure)
> Continuous amplitude integrated electroencephalography (aEEG) monitoring
> Attention to other clinically appropriate aspects of care (glucose, antibiotics, anticonvulsants, sedation, respiratory management etc)
> Continuous rectal or oesophageal temperature monitoring; the measured temperature to be displayed continuously in order to allow trends to be detected and managed. If a rectal probe is used, insert to at least 5 cm from the anus and secure probe to upper inner thigh

*No feeds are to be given during cooling

Process

> Typically, the process of hypothermic neuroprotection involves elements of PASSIVE and ACTIVE cooling, though in some centres, cooling may be achieved by the use of a proprietary servo-controlled cooling mattress

Non-level 6 setting

Preliminary steps

> Ensure adequate resuscitation and stabilisation; target oxygen saturations of 90 - 95%, mean blood pressure 40 - 50 mmHg and glucose > 3.5 mmol/L

If term or near term (≥ 35 weeks), with a significant perinatal event, need for significant resuscitation and acidosis as previously defined (see inclusion criteria above), strongly consider consultation with a neonatal consultant at FMC or WCH, to discuss possible hypothermic neuroprotection. Contact can be made directly with either centre or ideally via MedSTAR – call 13STAR (137827) and select "option 1"

> If a decision is made to initiate cooling, then ensure the following:
    > Discuss and advise parents of planned intervention (see Appendix 1 - Parent Information); note that this should be actioned only after level 6 consultation and an agreed decision to initiate cooling
    > Document the time that cooling is started
    > Neonate to be nursed naked on an open warmer with the radiant heater turned off and with a nappy positioned but unfastened

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- Monitor heart rate, respiratory rate and saturations continuously
- Measure and document rectal temperature with a digital thermometer inserted 2-3cm from the anal verge every 5-10 minutes
- The rectal temperature goal is 33 – 34°C
- Note that core temperature is likely to be slightly above rectal temperature measured at 2-3 cms; MedSTAR carry rectal probe thermometers and will use these to finesse hypothermia following their arrival
- Once the decision to cool has been made, aim to achieve the target temperature zone within 1 hour

- **The process of cooling (PASSIVE +/- ACTIVE cooling) will be determined by the relevant Neonatal Consultant, depending on the capabilities of the referring centre and in consultation with the local team**
- PASSIVE cooling is a process by which the neonate is allowed to cool because of an absence of thermal support. PASSIVE cooling may be considered while the severity of the neonate's clinical encephalopathy is being assessed
- ACTIVE cooling involves the use of designated cold (never frozen) packs, and is sometimes needed to bring the core temperature into the target range. Active cooling can be used to initiate hypothermia or to augment passive cooling
- PASSIVE cooling involves the following:
  - Neonate to be nursed naked, on an open warmer with radiant heater turned off and a nappy in position but left unfastened
  - Do not nurse on a sheepskin
  - If head box oxygen is required, do not humidify; if ventilated, use standard humidifier settings
  - Record time of commencing hypothermia and document core temperature every 15 minutes
  - If temperature approaches 33.5°C, then use warm blanket or radiant warmer on manual control to maintain temperature in the target range of 33 - 34°C
- ACTIVE cooling involves the following:
  - Designated cold packs should never be placed directly in contact with the skin; they should be wrapped in cotton sheet or appropriate material
  - As a guide, only 1 pack if temperature is between 34 – 35.5°C or 2 packs if temperature ≥ 35.5°C, placed either under the shoulders/upper back/head, across the chest/body or against the flanks
  - Continuously monitor core temperature and remove packs as temperature approaches target; aim to maintain temperature in the range 33 - 34°C
  - Consider sedation if neonate is shivering or appears uncomfortable; note that sedation may reduce the need for active cooling
- In applying the ACTIVE cooling protocol (above) wet cloths are a suitable alternative to co

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packs if the latter are not available

- Target rectal temperature (at 2-3 cm with digital thermometer) is 33 - 34°C; to be achieved within 1 hour of initiating cooling
- Monitor closely as rectal (core) temperature approaches 34°C
- Discontinue ACTIVE cooling at a rectal temperature of 33.5°C and consider mild thermal support (overhead heater on manual control, or blanket) if temperature continues to fall
- All neonates in whom a decision is made to initiate hypothermic neuroprotection to be retrieved to FMC or WCH via MedSTAR
- MedSTAR teams carry cool packs and deep rectal temperature probes in order to maintain hypothermic neuroprotection and monitoring during the retrieval process

Related issues

- Hypothermia is usually well tolerated, but does alter physiology and caregivers should be cognisant of the anticipated effects on vital signs and metabolism. Thus, hypothermia may cause sinus bradycardia and mild thrombocytopenia; it has also been shown to alter pharmacology, with a general increase in half-life of diverse medications [14]

Continuing hypothermic neuroprotection in a level 6 centre

- Hypothermia is continued for 72 hours in level 6 centres according to NICU specific cooling protocols which follow the general principles stated above

Reconsider hypothermia if:

- Severe coagulopathy
- Cardiac arrhythmia requiring treatment
- Deterioration in condition leading to redirected / palliative care based on discussions between parents and staff

Long term follow up

- All babies with grade 2 to 3 HIE and all babies who have received therapeutic hypothermia as treatment for HIE, should be enrolled in a long term neurodevelopmental assessment program

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Appendix 1 – Parent information

Advice to parents regarding hypothermic neuroprotection

Criteria	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 I in 1,000 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 injury, which may continue beyond the episode around the time of birth
Prognosis	A number of those babies who survive after this degree of injury to their brain may develop long-term disabilities. These disabilities include cerebral palsy and severe learning difficulties
Treatment	In the past there were no treatments to reduce the severity of brain injury in these newborn babies Recent research has shown that cooling these babies reduces the brain injury, increases the chances of survival and reduces the severity of possible long-term disability
What does the treatment entail	Your baby will receive cooling therapy in addition to standard intensive care support Your baby's temperature will be slowly lowered and kept between 33 to 34°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

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Abbreviations

ABG	Arterial blood gas
APPT	Activated Partial Thromboplastin Time
aEEG	Continuous amplitude integrated electroencephalography
°C	Degrees Celsius
EEG	Electroencephalogram
FMC	Flinders Medical Centre
HIE	Hypoxic ischaemic encephalopathy
INR	International Normalised Ratio
IV	Intravenous
LFT	Liver Function Tests
mmHg	Millimetres of mercury
mmol/L	Millimoles per litre
pH	a measurement of hydrogen ion concentration
pCO_2	Partial pressure of carbon dioxide
PGLs	Plasma glucose levels
SaO2	Percentage of oxygen saturation of available haemoglobin
WCH	Women's and Children's Hospital

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