Newborn Clinical Network

Consensus Statement for Treatment of Neonatal Encephalopathy

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Acknowledgements
Neonatal Encephalopathy working group of the PMMRC.

Disclaimer
The content of this consensus statement do not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

Public Domain Notice
This consensus statement is intended for use by secondary care practitioners involved in the care of newborns at risk of neonatal encephalopathy. It provides the best evidence currently available to assist informed decision making by parents/caregivers and their health care providers to improve their health outcomes.

Glossary
ADH  Antidiuretic Hormone
aEEG  Amplitude integrated Electroencephalogram
ANZNN  Australian & New Zealand Neonatal Network
HIE  Hypoxic Ischemic Encephalopathy
ILCOR  International Liaison Committee on Resuscitation
MRI  Magnetic Resonance Imaging
NE  Neonatal Encephalopathy
Background

Neonatal Encephalopathy (NE) is “a clinically defined syndrome of disturbed neurological function in the earliest days of life in the term infant, manifested by difficulty with initiating and maintaining respiration, depression of tone and reflexes, sub normal level of consciousness and often seizures”.

Three clinical stages of encephalopathy are described.

Figure 1. Clinical stages

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>Mild  &lt;br&gt; Duration &lt; 24 hours with hyperalertness  &lt;br&gt; Uninhibited Moro and stretch reflexes  &lt;br&gt; Sympathetic effects  &lt;br&gt; Normal electroencephalogram</td>
</tr>
<tr>
<td>Stage 2</td>
<td>Moderate  &lt;br&gt; Reduced consciousness  &lt;br&gt; Hypotonia  &lt;br&gt; Decreased spontaneous movements with or without seizures</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Severe  &lt;br&gt; Stupor  &lt;br&gt; Flaccidity  &lt;br&gt; Seizures  &lt;br&gt; Suppressed brain stem and autonomic functions  &lt;br&gt; The EEG may be isopotential or have infrequent periodic discharges</td>
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The rate of NE varies with population studied but in New Zealand the rate of moderate to severe (stage 2-3) is approximately 1.3/1000 live term births.

The terminology NE is preferred to Hypoxic Ischemic Encephalopathy (HIE) as it is not always possible to document a significant hypoxic-ischemic insult and there are potentially several other aetiologies.

Other conditions such as metabolic disease, infection, drug exposure, nervous system malformation and neonatal stroke may present as a neonatal encephalopathy. The requirement for investigation to exclude these possibilities will depend on the presentation, history and clinical features of the individual case.

Initial Management

Recognition and documentation of NE is vital to subsequent management and neonatal outcome. So there should be a low threshold for discussion with Senior Paediatric team.

1. Adequate resuscitation should be instituted at birth, as per standard guidelines.
2. Cord gases should be collected if perinatal asphyxia is suspected.
3. A low Apgar score at 5 minutes indicates an abnormal condition at birth but it is not exclusive to asphyxia so drug exposure, trauma, hypovolemia, infection, or congenital anomalies may need to be excluded.
4. A note should be made of:  
   - time for regular spontaneous ventilation to be established  
   - time to first detection of a heart rate  
   - time to Heart rate > 100 - slow recovery of the heart rate (>100bpm) despite adequate resuscitation may indicate a severe insult.
• meconium staining of umbilical cord and skin suggests prolonged exposure to meconium (> 3 hrs)
• Cord or initial pH, base excess and Lactate

5. Observe neurological signs and evaluate severity of the encephalopathy as per Figure 1. If available also consider cotside amplitude integrated EEG monitoring
6. Aim to complete assessment & initiate plan within the first 60 min after birth
7. Discuss with local Level III centre with respect to appropriate transfer and potential use of passive cooling
8. If appropriate initiate passive cooling and monitor temperature either continuously via rectal probe or every 15 min in axilla
9. Encephalopathy progresses over time so serial observation is important. Use of the table in Appendix 1 may assist in documenting progression
10. Organise for the placenta to undergo histological examination

In addition to documenting the clinical examination, it is useful to record status of cotside EEG if this is performed including comment on background activity and presence or not of seizures.

Appropriate transfer
Once stabilised, the infant can be transported to level 3 centre for cooling and ongoing care.

Transfer arrangements are covered by local practice and guidelines. Decisions are made based on the best available clinical information and require timely discussion between the clinicians. Data from the figure in Appendix 1 may inform this discussion.

Two types of transfers are possible:
• Home / birth unit to level 2 or level 3
  o Ambulance for home birth, retrieval team usually requested by a primary unit
  o It is important to avoid delay in accessing appropriate treatment
  o Cardio-respiratory support may be required
  o For short urgent transfers the focus may be on cardiorespiratory stabilization
• Level 2 to level 3
  o Typically done by level 3 retrieval team
  o May involve use of passive cooling and temperature monitoring

NB. Temperature monitoring during transfer is important and care should be taken to ensure that overcooling does not occur.

Ongoing Management (at a cooling centre)
Each centre will have specific management/neonatal intensive care guidelines but the basic principle is 72 hrs of cooling and supportive care.

Indications for Cooling
Since 2010, ILCOR and other bodies have recommended cooling for moderate to severe hypoxic ischaemic encephalopathy in term infants.

The diagnosis of encephalopathy severity can be made on clinical grounds but this may be supported by aEEG findings including abnormal baseline, discontinuity, and presence of seizures.
Clinical trials investigating cooling have had strict entry criteria. Some infants may benefit from hypothermia but fall outside the standard entry criteria from the published trials, thus the decision to cool or not may not be entirely clear. A pragmatic approach to initiation of cooling in borderline situations such as <36 weeks gestation has been suggested and reported to be feasible. A similar approach is advocated for cases of postnatal collapse and also in growth restricted infants <1800g, in which it has been reported to be feasible with no evidence that it is harmful.

Despite the lack of benefit in animal studies starting beyond a 6 hour limit, it is unlikely that cooling would be harmful. In the absence of clear trial data a pragmatic approach has again been suggested.

There is no suggestion from the available studies that cooling for longer than 72 hours or deeper that 33.5 degrees produces any benefit in full term neonates with moderate or severe hypoxic ischemic encephalopathy. Indeed these trials were stopped early as there was concern over potential for increased mortality.

Use of cooling for other conditions such as sepsis or metabolic disease is outside the remit of this document and should be examined on the merit of the individual case.

Contraindications to cooling

In general it is accepted that babies who are moribund or have severe life limiting congenital abnormalities would not benefit from cooling. Other situations are unlikely to be absolute contraindications and should be assessed on individual basis.

Coagulation abnormality should not be considered as an absolute contraindication to cooling. However, the abnormality must be aggressively corrected prior to initiation of cooling as bleeding may be exacerbated by the effect of a lower temperature on the clotting cascade. Subgaleal haemorrhage has been reported to have unfavourable outcome and one author has recommended that even after correction of clotting it was their local practice to only cool to 35 degrees. Although experimental data to support this practice is lacking, clinicians need to be aware of the concerns particularly with subgaleal haemorrhage so decisions can be made on a clinical basis.

Pulmonary hypertension may also be exacerbated by hypothermia and clinicians may consider warming by one or two degrees to improve oxygenation.

Supportive Care

- Monitor blood gases, electrolytes, creatinine and fluid balance
- Inotropes and volume expansion may be cautiously used to maintain blood pressure and renal blood flow
- Fluid overload is a potential hazard due to acute tubular necrosis or the presence of inappropriate ADH secretion
- Fluid management should include observation of glucose level
- Urine output must be carefully measured and urinary catheterisation should be considered (particularly if opiates given)
- Other organ impairments such as persistent fetal circulation require specific measures
- Echocardiogram will help to rule out structural cardiac disease and will assist with assessment of cardiac function
- aEEG monitoring is indicated during the cooling episode and seizures require prompt treatment as cerebral oxygen use is increased almost fivefold during a seizure
- An opiate infusion is indicated to provide comfort during cooling
- The use of mannitol or steroids is not supported by any controlled studies
All affected infants, particularly potential cooling candidates, should have serial clinical neurologic assessment to assess progression of the encephalopathy.

There is little comparative data on efficacy of different cooling systems so no system is recommended over any other. However, modern servo controlled systems are easier to use than older systems.

Follow up and investigation

Staging based on serial clinical examination is useful in predicting prognosis after NE. All infants should have a convalescent neurological examination performed and the results documented in notes and discharge summary.

For infants with moderate to severe (Stage 2 or 3) NE, further investigations should be performed to assist with prognosis.

- MRI provides excellent prognostic information.\textsuperscript{14,15,16,17} It is a superior test to CT in determining brain abnormalities in the term neonate and eliminates the use of ionizing radiation, so should be considered the standard investigation.
- Diffusion weighted imaging is a useful adjunct to conventional sequence imaging but appearances resolve with time so it is important to discuss optimal timing of imaging with the local radiology service. An early MRI between 48 and 96 hours will show acute changes but may not be possible during or soon after cooling. Later imaging at 10-14 days will demonstrate conventional T1 and T2 changes.\textsuperscript{15}
- Where available a convalescent formal EEG performed at approximately 7 days will provide useful prognostic information\textsuperscript{17,18} and is not changed dramatically by the cooling.

Discussion of the examination findings and investigation results with parents is an important part of tertiary/secondary clinical care and should always occur before transfer back to referring centre.

Long-term follow up and audit of Perinatal Asphyxia outcome

Infants who have undergone cooling for NE are recorded in ANZNN dataset.

Infants who have had moderate to severe NE should undergo a structured follow-up process, which should be discussed with parents, preferably at a discharge planning meeting.

A neurological examination should be done at 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.

The number of children affected by NE per year in New Zealand is small and collaborative approach to both audit and research in NZ is strongly supported.
### Appendix 1. Simplified Sarnat Criteria

<table>
<thead>
<tr>
<th>Severity</th>
<th>Mild encephalopathy</th>
<th>Moderate encephalopathy</th>
<th>Severe encephalopathy</th>
<th>1h</th>
<th>2h</th>
<th>3h</th>
<th>4h</th>
<th>5h</th>
<th>6h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of consciousness</td>
<td>Hyperalert</td>
<td>Decreased = Reduced response to non-painful stimulation (&quot;lethargic&quot;)</td>
<td>Absent = only responds to painful stimuli (&quot;Stupor&quot;); or no or minimal response to pain (&quot;coma&quot;)</td>
<td>Normal Mild Mod Severe</td>
<td>Norm Mild Mod Severe</td>
<td>Norm Mild Mod Severe</td>
<td>Norm Mild Mod Severe</td>
<td>Norm Mild Mod Severe</td>
<td>Norm Mild Mod Severe</td>
</tr>
<tr>
<td>Spontaneous activity</td>
<td>Normal or increased</td>
<td>Decreased</td>
<td>None</td>
<td>Norm Mild Mod Severe</td>
<td>Norm Mild Mod Severe</td>
<td>Norm Mild Mod Severe</td>
<td>Norm Mild Mod Severe</td>
<td>Norm Mild Mod Severe</td>
<td>Norm Mild Mod Severe</td>
</tr>
<tr>
<td>Tone</td>
<td>Normal or increased in trunk AND extremities</td>
<td>Hypotonia = reduced trunk OR extremity tone OR both</td>
<td>Flaccid = no tone</td>
<td>Norm Mild Mod Severe</td>
<td>Norm Mild Mod Severe</td>
<td>Norm Mild Mod Severe</td>
<td>Norm Mild Mod Severe</td>
<td>Norm Mild Mod Severe</td>
<td>Norm Mild Mod Severe</td>
</tr>
<tr>
<td>Suck reflex</td>
<td>Normal or incomplete</td>
<td>Incomplete</td>
<td>Absent</td>
<td>Norm Mild Mod Severe</td>
<td>Norm Mild Mod Severe</td>
<td>Norm Mild Mod Severe</td>
<td>Norm Mild Mod Severe</td>
<td>Norm Mild Mod Severe</td>
<td>Norm Mild Mod Severe</td>
</tr>
<tr>
<td>Moro reflex</td>
<td>Strong, low threshold</td>
<td>Incomplete</td>
<td>Absent</td>
<td>Norm Mild Mod Severe</td>
<td>Norm Mild Mod Severe</td>
<td>Norm Mild Mod Severe</td>
<td>Norm Mild Mod Severe</td>
<td>Norm Mild Mod Severe</td>
<td>Norm Mild Mod Severe</td>
</tr>
<tr>
<td>Respiratory abnormality</td>
<td>Normal</td>
<td>Periodic breathing</td>
<td>Apnoea</td>
<td>Norm Mild Mod Severe</td>
<td>Norm Mild Mod Severe</td>
<td>Norm Mild Mod Severe</td>
<td>Norm Mild Mod Severe</td>
<td>Norm Mild Mod Severe</td>
<td>Norm Mild Mod Severe</td>
</tr>
</tbody>
</table>

Circle to indicate whether the sign is consistent with normal, mild, moderate or severe NE.
References

10. Austin T et al. To cool or not to cool? Hypothermia treatment outside trial criteria Arch Dis Child Fetal Neonatal Ed 2012;0:F1–F3.