

South Australian Perinatal Practice Guideline

Hypoxic Ischaemic Encephalopathy

(including Neonatal Hypothermic Neuroprotection)

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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

Explanation of the Aboriginal artwork:

The Aboriginal artwork used symbolises the connection to country and the circle shape shows the strong relationships amongst families and the Aboriginal culture. The horse shoe shape design shown in front of the generic statement symbolises a woman and those enclosing a smaller horse shoe shape depicts a pregnant women. The smaller horse shoe shape in this instance represents the unborn child. The artwork shown before the specific statements within the document symbolises a footprint and demonstrates the need to move forward together in unison.



Australian Aboriginal Culture is the oldest living culture in the world yet Aboriginal people continue to experience the poorest health outcomes when compared to non-Aboriginal Australians. In South Australia, Aboriginal women are 2-5 times more likely to die in childbirth and their babies are 2-3 times more likely to be of low birth weight. The accumulative effects of stress, low socio economic status, exposure to violence, historical trauma, culturally unsafe and discriminatory health services and health systems are all major contributors to the disparities in Aboriginal maternal and birthing outcomes. Despite these unacceptable statistics the birth of an Aboriginal baby is a celebration of life and an important cultural event bringing family together in celebration, obligation and responsibility. The diversity between Aboriginal cultures, language and practices differ greatly and so it is imperative that perinatal services prepare to respectively manage Aboriginal protocol and provide a culturally positive health care experience for Aboriginal people to ensure the best maternal, neonatal and child health outcomes.

Purpose and Scope of PPG

The purpose of this guideline is to provide clinicians with information on recognising those infants with hypoxic ischaemic encephalopathy (HIE) who would benefit from therapeutic cooling, including assessment, monitoring, consultation and referral. Specific detail for referral sites on commencing active or passive cooling in consultation with a neonatologist is included. Clinical management in Neonatal Intensive Care sites using a Tecotherm device is detailed.

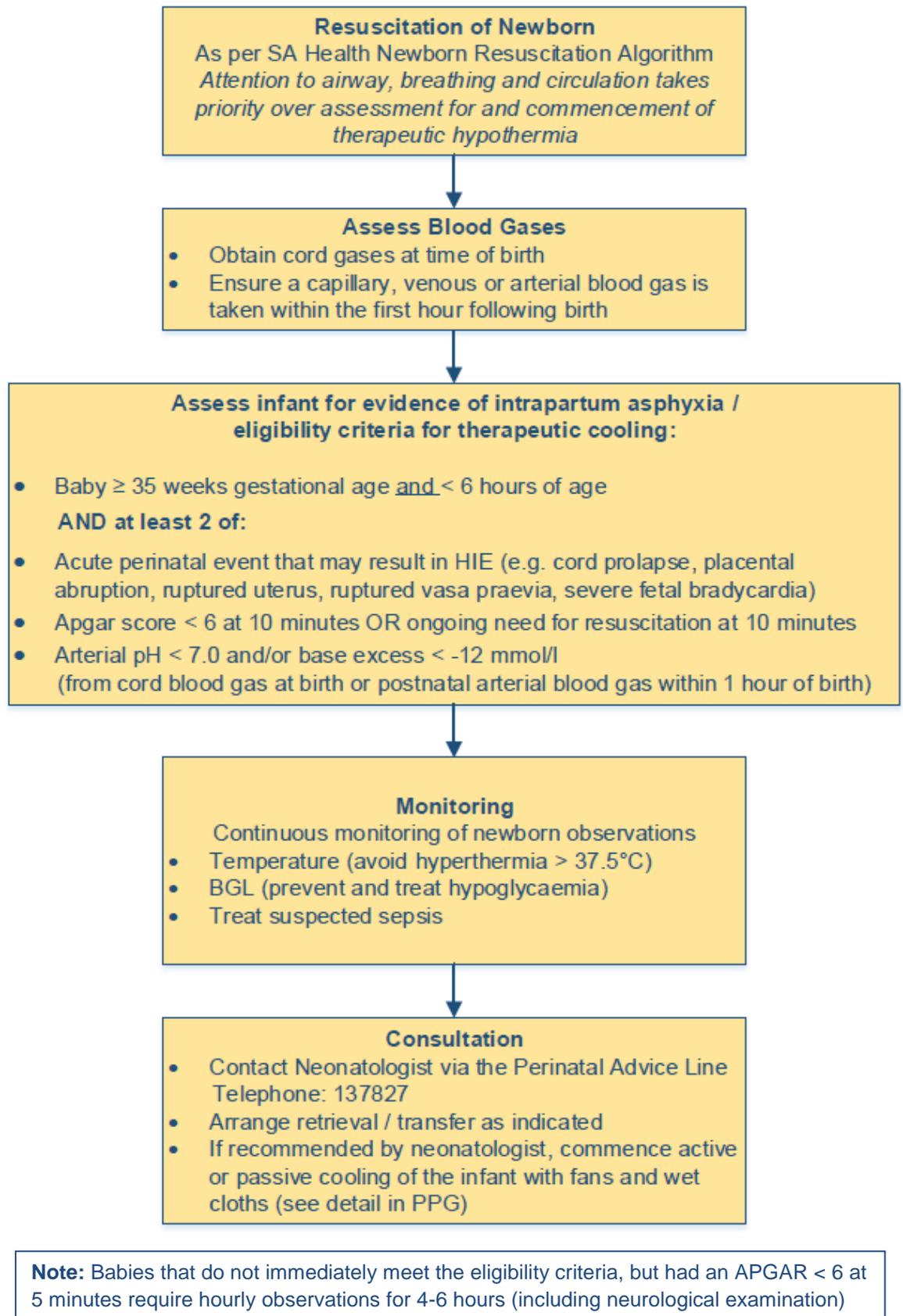
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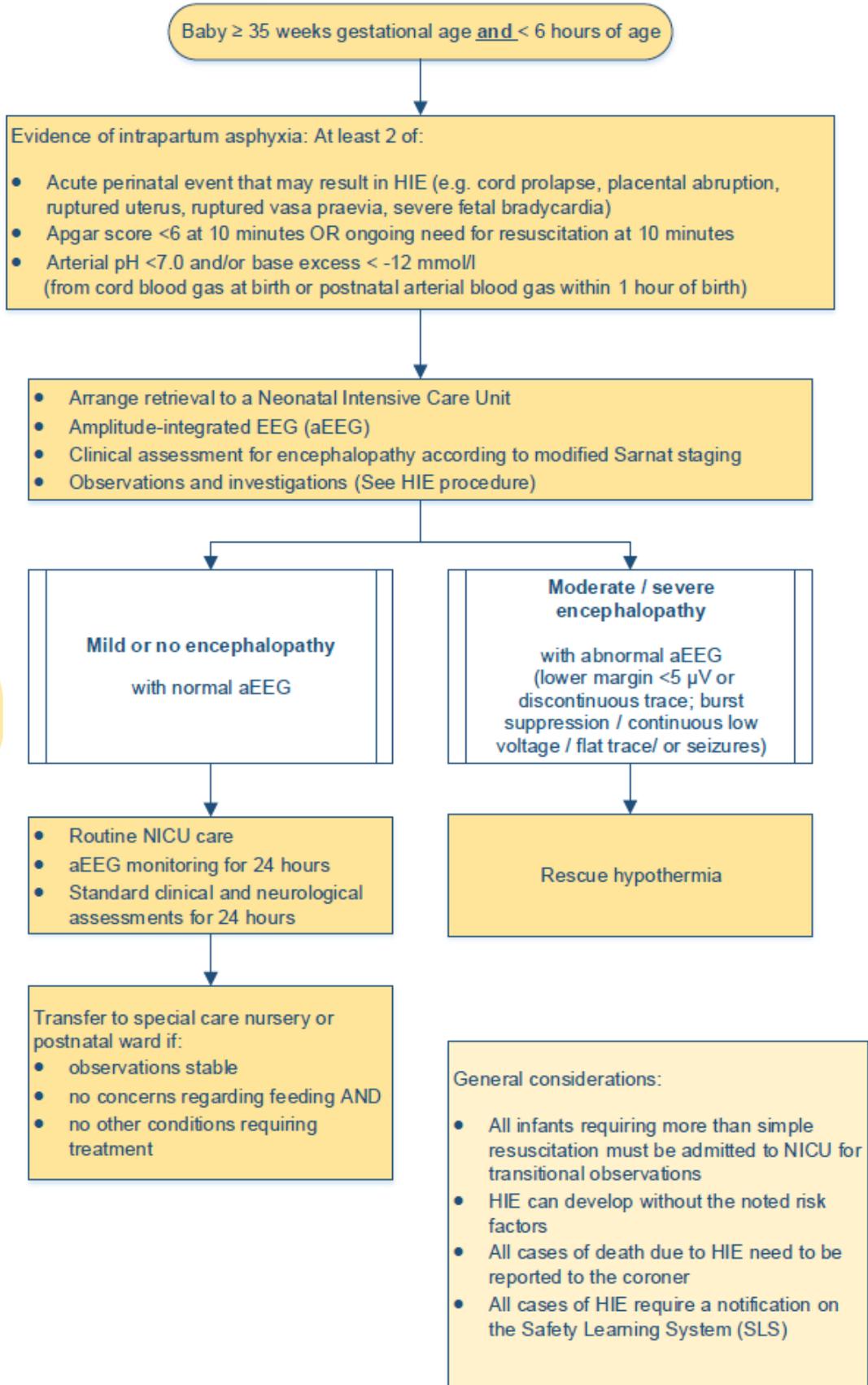
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Flowchart 1: Initial Management of HIE in Referral Sites



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Flowchart 2: Management of HIE in Level 6 Neonatal Units



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Summary of Practice Recommendations

All infants requiring more than simple resuscitation should be admitted to a NICU for observations.

Commencement of hypothermic neuroprotection should occur within 6 hours of birth if indicated.

It can be difficult to assess the presence or absence of HIE. Have a low threshold for consultation with an on-call Neonatologist.

HIE is a condition that evolves with time. Clinicians need to think about HIE as a delayed consequence of asphyxia and be alert to careful observations and serial neurological assessment.

Abbreviations

%	Percent
aEEG	Amplitude integrated EEG
aPPT	Activated partial thromboplastin time
°C	Degrees Celsius
bpm	Beats per minute
BE	Base Excess
BGL	Blood glucose level
BP	Blood pressure
cm	Centimetre
CSF	Cerebrospinal fluid
ECG	Electrocardiograph
EEG	Electroencephalograph
FFP	Fresh frozen plasma
g/L	Grams per litre
HIE	Hypoxic ischaemic encephalopathy
INR	International normalized ratio
MAS	Meconium aspiration syndrome
mg	Milligrams
microg	Micrograms
min	Minute(s)
mmHg	Millimetres of mercury
mmol/L	Millimole(s) per litre
MRI	Magnetic resonance imaging
NICU	Neonatal Intensive Care Unit
NSAT	Neonatal skin assessment tool
PAL	Perinatal advice line
pCO ₂	Partial pressure of carbon dioxide
PPG	Perinatal Practice Guideline
PT	Prothrombin time
SaO ₂	Saturation of oxygen
sec	Second(s)
TPN	Total parenteral nutrition

Definition

Hypoxic Ischaemic Encephalopathy	Lack of sufficient oxygen and blood perfusion to the brain, resulting in brain injury
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Hypoxic Ischaemic Encephalopathy (including Neonatal Hypothermic Neuroprotection)

Background

Following a hypoxic ischaemic insult, neuronal death occurs in two phases:

1. Primary neuronal death: This is related to cellular hypoxia leading to primary energy failure and cellular depolarisation.
2. Secondary phase: After a latent phase (6-100 hours) neuronal death may be initiated by a cascade of pathologic processes and is associated with marked encephalopathy. This involves cytotoxic oedema, mitochondrial failure, accumulation of excitotoxins, active cell death, nitric oxide synthesis and cytotoxic actions of activated microglia. Seizure activity is increased during this phase.

Clinical Presentation

Infants with HIE present with neurological symptoms, whose severity is classified based on the modified Sarnat staging (see [Modified Sarnat Classification Table](#)).¹ There may be evidence of other end-organ damage such as coagulopathy, raised liver enzymes, acute renal failure, hypotension, pulmonary hypertension and/or respiratory failure.

Principles of Medical Management

Evidence from high quality randomised controlled trials indicates that 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.² Hence, infants with moderate or severe HIE should receive therapeutic hypothermia to maintain core temperature at 33-34°C. In order to be effective, cooling should commence as soon as possible.³ There is strong evidence that cooling initiated before 6 hours of age is effective. The evidence for the benefit of cooling initiated later than 6 hours is weaker. Few relevant studies have been conducted.^{4,5}

Therapeutic hypothermia should be continued for 72 hours.

If evidence or concern for hypoxic injury, cease overhead heater for passive cooling and obtain a blood gas.

It may be difficult to assess the presence or absence of HIE. In all cases resuscitation and early stabilisation are the priority.

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

Early consultation with a Neonatologist is recommended. Management discussions and transfer can be facilitated by calling the Perinatal Advice Line on 137827.

Clinical management for referring centres (see [Flowchart 1](#))

1. Resuscitation

Resuscitation as per the *SA Health Newborn Life Support Algorithm* (available at www.sahealth.sa.gov.au/perinatal), and local neonatal resuscitation and escalation guidelines.

The priority in a situation where therapeutic hypothermia is being considered is to ensure appropriate resuscitation of the infant.

2. Measure cord gases

Ensure a capillary, venous or arterial gas is taken within the first hour following birth.



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3. Assess eligibility criteria for therapeutic hypothermia

Newborn is ≥ 35 weeks and < 6 hours of age and any 2 of the following:

- Acute perinatal event that may result in HIE (e.g. placental abruption, cord prolapse etc.)
- Apgar score < 6 at 10 minutes **OR** ongoing need for resuscitation at 10 minutes
- Arterial cord pH < 7.0 and/or base excess < -12 mmol/L **OR** postnatal arterial gas within 1 hour of birth pH < 7.0 and/or base excess < -12 mmol/L

Note: Babies who do not immediately meet the eligibility criteria but have required resuscitation with an APGAR < 6 at 5 minutes require closer monitoring as HIE can be a delayed consequence of asphyxia. The following observations should be undertaken regularly for the first 4-6 hours of life:

- temperature, heart rate, respiratory rate and effort (as per RADAR charts)
- neurological assessment using the [Modified Sarnat Classification](#)

Observation should occur in an appropriate area; for example, in an incubator or nursery and not on the mother's chest.

4. Monitoring

Unwell infants require continuous monitoring and observation as their condition may change rapidly.

1. Monitor temperature to avoid hyperthermia (Temp $> 37.5^{\circ}\text{C}$)
2. Prevent and treat hypoglycaemia (see *Neonatal Hypoglycaemia* PPG available at www.sahealth.sa.gov.au/perinatal)
3. Treat suspected sepsis (see *Early Onset Neonatal Sepsis* PPG available at www.sahealth.sa.gov.au/perinatal)

5. Consultation

It can be difficult to assess the presence or absence of HIE. Have a low threshold for early consultation with a Neonatologist.

Call the Perinatal Advice Line (**phone: 137827**) to discuss suitability for therapeutic hypothermia and to arrange retrieval/transfer to a level 6 neonatal unit if indicated.

Following discussion with a Neonatologist through the PAL, there may be a recommendation to commence passive cooling prior to retrieval/transfer to a level 6 neonatal unit.

6. If no cooling machine available and cooling is required at referring sites

Cooling should only be commenced at referring sites following consultation with a neonatologist. Use an oscillating fan and cold wet cloths. If further measures are required, use cold packs from the fridge.

NEVER use ice packs from the freezer as frozen packs because of cold burns due to intense local vasoconstriction.

Wrap the cool packs in a cloth nappy and place around the head, neck and shoulders, axillae and groins.

Remove the cold packs when the rectal temperature reaches 33°C as this prevents excessive cooling.⁶

Do not reduce the temperature of humidified gases. Reduction of inspired gas temperature reduces humidification and may lead to endotracheal tube obstruction.

Document when and where the packs are placed, and when they are removed.

Document skin integrity and report any discoloration or concerns using neonatal skin assessment tool (NSAT) form.



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Clinical management for Neonatal Intensive Care Units

1. Resuscitation

Resuscitation as per the SA Health *Newborn Life Support Algorithm* (available at www.sahealth.sa.gov.au/perinatal), and local neonatal resuscitation guidelines.

2. Hypothermia Therapy / Cooling in Neonatal Intensive Care Units

The decision to cool a neonate with HIE is made by the on call Neonatologist.

Eligibility Criteria

Active cooling is commenced if the following eligibility criteria met:

1. Newborn is ≥ 35 weeks and < 6 hours of age and any 2 of the following:
 - Acute perinatal event that may result in HIE (e.g. placental abruption, cord prolapsed etc.)
 - Apgar score < 6 at 10 minutes OR Ongoing need for resuscitation at 10 minutes
 - Arterial pH < 7.0 OR BE < -12 mmol/L or lower (from cord OR baby arterial gas < 60 minutes of age)
2. Moderate to severe encephalopathy (modified Sarnat) +/- abnormal aEEG
 - lower margin $< 5\mu\text{V}$ or discontinuous trace OR
 - burst suppression/continuous low voltage/flat trace OR
 - evidence of seizures

Note: Therapeutic hypothermia may be considered in infants between 6 and 10 hours of age.

Exclusion Criteria:

1. Major congenital abnormalities likely to render therapeutic hypothermia ineffective or unsafe
2. Uncontrolled severe clinical coagulopathy not responding to appropriate therapy
3. Infant not expected to survive

3. Respiratory support

Intubation and ventilation are frequently required due to altered conscious state (infant obtunded, ineffective spontaneous breathing or seizures).

Meconium aspiration syndrome (MAS) is a typical co-morbidity

Due to the evolving nature of HIE, where a baby is not intubated, careful monitoring and a low threshold for endotracheal intubation should be maintained for the purpose of airway protection.

An arterial blood gas obtained within 1 hour of birth is useful to assess the degree of postnatal hypoxia.

Initial frequency of arterial blood gas analysis should be 4-6 hourly until acidosis is corrected and low normocarbina is achieved (pCO_2 35-45 mmHg). Subsequent frequency may be dictated by blood glucose and electrolyte management.

Maintain preductal oxygen saturations (SaO_2) above 93%. Persistent hypoxia can be due to pulmonary hypertension. Rarely, hypothermia treatment needs to be discontinued or modified because of severe hypoxaemia due to pulmonary hypertension.

4. Circulatory support

Obtain umbilical or peripheral arterial access for blood pressure monitoring and blood sampling.

Insert a dual lumen umbilical venous catheter.

For hypotension:

Volume replacement - administration of blood products (fresh frozen plasma [FFP], cryoprecipitate, platelet transfusion and packed red cell transfusions). Targeted approach required, e.g. cryoprecipitate for low fibrinogen.



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Inotropic support

Aim for mean invasive blood pressure of 45-55mmHg.

If pulmonary hypertension is suspected or confirmed (on echocardiogram), optimise pCO₂, BP and pH.

Sinus bradycardia is common during hypothermia treatment. Obtain 12-lead ECG if there are rhythm abnormalities.

5. Metabolic

Obtain plasma glucose level on admission. Correct hypoglycaemia; aim for blood glucose level (BGL) above 3.5 mmol/L.⁷

Provide 4-6mg/kg/min of glucose infusion rate and check BGL as per protocol

Infusion of concentrated dextrose solution may be required

Correct metabolic acidosis with targeted circulatory support and fluid volume where necessary. Routine use of sodium bicarbonate is NOT recommended: Use at consultant discretion only.

Obtain liver function tests on admission. Persistent hypoglycaemia and /or metabolic acidosis should raise suspicion for inborn errors of metabolism where consultation with a Metabolic Specialist is advised.

6. Renal support and fluid management

Acute kidney injury is common. Strict fluid balance +/- fluid restriction may be necessary.

Obtain formal electrolytes and creatinine on admission, then electrolytes as per local guidelines.

Commence dextrose infusion initially at target volumes of 25-40ml/kg/day.

- This can be increased through custom TPN
- Once renal function is recovering Standard Term parenteral nutrition (12% glucose) can be considered.⁸

Insert urinary catheter for assessment of fluid balance and prevention of urinary retention.

Enteral Nutrition

Enteral nutrition to a maximum of 20 mL/kg/day of breast milk may be commenced at 24 hours of age in the stable infant undergoing therapeutic hypothermia.⁹



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7. Neurological

Perform a structured neurological examination on admission, using modified Sarnat staging system¹ to determine eligibility for hypothermia treatment.

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: Modified Sarnat Classification¹

Variable		Mild encephalopathy Stage I	Moderate encephalopathy Stage II	Severe encephalopathy Stage III
Level of consciousness		Alert	Lethargic	Comatose
Muscle Tone		Normal or hypertonic	Hypotonic	Flaccid
Tendon reflexes		Increased	Increased	Depressed or absent
Myoclonus		Present	Present	Absent
Seizures		Absent	Frequent	Frequent
Complex reflexes	Suck	Active	Weak	Absent
	Moro	Exaggerated	Incomplete	Absent
	Grasp	Normal-exaggerated	Exaggerated	Absent
	Oculocephalic (doll eye)	Normal	Overactive	Reduced or absent
Autonomic function	Pupils	Dilated, reactive	Small, reactive	Variable / fixed
	Heart Rate	Normal or tachycardia	Bradycardia	Bradycardia
	Respiration	Regular	Periodic breathing	Ataxic, apnoeic
EEG		Normal	Low voltage, periodic or paroxysmal	Periodic or isoelectric

Record assessment on *Encephalopathy chart*.

Perform regular neurological examination (daily) and documentation thereafter until discharge.

Commence continuous aEEG monitoring on admission, during cooling and rewarming phases.

Seizures

Treat all clinical seizures (and electrographic seizures).^{10,11}

Phenobarbital is first line treatment (see *Phenobarbital Neonatal Medication Guideline* available at www.sahealth.sa.gov.au/neonatal).

If seizures are refractory to treatment, discuss further management with consultant responsible. Consider alternative anti-convulsion agents (e.g. benzodiazepine, phenytoin, levetiracetam).^{12,13,14}

Analgesia

Hypothermia appears to be uncomfortable, even painful.

An infusion of morphine at 5-10microg/kg/min may be beneficial.

8. Haematology

Obtain full blood count and coagulation profile on admission.

Obtain EDTA specimen for group and match.

Ensure Vitamin K administered via intramuscular route (see *Vitamin K Neonatal Medication Guideline* available at www.sahealth.sa.gov.au/neonatal).

If evidence of coagulation abnormalities, consider FFP / cryoprecipitate / platelet transfusion.

Aim for INR <1.9; aPPT 40-60 sec; PT <16s; fibrinogen ≥1.5 g/L (Note: hypothermia in itself can prolong in vitro coagulation tests).



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9. Infection

If sepsis suspected, obtain blood culture on admission and commence antibiotics.

Gentamicin level should be performed PRIOR to second dose.

Cerebrospinal fluid (CSF) analysis should be performed if indicated when clinically stable (usually post hypothermia treatment).

Investigations:

Blood investigations

- Full Blood Examination
- Electrolytes
- Liver function testing and Urinalysis
- Coagulation profile: activated partial thromboplastin time (aPTT), INR (international normalized ratio), prothrombin time (PT), fibrinogen
- Occasionally: cardiac troponin

Imaging

- Cranial ultrasound should be performed as soon as practical to exclude neurosurgical cause for HIE or structural brain abnormality. Cranial ultrasound lacks sensitivity in newborn babies for evaluating the nature and extent of the injury.
- Arrange MRI on day 4-7 of life if HIE. MRI can be done earlier if needed to rule out alternative diagnosis (e.g. ischaemic/haemorrhagic stroke, cerebral malformation), or if imaging is critical for clinical decision making (e.g. redirection of care).

aEEG and a formal EEG

It is very important to apply the leads and start recording the amplitude integrated EEG as soon as possible after admission. This will assist in the diagnosis of HIE and identification of seizures.¹⁵

- A formal EEG (via Neurophysiology Department) should be arranged in the first 1-2 weeks for infants who have seizures.
- Obtain neurology consult.
- Frequent neurological examination.

Metabolic studies

Metabolic studies are not done on a routine basis but should be considered if the cause of HIE is unclear.

- Urine amino and organic acids, serum ammonium levels, CSF
- Amino acids and neurotransmitters if the cause of HIE is unclear. Rare metabolic conditions can mimic HIE. Specialist advice is recommended prior to obtaining these specimens

In cases where death is imminent / palliation is about to occur

Consider collecting metabolic studies and blood for chromosomal/microarray testing. Seizures can be a presentation of metabolic conditions or developmental brain anomalies associated with chromosomal/genetic defects. Contact the Metabolic consultant on call for advice.

All deaths should be discussed with the Coroner.

If directed, formally report the death to the coroner.

In non-coronial cases an autopsy should be recommended to the parents. In most cases of presumed asphyxia a cause is not immediately apparent.



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Hypothermia treatment

Tecotherm Device

Set-up with Tecotherm device:

- Use an open Intensive Care Incubator. The infants are then easier to monitor and to regulate temperature
- Cardio-respiratory monitor with an oesophageal or rectal temperature probe - provides accurate temperature measurement in the desired low temperature range
- Apply skin probe and connect to the Cooling machine, place cooling mattress covered with blue sheet under baby. To commence cooling set machine to Servo control complete treatment mode.
- Insert oesophageal probe. Insertion distances:
 - Nasal insertion depth = (Body length (in cm) / 4) + 3 cm
 - Oral insertion depth =(Body length (in cm) / 4) + 2 cmThis places the tip of the thermistor at T7/T8, which is just behind the left atrium.
- NB. If you have to use a rectal probe, insert temperature probe to 6-8 cm and secure with tape. Insert at this distance to accurately monitor the core temperature.
- Attach to cooling machine. If no cooling machine available attach to Philips X2 module

Check probe insertion distance hourly.

Open Intensive Care Incubator is placed in manual mode.

Monitor temperature continuously and document skin and oesophageal temperature hourly.

Digital thermometers register from 32°C

Temperature is monitored to maintain a core temperature between 33°C and 34°C.

It is currently considered important to achieve this target temperature within 6 hours of birth and to maintain it for 72 hours for neuroprotection.

Nursing care during hypothermia therapy

Abnormalities of the aEEG have prognostic significance. Medical staff and nursing staff are to document predominant aEEG background in medical records once per shift, including occurrence of seizures. Also mark events and clearly describe circumstances on the aEEG log.

Continue usual NICU observations.

Pending arterial line placement: 15-minutely Doppler blood pressure measurements must be recorded.

Note: Sinus bradycardia (80–100bpm/min) is common with hypothermia; therefore adjust the low alarm limit to 80 beats per minute on Philips monitoring system. This needs to have medical approval.

Skin integrity

The sedated or obtunded infant is prone to problems with skin integrity / fat necrosis.

Change infant position regularly as tolerated to reduce pressure.

Perform assessment and document accordingly using neonatal skin assessment tool (NSAT)

If cooling device not available make sure that no ice packs are used on infant's skin and that the infant is not lying on wet sheets.

Rewarming

Commenced after 72 hours of hypothermia treatment.

Continue to monitor core temperature.

If no cooling device available and manual cooling utilised then follow rewarming steps.

Secure the skin probe to the abdomen and set skin temperature probe to 35°C. Turn the intensive care cot temperature control to servo control. This is generally sufficient to re-warm the infant at an appropriate rate.



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Maintain the oesophageal temperature probe and avoid warming faster than 0.5 °C per hour over 6–8 hours.

Rapid warming may increase the metabolic rate and oxygen consumption of poorly perfused tissues and cause tissue hypoxia.

To avoid rapid warming it may be necessary to re-initiate cooling techniques.

Follow up

All babies receiving cooling therapy are enrolled into the Neonatal Long Term Follow up program.



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