Hypoxic-Ischemic Encephalopathy and Therapeutic Hypothermia

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on behalf of the
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Neonatal encephalopathy presumed to be due to hypoxic-ischemic injury is a leading cause of morbidity and mortality worldwide. Different and overlapping definitions and nomenclature for neonatal encephalopathy related to impaired gas exchange at the time of delivery have made it complex to diagnose and measure. Based on an annual term birth rate of greater than 110,000 infants in the state of Georgia and the reported incidence of hypoxic-ischemic encephalopathy (HIE) of 1.5 per 1,000 live births, the estimated number of infants with HIE eligible for therapeutic hypothermia (TH) treatment is 165 infants annually.[1] Some state-specific guidelines and data have been previously reported and can allow for best-practice recommendations and quality improvement between institutions.[2-4]

Data from many large, randomized trials demonstrate that standard TH , defined as reducing the core temperature to 33.5°C for 72 hours from either whole-body hypothermia or selective head cooling, is generally well-tolerated and reduces the risk of death or moderate/severe disability in infants with perinatal HIE.[5] Standard TH also reduces the risk of death and disability as individual outcomes.[5] While there were some differences in subject selection, most infants in these trials were term or near-term with evidence of impaired fetal gas exchange, as evidenced by perinatal acidosis and/or sentinel event, with evidence of moderate or severe encephalopathy on exam. Perinatal risk factors (versus chronic signs of fetal compromise) and initial level of encephalopathy are important indicators of response to TH.[5,6] Two subsequent studies that followed subjects to school-age found that outcome benefits persisted at school-age.[7,8] Evidence has shown that standard TH has more benefit for infants with moderate compared to severe encephalopathy.[9] For some infants with severe encephalopathy and multi-system organ dysfunction, following conversations between the patient's family and referring and accepting physicians, it may be appropriate to *not* proceed with TH and to allow the infant to continue current care near the mother.

Of note, *hyperthermia* has been associated with adverse outcomes.[10] Additionally, deeper and longer TH were not found to be beneficial and perhaps associated with harm.[11] Randomized trials to date have also notably excluded infants who had undergone passive cooling without the use of a servo-controlled device prior to enrollment.[9] Evidence of severe hypothermia associated with passive cooling have been reported.[12,13] The effectiveness of TH initiated between 6 and 24 hours after birth ("late" TH) is uncertain.[14]

Therapeutic drift in treating infants outside of the context of clinical trials has become prevalent over the last decade This drift includes infants without clear evidence of hypoxia-ischemia, younger infants, infants with mild encephalopathy, and infants in other settings.[15-17] Notably, only a small number of infants born at 35 weeks gestation were included in early trials.[18,19] A randomized trial evaluating TH in infants 33-35 weeks gestation has completed enrollment (NCT01793129) and found no benefit to TH in infants < 36 weeks gestation.[20] Published results of this entire study are expected soon. Additionally, while infants with mild HIE have increased risk for brain injury and neurodevelopmental impairment, high-quality evidence showing benefit of TH remains lacking.[21-25] Randomized trials and comparative-effectiveness studies evaluating the impact of TH in infants with mild HIE continue to be enrolling infants (NCT03409770; NCT04176471; NCT04621279). A recent trail of TH for moderate or severe encephalopathy in low- and middle-income countries found no benefit to the composite outcome of death or disability and an increased risk for death with TH.[26] Research is ongoing into adjunctive therapy in addition to TH for infants with moderate or severe HIE. A trial studying the impact of erythropoietin in addition to TH did not find a difference in death or disability.[27] Research into possible additional therapies to supplement TH includes melatonin, sildenafil, and stem cells.[28]

Of note, HIE is a systemic disease that is often associated with multi-organ dysfunction. A proposed multi-system care-bundle has been proposed by the Newborn Brain Society.[29] Recognition of the importance of involving families in the care of these infants during the hospital stay and of connecting them to resources, including peer support, is a crucial step to providing them a solid foundation of support for their medical journey both in and out of the hospital.[30] Allowing parents to feed the infant, particularly with maternal breast milk, and to hold the infant during hypothermia give opportunities for parental engagement early after birth.[31-35]

Substantial variations exist between centers in both volumes of patients treated and in clinical management of infants with HIE.[2,3,36] Outreach education programs aimed at optimizing neuroprotection for infants with HIE through appropriate identification and stabilization have been shown to reduce death and brain injury.[37] Opportunities for clinical care improvement include ensuring eligible infants are offered TH within an appropriate timeframe, avoiding hyperthermia and severe hypothermia, implementing TH in a timely manner, initiating TH on transport, performing serial examinations to follow progression of encephalopathy, applying neuromonitoring earlier, and decreasing times to first enteral and oral feed and times to initial parental holding. Up to 18% of eligible infants with moderate or severe encephalopathy are not offered TH within the correct timeframe due to delay or misdiagnosis.[38] Standardized pathways have been demonstrated to increase the complete and timely evaluation of infants at risk for HIE.[39-41] These guidelines have also been shown to decrease the application of TH outside of clinical guidelines based on aforementioned clinical trials, which would decrease TH use where its benefit remains unclear and may result in needless complications.[42] Creation of standardized practice guidelines for identification of infants with encephalopathy eligible for TH in the state of Georgia is feasible and may improve the care of these high-risk infants.

Clinical Practice Considerations

- **Therapeutic hypothermia at a core target temperature of 33.5°C for 72 hours, herein referred to as standard cooling, improves survival without disability for neonates with moderate/severe encephalopathy.**
- **Studies to date report no benefit from deeper or longer TH, compared to standard cooling (33.5°C for 72 hours.). Additionally, deeper or longer TH may lead to harm. Thus, the focus of care should be on standard cooling.**
- **TH can be implemented during transport. Large trials to date did not include infants who underwent passive cooling. Passive cooling carries risk for severe hypothermia and if used, requires extreme caution with frequent temperature monitoring.**
- **There is uncertainty about the benefit of late TH after 6 hours of age, although there may be a modest benefit.**
- **Prior trials of TH included very few infants with gestational age < 36 weeks. A multicenter trial evaluating TH in infants 33-35 weeks gestation with moderate or severe encephalopathy has been completed, and complete publication is expected in the near future. Initial findings show no benefit in this population.**
- **There is no evidence from clinical trials that TH improves survival or neurodevelopmental impairment in infants with mild encephalopathy. Additionally, there is a lack of detailed evidence on potential risks. Several trials are ongoing regarding TH in this population.**

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