Guideline for the management of Infants with Moderate or Severe Perinatal Asphyxia requiring cooling.

Perinatal asphyxia is an insult to the fetus or newborn infant due to the lack of oxygen (hypoxia) and/or lack of perfusion (ischaemia) to various organs. It is a major cause of death and acquired brain damage with an incidence of 2/1000 live births in the UK. Acute asphyxia leads to intracellular energy failure resulting in immediate cell injury. Following this, cerebral metabolism may recover only to deteriorate in the secondary reperfusion phase. This ‘delayed phase of neuronal injury’ starts at about 6 hours after the initial injury and is characterised by cerebral oedema and apoptosis. There is therefore a potential therapeutic window of 6 hours. Therapeutic hypothermia has been shown to be an effective treatment if initiated in the first 6 hours of life. A Cochrane review concludes that therapeutic hypothermia results in both a clinically important and statistically significant reduction in the combined outcome of mortality or major neuro-developmental disability at 18 months of age. (The NNT in order to prevent one adverse outcome is only 7).

Indications for cooling:
Babies should be assessed for 3 criteria A, B and C.

Criteria A: Infants ≥ 36 weeks gestation with one of the following:
1) Apgar score <5 at 10 minutes after birth or
2) Continued need for resuscitation at 10 minutes after birth or
3) pH ≤ 7 from umbilical cord, or any blood sample obtained from the infant within the first hour of life or
4) Base deficit ≥16 mmol in the umbilical cord or any blood sample from the infant within first hour of life.

If A is met, then assess for encephalopathy using criteria B

Criteria B: Moderate or severe encephalopathy consisting of:

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<thead>
<tr>
<th>Parameter</th>
<th>Moderate Encephalopathy</th>
<th>Severe Encephalopathy</th>
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<tbody>
<tr>
<td>Level of consciousness</td>
<td>Reduced response to stimulation</td>
<td>Absent response to stimulation</td>
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<tr>
<td>Spontaneous Activity</td>
<td>Decreased Activity</td>
<td>No activity</td>
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<tr>
<td>Posture</td>
<td>Distal flexion, complete extension</td>
<td>Decerebrate</td>
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<tr>
<td>Tone</td>
<td>Hypotonia (focal or general)</td>
<td>Flaccid</td>
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<tr>
<td>Suck</td>
<td>Weak</td>
<td>Absent</td>
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<tr>
<td>Moro</td>
<td>Incomplete</td>
<td>Absent</td>
</tr>
<tr>
<td>Pupils</td>
<td>Constricted</td>
<td>Constricted</td>
</tr>
<tr>
<td>Heart rate</td>
<td>Bradycardia</td>
<td>Variable</td>
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<tr>
<td>Respiration</td>
<td>Periodic breathing</td>
<td>Apnoea</td>
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If the baby meets criteria A & B, then begin passive hypothermia (see below). Where amplitude integrated EEG (aEEG) monitoring is available assess for criteria C. Do not wait until the aEEG is available until cooling is started. If the aEEG is subsequently completely normal, cooling may be discontinued later. An aEEG record of at least 30 minutes duration should be obtained within the first 6 hours of life and should show one of the following if therapeutic hypothermia is to be initiated:

1) Normal background with some electrical seizure activity - Fig B
2) Moderately abnormal background - Fig C
3) Severely abnormal background/burst suppression - Fig D

**Fig A:** Shows a CFM trace with normal background activity. Upper border of trace >10µV and lower border of trace >5µV

**Fig B:** Shows a normal background activity with seizures. Seizures appear as an abrupt rise in voltage

**Fig C:** Shows a moderately abnormal trace with the upper border >10µV and the lower border <5µV. This appearance may also be seen following administration of anticonvulsants and sedatives

**Fig D:** Shows a severely abnormal trace with upper border <10µV and lower border <5µV. Often there will be bursts of high voltage – burst suppression pattern.

**Management on Labour Ward:**

Dry and wrap the baby and ventilate in air for 60-90 seconds. Apply an oxygen saturation probe. If the infant’s condition and oxygen saturations do not improve, introduce O₂ as required.

If there is a continued need for resuscitation at 5 minutes, turn the overhead heater off to avoid hyperthermia. Allow passive hypothermia to occur by not actively re-warming the child. Take the temperature and aim for a target temperature of 34°C to 35°C for initial passive hypothermia. (Be careful as accidental over cooling can easily occur).

Transfer to the NICU, nurse in an incubator, with the temperature set at the minimal temperature of 27°C, insert a rectal thermometer and apply the aEEG electrodes and monitor.

**Management on the NICU**

1. Obtain full maternal history including signs of pyrexia and/or infection, induction of labour, use of syntocin, instrumental delivery, document the CTG, cord gas, Apgar scores at 1, 5 & 10 minutes and time to first gasp.
2. Insert a rectal temperature probe up to 2-3 cm and tape to the thigh. Maintain the rectal temperature between 33°C -34°C for 72 hours. One additional temperature probe should be placed over the back of the infant to check that the temperature set on the cooling equipment is being delivered. This is a safety measure. Start with the set temperature of 20°C in the Tecotherm and increase the temperature accordingly as the rectal temperature drops to 33-34°C. Typically within a few hours the set
The temperature of the Tecotherm will be 25 to 30°C. The set temperature will vary with each baby and is dependant on both infant size and activity. If the servo-controlled Tecotherm is used, the target rectal temperature is set at 33.5°C.

3. Obtain central access: double lumen UVC and a UAC.
4. Send bloods for: full blood count, electrolytes, clotting screen, liver function test, blood glucose, blood gases and lactate.

If criteria C is not fulfilled (abnormal aEEG in any 30 minute time period within the first 6 hours of life), cooling is not indicated as infants with normal aEEGs are at very low risk for neurological damage. If cooling has been commenced, then rewarm slowly over 4-6 hours. Avoid hyperthermia in these babies for the first few days after birth as hyperthermia is known to increase neurological injury.

Consider NOT cooling: if
1) the gestation is < 36 weeks.
2) moribund with persisting severe encephalopathy (as outcome is not improved by cooling).
3) the Infant is likely to require surgery in the first three days of life.

Cooling should be used with caution in babies with unstable respiratory and cardiovascular function including those with PPHN (persistent pulmonary hypertension). However, PPHN is not a contraindication for therapeutic hypothermia.

Potential adverse effects of cooling:
Impaired cardiac function, disordered coagulation, thrombocytopenia, hypokalaemia, increased risk of sepsis, subcutaneous fat necrosis have all been reported with hypothermia.

**Specific management:**

Poor skin perfusion occurs during cooling, thus inspect the back at least 12 hourly and vary the position 6 to 12 hourly from flat to slightly tilted in the supine position.

Once cooling is established, aim for minimal handling.

**Respiratory:**
Ventilate only if required. Cooled neonates can often be managed on CPAP.
Use humidified and heated gases as normal. Patients may need frequent suctioning as the ETT secretions become “sticky” when cold, this usually happens by day 2 or 3.
Avoid hypocapnia. Keep PaO₂ 8 to 13 kPa, and PCO₂ 6 to 8 kPa (the blood gas analyser assumes the temperature is 37°C and so will over-read by 0.83kPa/°C drop in temperature in cooled infants.)

**Cardiovascular:**
Hypothermia causes sinus bradycardia: the heart rate drops by 14 beats/min/°C drop in temperature.
Observe for hypotension. There may be a borderline increase in the requirement for inotropic support in cooled patients.
Keep the MABP within the normal range of 45 - 65 mm of Hg.
Treat hypotension as per local hypotension guidelines. Echocardiographic assessment of the degree of filling may prove useful (cooled patients may develop capillary leak and an echo will help guide volume replacement).

**Fluids:**
Start with 40 to 60 ml/kg/day of 10% dextrose.
Closely monitor urea and electrolytes and urine output. Aim for normal electrolyte levels.
Monitor the blood glucose regularly as there may be a need for higher than normal glucose infusion rate (GIR). Normal GIR is 4-6 mg/kg/min.
Fluid boluses should be used with caution as it can lead to marked oedema - cooling can exacerbate oedema because of capillary leak. Keep nil by mouth during cooling.

**CNS:**
The stress of shivering and feeling cold may interfere with neuro-protection. Sedate with morphine infusion 10-25 mcg/kg/hour. Hypothermia reduces morphine metabolism so potentially toxic serum concentration of morphine may occur with infusions >10 mcg/kg/hour. Reduce the morphine infusion to 5 - 8 mcg/kg/hour after 12 to 24 hours and continue to monitor for signs of stress.
If the patient has a normal heart rate despite hypothermia, consider increasing the morphine infusion as stress can cause this clinical picture.
Use vecuronium infusion for paralysis if required. As drug accumulation occurs during hypothermia, unpredictable drug levels may occur. Stop vecuronium at 12 to 24 hours and resume when movements occur.

**Seizure management (please refer to local guideline):**
Phenobarbitone 20 mg/kg IV over 20 minutes for up to 2 doses. The half life of phenobarbitone is increased during cooling.
If seizures persist use Phenytoin 20 mg/kg, BUT use only one dose. Beware of cardiac toxicity particularly if cardiovascularly compromised.

If seizures continue, start a Midazolam or Clonazepam infusion, dependant on local policy.

If seizures difficult to control, a Lidocaine infusion may be used. Do not use if phenytoin has been given as both drugs given together will cause cardiac depression.

**Haematology:**

Hypothermia causes a significant increase in thrombocytopenia with concomitant reduction in platelet function, thus aim to keep platelets >50×10⁹/mm³.

Hypothermia increases blood viscosity, so keep the haematocrit ≤65.

Cooling may worsen abnormal clotting. Treat clotting abnormalities aggressively as per local policy.

**Infection:**

Chorioamnionitis predisposes to the development of hypoxic ischaemic encephalopathy (HIE), therefore always treat with antibiotics. Use first line antibiotics as per local policy. Remember to check Gentamicin level before giving the 2nd dose as HIE may affect renal function.

**Neuro imaging:**

Perform a cranial USS soon after birth and at 24 hours with doppler imaging of the anterior cerebral artery to obtain the resistive index (RI). A resistive index of <0.5 is indicative of a poor prognosis as it suggests compensatory vasodilatation is occurring after the hypoxic-ischaemic insult.

Obtain an MRI scan between 5 and 14 days as this is helpful for prognosis. Normal myelination pattern in the posterior limb of the internal capsule is associated with normal motor outcome. Extensive white matter abnormalities and loss of grey white differentiation are associated with an abnormal outcome.

Cooled neonates should be followed up for at least 2 years to ascertain neuro-developmental outcome.

**Re-warming:**

After 72 hours, start to rewarm the baby.

Increase the baby's temperature by 0.5°C/hour. This should take 6 to 8 hours. Continue to record the rectal temperature throughout this period.

Rapid re-warming may cause seizures or hypotension. If this happens, stop re-warming and re-cool and attempt re-warming again after 6-8 hrs. Treat seizures and hypotension as per local policy.

**Therapeutic hypothermia for infants born outside cooling centres:**

If a baby is born with signs of perinatal asphyxia, assess for eligibility criteria A & B and if fulfilled treatment should be started locally whilst transport to a cooling centre is being arranged (Cooling centres are UHW Cardiff, RGH Newport and Singleton hospital, Swansea).

Switch the overhead warmer off.

Insert a rectal temperature probe if available and keep the temperature at 33 to 34°C.

Continue with standard intensive care with the addition of passive hypothermia.

**Do not** use fans/cold compresses as they will overcool the infant and this may be as detrimental to the patient as hyperthermia.

Transport the infant to a cooling centre in a transport incubator. Ensure the transport incubator temperature has been lowered to 25°C. If active cooling is indicated during transport, consider using a phase controlled mattress or a servo controlled cooling machine e.g. Tecotherm.

Rectal temperature should be recorded every 15 minutes during the transport to ensure the baby’s rectal temperature is within therapeutic range. It is very important to avoid overcooling the baby.

**‘Off Label’ use of therapeutic hypothermia:**

Evidence of cooling outside the currently recommended guidelines is weak and unavailable. However, there are circumstances where there may be theoretical benefits of cooling e.g:

- Borderline preterm/late preterm infant,
- Acute documented post-natal collapse with a neurological diagnosis consistent with acute encephalopathy.

In these situations cooling may be initiated after detailed discussions with parents.

**References:**


Anitha James, Shobha Cherian July 2013. To be reviewed July 2016