The Hierarchy of Evidence

The Hierarchy of evidence is based on summaries from the National Health and Medical Research Council (2009), the Oxford Centre for Evidence-based Medicine Levels of Evidence (2011) and Melynyk and Fineout-Overholt (2011).

I	Evidence obtained from a systematic review of all relevant randomised control trials.
II	Evidence obtained from at least one well designed randomised control trial.
III	Evidence obtained from well-designed controlled trials without randomisation.
IV	Evidence obtained from well designed cohort studies, case control studies, interrupted time series with a control group, historically controlled studies, interrupted time series without a control group or with case- series
V	Evidence obtained from systematic reviews of descriptive and qualitative studies
VI	Evidence obtained from single descriptive and qualitative studies
VII	Expert opinion from clinicians, authorities and/or reports of expert committees or based on physiology

Reference ***(include title, author, journal title, year of publication, volume and issue, pages)***	**Evidence level (I-VII)**	**Key findings, outcomes or recommendations**
Wincoop. M.V, Biji-Marcus.K.D, Lilien.M, Hoogan. A.V.D, Groenendaal.F. 2021, Effect of Therapeutic Hypothermia on Renal and Myocardial Function in Asphyxiated (near) Term Neonates: A Systematic Review and Meta-analysis. PLoS One 16 (2).	I	- 90% of Neonates with severe HIE develop severe long term disabilities including seizures, mental retardation and cerebral Palsey. - Incidence of 50-%0% renal injury is a common organ dysfunction after perinatal asphyxia - Acute kidney Injury indicated by urine output 0.5mls/kg/hr for over 6 hrs
Sarnat. H. B, Flores-Sarnat.L, Fajardo.C, Leijser.L.M, Wusthoff.C, Mohammad.K, 2020, Sarnat Grading Scale for Neonatal Ecephalopathy after 45 years: An update Proposal, Pediatric Neurology, 113, 75-79.	IV	- Sarnat scale for the classification of HIE - Table adapted from the one in this article.

Queensland Clinical Guidelines, Hypoxic Ischemic Encephalopathy (HIE), Queensland Health 2021	IV	- HIE clinical features - Parents of babies with HIE usually experience acute distress due to the seriousness of their babies condition. - Facilitate the parents' involvement in their babies care - Aim for neutrothermia until baby meets inclusion criteria for TH - Monitor urine output and consider testing for amino acids, ketones, reducing substances - Maintain SpO2 greater than or equal to 92% - Maintain arterial pressure above 35-40 mmHg - Avoid hyperoxia as it is a risk factor for adverse outcomes in babies with HIE treated with TH - Over-ventilation and consequent hypercarbia and high pH that may lead to severe brain hypoperfusion, cellular alkalosis and worse neurodevelopmental outcomes. - Reduce environmental stimulation- noise and light - If aEEG is used, continue during rewarming

Therapeutic Hypothermia for Hypoxic Ischemic Encephalopathy: initiation in special care nurseries Safer Care Victoria Updated 17th Feb 2021	VII	- Controlled passive hypothermia- technique used in SCN in Victoria under the guidance of piper to initiate hypothermia treatment prior to retrieval and transport to NICU. Baby is undressed with radiant warmer off. Refrigerated gel packs are used to lower the temperature - Criteria for hypothermia treatment- moderate or severe encephalopathy between one and six hours after birth. o At least two of: apgar score 5 or less at 10mins, ongoing resuscitation or ventilation at 10 mins, cord ph <7.0 or blood gas ph <7.0 or base deficit 12 or above within one hour of birth o Gestation 35 weeks and above o Less than 6 hours o No- birthweight <1.8kg, major congenital abnormalities that are a likely result in death, overt bleeding, death is considered imminent

Chiang.M-C, Jong.Y-J, Lin. C-H (2017) Therapeutic Hypopthermia for Neonates with Hypoxic Ischemic Ecephalopothy, Paediatrics and Neonatology, 58, 475-483.	V	- Target core temperature of patient should be maintained around 33- 34oC during transport - Rewarming should be performed slowly and core temperature should rise no more than 0.5oC an hour. - Rebound seizures have been noted during the rewarming stage. - Rapid rewarming may adversely affect outcomes and slow rewarming may help preserve the benefits f cooling. - Rapid rewarming may cause electrolyte imbalances (hypoglycemia and hyperkalemia) - Core body temperature should be recorded frequently and regularly during the period of cooling and rewarming to avoid overcooling or hyperthermia.

Sakr. M, Balasundaram, 2022, Neonatal Therapeutic Hypothermia, Stat pearls.	V	- Complications of therapeutic hypothermia: Bradycardia, hypotension, impaired surfactant production, worsening oxygenation, shift of oxyhaemoglobin curve, electrolyte imbalances (hypokaelemia, hyponatremia, hypomgnesemia, hypophosphatemia), coagulopathy, sepsis, delayed gastric emptying, altered pharmacokinetics and pharmacodynamics. - During rewarming, the following complications can occur: higher risk of seizures, apneoa, hypotension, PPHN. - Neonates are preferably kept nil orally during hypothermia.
Lutz. I.C, Allegaert.K, Hoon.JN and Marynissen.H, 2020, Pharmacokinetics during Therapeutic Hypothermia for Neonatal Hypoxic Ischemic Ecephalopothy: a Literature Review. BMJ Paediatrics Open.	II	- Systematic search of literature - Therapeutic Hypothermia reduces mortality by 8.8% and severe morbidity by 15.4%. - Current approach is to cool neonate to 33.5% for duration of 72 hours within 6 hours of birth and a subsequent rewarming at a rate of 0.3-0.5oC per hour. - The clearance of morphine and its metabolites were decreased during therapeutic hypothermia

Jacobs S.E., Berg M., Hunt R., Tarnow Mordi W.O., Inder T.E., Davis P.G. (2013). Cooling for newborns with hypoxic ischemic encephalopathy. Cochrane Database Systematic Review. 31 (1)	I	- Beneficial in term and late preterm infants with HIE - Reduces mortality without increase in major disabilities in survivors - Benefits outweigh the short term adverse effects - Should be instituted in all term/ late preterm infants showing moderate to severe HIE before 6 hours of age - **-** Four trials reported the effect of hypothermia on the presence of pulmonary hypertension of the newborn (Shankaran 2002; Eicher 2005; NICHD Study 2005; TOBY Study 2009). Meta-analysis of the four trials showed no significant effect of hypothermia on PPHN of the newborn and therefore it should not be considered as contraindication for therapeutic hypothermia.

Mosalli, R. (2012) *Whole Body Cooling for Infants with Hypoxic Ischemic Encephalopathy.* Journal of Clinical Neonatology. 1 (2). 101-106.	I	- Pressure area care: Change the position every 6 h during care: flat- supine, right or left side to avoid pressure sores on cold edematous skin. - Fluid Restriction- 40-60mls/kg/day. - Sedation: For ventilated babies, the following should be followed: Give a loading dose of morphine. Then start an infusion at a rate of 10-20mck/kg/min. Consider early weaning after 12 h. At 48 h, discontinuation of morphine should be considered to reduce the risk of accumulation and toxicity. Morphine should be made up in 10% dextrose to avoid hypoglycemia.
Murray, D. M., O'Connor, C. M., Ryan, A. C., Korotchikova, I., Boylan, G. B. (2016) *Early EEG Grade and Outcome at 5 Years After Mild Neonatal Hypoxic Ischemic Encephalopathy.* PEDIATRICS. 138 (4)	IV	- Survivors of untreated mild HIE, graded clinically or by early EEG have higher rates of disability than their peers and have cognitive outcomes similar to that of children with moderate encephalopathy in an uncooled HIE cohort.

Laptook et al, (2017) *Effect of Therapeutic Hypothermia Initiated After 6 Hours of Age on Death or Disability Among Newborns With Hypoxic-Ischemic Encephalopathy A Randomized Clinical Trial.* American Medical Association. 318 (16).	II	- Therapeutic Hypothermia initiated at 6 to 24 hours after birth may have benefit but there is uncertainty in its effectiveness. Further research is required to explore the effectiveness of TH in infants >6 hours of age. - The results of this trial should not change the priority of early identification of infants with hypoxic-ischemic encephalopathy and initiation of hypothermia at less than 6 hours.