



Commentary

Volume 16 Issue 2 - August 2026
DOI: 10.19080/AJPN.2026.16.555990

Acad J Ped Neonatol

Copyright © All rights are reserved by Steven M Donn

Hypothermic Neuroprotection Following Intrapartum Hypoxia-Ischemia: A Cool Idea, but not a Panacea



Steven M Donn*

Department of Pediatrics, Division of Neonatal-Perinatal Medicine, CS Mott Children's Hospital, Michigan Medicine, Michigan, USA

Submission: August 13, 2025; **Published:** August 19, 2025

***Corresponding author:** Steven M Donn, Department of Pediatrics, Division of Neonatal-Perinatal Medicine, CS Mott Children's Hospital, Michigan Medicine, Michigan, USA

Keywords: Hypothermia; Cerebral; Neurotransmitters; Brain Injury; Cooling

Introduction

Hypothermic neuroprotection to ameliorate intrapartum hypoxic-ischemic brain injury was introduced to the neonatal community around the turn of the millennium. Also referred to as "cooling," hypothermia as a neuroprotective mechanism may have been first recognized in Russia a hundred years earlier, when it was observed that near drowning victims appeared to have better outcomes at colder water temperatures. The exact mechanism through which hypothermia modulates brain injury is not known. Plausible mechanisms include better maintenance of the cerebral energy state, attenuation of the release of excitatory neurotransmitters, decreased caspase-3 activation and apoptosis, reduction of free radicals, and modulation of microglial activation and cytokine production [1].

Studies in animal models concluded that there exists a therapeutic window from the time the brain is injured, where intervention might be beneficial for a limited time, generally considered to be six hours [2]. It should be noted, however, that in these animal studies, conditions can be well controlled and timing is relatively exact. Nevertheless, these observations led to the performance of randomized clinical trials in human newborns. The three largest trials [3-5] had very similar entry criteria and treatment protocols, focusing on newborns experiencing an intrauterine sentinel event, who were encephalopathic and had metabolic evidence of recent hypoxemia. Treatment had to be initiated within six hours of birth and consisted of moderate hypothermia achieved by either selective head cooling using a

design-specific device, or whole-body cooling using a standard cooling blanket.

The results were similar; there was a modest reduction in long term neurologic sequelae in mild to moderately affected treated infants compared to their non-cooled counterparts. Shortly thereafter, cooling became the standard of care. However, major flaws in the original trials have never been adequately addressed, namely that the exact timing of brain injury was not known in the overwhelming majority of subjects (and thus it is unknown how many of these infants had sustained injury more than six hours earlier and were beyond the therapeutic window), and body temperature was not controlled in the non-cooled controls, some of whom were febrile (which could have exacerbated brain injury). Additionally, small subject numbers prevented stratifying by the underlying condition, especially sepsis, which was subsequently shown to be less responsive to hypothermic neuroprotection [6]. Nevertheless, cooling became the standard treatment around 2014.

The American Academy of Pediatrics recognized this, but it also issued a caution that infants should be treated under protocols that closely followed those used in the clinical trials [7]. What has happened, however, is a process referred to as "therapeutic drift." Because hypothermia is a relatively benign intervention with few significant complications, the criteria have been expanded without adequate clinical evaluation. Infants, less than 34 weeks of gestation, are often included, as are those with postnatal ages

beyond 6 hours. Metabolic criteria are often relaxed, and many infants are treated despite being beyond the therapeutic window. Infants with pre-existing central nervous abnormalities are frequently depressed at birth and have a difficult transition to extrauterine life.

In fact, it was Sigmund Freud who first suggested this chicken and egg scenario, that perhaps the depression at birth was the effect of a prior brain injury rather than the cause of it [8]. Therapeutic drift results in the treatment of infants who do not really qualify and who may thus exhibit disparate outcomes. Because of the severe consequences of hypoxic-ischemic brain injury, affected infants are often the subjects of medical malpractice litigation [9]. Failure to provide hypothermic neuroprotection is a frequent allegation and incorrectly assumes that cooling would have made a substantial improvement in outcome. This has been shown to be incorrect. A systematic review and meta-analysis performed by Azzopardi et al determined that the Number Needed to Treat was 6 to 7, meaning that only 14-17% of cooled infants achieve the desired endpoint [10].

That is not to say eligible infants should not be cooled, but expectations need to be realistic. Health care providers can also protect themselves by carefully documenting why they decided not to provide hypothermia. Enumerate all the reasons why the baby did not meet inclusion criteria or if exclusionary criteria were present. This may require some effort in the age of "drop down menus" in the electronic medical record. While some infants will benefit from hypothermic neuroprotection, it is not the "be all, end all" treatment that some believe. Hypoxic-ischemic brain injury is multi-factorial, and its pathogenesis is highly variable. It is likely that effective treatments will eventually require multiple components in addition to hypothermia.

References

1. Sahni SK, Sanocka UM (2008) Hypothermia for hypoxic-ischemic encephalopathy. *Clin Perinatol* 35(4): 717-734.
2. AJ Gunn, TR Gunn, MI Gunning, CE Williams, PD Gluckman (1998) Neuroprotection with prolonged head cooling started before postischemic seizures in fetal sheep. *Pediatrics* 102(5): 1098-1106.
3. PD Gluckman, JS Wyatt, D Azzopardi, R Ballard, AD Edwards, et al. (2005) Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomized trial. *Lancet* 365(9460): 663-670.
4. S Shankaran, AR Laptook, RA Ehrenkranz, JE Tyson, SA McDonald, et al. (2005) Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. *N Engl J Med* 353(15): 1574-1584.
5. D Azzopardi, P Brocklehurst, D Edwards, H Halliday, M Levene, et al. (2008) The TOBY study. Whole body hypothermia for the treatment of perinatal asphyxia encephalopathy: a randomized controlled trial. *BMC Pediatr* 8: 17.
6. Andersen M, Andersen HB, Andelius TCK, LH Hansen, R Pinnerup, et al. (2023) No neuroprotective effect of therapeutic hypothermia following lipopolysaccharide-sensitized hypoxia-ischemia: a newborn piglet study. *Front Pediatr* 11: 1268237.
7. Committee on Fetus and Newborn, Papile LA, Baley JE, et al. (2014) Clinical report: hypothermia and neonatal encephalopathy. *Pediatrics* 133: 1146-1150.
8. Raju TNK (2002) Cerebral palsy and its causes: historical perspectives. In Donn SM, Sinha SK, Chiswick ML (eds.). *Birth Asphyxia and the Brain*. Armonk, NY, Futura Publishing Co pp: 3-22.
9. Donn, SM, Fanaroff JM (2018) Medico-legal implications of hypothermic neuroprotection in the newborn. *J Neonatal Perinatal Med* 11(2): 109-114.
10. Edwards AD, Azzopardi DV (2006) Therapeutic hypothermia following perinatal asphyxia. *Arch Dis Child Fetal Neonatal Ed* 91(2): F127-31.



This work is licensed under Creative Commons Attribution 4.0 License
DOI: [10.19080/AJPN.2026.16.555990](https://doi.org/10.19080/AJPN.2026.16.555990)

Your next submission with Juniper Publishers will reach you the below assets

- Quality Editorial service
- Swift Peer Review
- Reprints availability
- E-prints Service
- Manuscript Podcast for convenient understanding
- Global attainment for your research
- Manuscript accessibility in different formats (Pdf, E-pub, Full Text, Audio)
- Unceasing customer service

Track the below URL for one-step submission

<https://juniperpublishers.com/online-submission.php>