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Therapeutic Hypothermia in Neonatal Hypoxic-Ischemic Encephalopathy: Current Evidence and Clinical Practice- A Literature Review

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ABSTRACT

Background: Hypoxic-ischemic encephalopathy (HIE) remains a major cause of neonatal mortality and long term neurodevelopmental impairment worldwide. Therapeutic hypothermia (TH) is currently the standard of care for newborns with moderate-to-severe HIE; however, several aspects of its use remain controversial.

Aim: The aim of this paper is to present the current state of knowledge regarding the use of therapeutic hypothermia in newborns with HIE with particular emphasis on mechanisms of action, eligibility criteria, course of therapy, clinical efficacy and adverse effects, as well as to discuss current controversies and directions for further research.

Material and methods: A narrative literature review was conducted using the PubMed database to identify studies on therapeutic hypothermia in newborns with hypoxic-ischemic encephalopathy. Publications from the past 11 years were included with particular emphasis on studies published within the last 5 years. Relevant original articles and review papers focusing on clinical outcomes and effectiveness were analyzed.

Results: Therapeutic hypothermia reduces the risk of death and severe neurodevelopmental disability in newborns with moderate and severe HIE. Its neuroprotective effects are associated with reduced cerebral metabolism, decreased oxidative stress, modulation of inflammatory response, and inhibition of apoptosis. However, its efficacy in mild HIE and in preterm infants remains inconclusive. The most common adverse effects include cardiovascular, metabolic, and hematological disturbances requiring close monitoring.

Conclusions: Therapeutic hypothermia is an effective and relatively safe treatment for HIE; however, it does not completely eliminate the risk of neurodevelopmental impairment. Further research is needed to optimize treatment protocols, expand its use to other populations and evaluate combination therapies.

Keywords: neonatal hypoxic ischemic encephalopathy, therapeutic hypothermia, neonatal asphyxia, hypothermia treatment, mild hypoxic ischemic encephalopathy, neonatal encephalopathy, therapeutic hypothermia neonatal complications, clinical efficacy of neonatal therapeutic hypothermia

1. INTRODUCTION

Hypoxic-ischemic encephalopathy (HIE) remains a serious neonatal problem, being one of the leading causes of death and permanent neurodevelopmental disorders in newborns. Therapeutic hypothermia (TH) is currently the standard treatment for moderate-to-severe HIE, reducing the risk of death and severe neurodevelopmental disability [1]. Despite its documented efficacy, there are areas requiring further research, including the use of hypothermia in preterm infants, its role in mild forms of encephalopathy, as well as the optimal duration and depth of therapy [2]. The development of diagnostic methods is also significant, particularly neuroimaging and neurophysiological monitoring, which enable early assessment of brain damage and the prediction of future neurological development [3].

2. MATERIALS AND METHODS

This study was conducted as a narrative review of the literature focusing on therapeutic hypothermia in newborns with hypoxic-ischemic encephalopathy (HIE). A literature search was performed primarily using the PubMed database. To ensure broader coverage, bibliographic references from selected journals, such as Journal of Education, Health and Sport; Quality in Sport, and Pedagogy; Psychology of Sport were also included. The search strategy was based on a combination of keywords and Medical Subject Headings (MeSH), including: “therapeutic hypothermia”, “hypoxic-ischemic encephalopathy”, “newborn”, “neonatal asphyxia”, and “neuroprotection”. Boolean operators (AND, OR) were applied to refine the search and improve relevance. The review included publications from the last 11 years (2015-2026), with particular emphasis on studies published within the past 5 years to reflect the most

recent evidence. Both original research articles and review papers were considered. Exclusion criteria comprised studies with a narrow scope not directly related to the clinical application of therapeutic hypothermia, outdated publications lacking current clinical relevance, non-peer-reviewed articles and studies not focused on human neonatal populations. In total, 42 narrowly focused publications and 28 outdated studies were excluded during the selection process. The final selection of studies was based on their relevance to the clinical outcomes, safety and effectiveness of therapeutic hypothermia in neonates with HIE.

3. RESEARCH RESULTS

The research results presented in this section are divided into eleven areas: Epidemiology, Pathophysiology of HIE, Sarnat Classification of HIE, Indications and eligibility for therapeutic hypothermia, Protocol and Clinical Course of Therapeutic Hypothermia, Newborns born at 35 weeks of gestation or earlier, Therapeutic hypothermia in mild hypoxic-ischemic encephalopathy, Extended, Delayed, and Deeper Therapeutic Hypothermia, Neurophysiological and neuroimaging diagnostics, Adverse effects, New areas of research and combination therapies.

3.1. Epidemiology

Hypoxic-ischemic encephalopathy (HIE) results from hypoxia during the perinatal period and is one of the leading causes of mortality and neurodevelopmental disorders in newborns. Its incidence in developed countries is estimated at approximately 1.5-1.9 per 1,000 live births, whereas in developing countries it is significantly higher, reaching 20-30 per 1,000 births [1,4-6]. The prognosis varies, and mortality ranges from 10% to 60%. A significant percentage of children experience permanent neurological sequelae [4-7].

3.2. Pathophysiology of hypoxic-ischemic encephalopathy

The mechanism of brain damage in the course of perinatal hypoxia is multistage and includes primary, latent, secondary, and tertiary phases. Severe hypoxia leads to a rapid reduction in the supply of oxygen and glucose, resulting in adenosine triphosphate (ATP) production failure and primary neuronal death. In cases of moderate injury, cerebral blood flow is redistributed from the cortex and cerebral hemispheres toward critical structures such as the brainstem, thalamus,

and basal ganglia [8,9]. Once oxygenation is restored, a latent phase begins, typically lasting about 6 hours, during which partial regeneration of energy metabolism and a transient improvement in cellular function are observed. At the same time, inflammatory processes and apoptotic cascades are triggered, leading to further neuronal damage. This period represents a critical therapeutic window for the implementation of therapeutic hypothermia, whose effects include a reduction in the brain's metabolic demand, a reduction in oxidative stress, a reduction in the inflammatory response, and the inhibition of apoptosis and receptor-mediated excitotoxicity [1,8,9]. Following the latent phase, the secondary phase develops, characterized by increased oxidative stress, mitochondrial dysfunction, cytotoxic edema, and progressive neuronal death, often leading to clinical deterioration and the onset of seizures [1,8,9]. This is followed by the tertiary phase, lasting for months, involving processes of neural tissue remodeling and delayed neuronal loss [8-10].

3.3. Sarnat Classification of Hypoxic-Ischemic Encephalopathy

The clinical presentation of hypoxic-ischemic encephalopathy (HIE) in term newborns was described in Sarnat's 1976 classification [1,2]. Since 2013, a modified version of this classification has been in use, based primarily on clinical assessment, sometimes supplemented by amplitude-integrated EEG (aEEG) recording prior to the initiation of therapeutic hypothermia [2,11]. Assessment using the Sarnat scale should be performed before treatment begins, then every 12 hours during therapeutic hypothermia, and once daily after its completion until discharge [3]. The modified classification distinguishes three grades of ENN. The mild form typically has a short-term course and is characterized by preserved alertness and normal reflexes. The moderate stage involves disturbances of consciousness in the form of stupor, hypotonia, and multifocal seizures. The severe form is characterized by profound disturbances of consciousness, generalized muscle flaccidity, and loss of brainstem reflexes [1,2,11,12]. Electroencephalography, although not a mandatory test, is an important tool to supplement clinical assessment. In the mild form, the EEG recording is usually normal; in the moderate form, generalized slowing of bioelectrical activity with a predominance of delta waves is observed; whereas in severe encephalopathy, an isoelectric or isopotential recording may occur [1,2]. Systematic documentation of clinical changes and EEG recordings allows for subsequent correlation with neuroimaging results, including brain MRI, and assessment of further neurological development [11].

Feature	Mild form	Moderate form	Severe form
Level of consciousness	Alert	Drowsiness	Severe impairment of consciousness (coma)
Muscle tone	Normal	Decreased (hypotonia)	Markedly decreased (flaccidity)
Posture	Normal	Distal flexion, complete abduction	Decerebrate posture
Neonatal reflexes	Normal	Weakened	Absent (including brainstem reflexes)
Seizures	Absent	Present (often multifocal)	May occur or lack responsiveness
Respiration	Normal	Bradycardia	Variable
Pupils	Normal	Constricted	Constricted
EEG	Usually normal	Generalized slowing (delta waves)	Isoelectric or isopotential

Table 1. Sarnat Scale [1-3,11].

3.4. Indications and eligibility for therapeutic hypothermia

The decision to treat a newborn with therapeutic hypothermia is based on meeting three sets of criteria: demographic, biochemical, and clinical [13]. Demographic criteria include gestational age ≥36 weeks, birth weight ≥1800 g, and the ability to initiate treatment within the first 6 hours of life. Biochemical criteria are met if the pH is ≤7.0 or the base deficit is ≥16 mmol/L on blood gas analysis performed within the first hour of life (from umbilical cord blood or neonatal blood). In cases of borderline values (pH 7.0-7.15 or base deficit 10-15.9 mmol/L) or the absence of available blood gas analysis, the presence of an acute perinatal event and an Apgar score of ≤5 at 10 minutes of life, or the need for assisted ventilation for ≥10 minutes after birth, is additionally required [1,13,14]. Once the above criteria are met, clinical criteria - specifically the newborn's neurological status - are assessed [1,13]. Children with symptoms of moderate-to-severe hypoxic-ischemic encephalopathy, including abnormal muscle tone, abnormal neonatal reflexes (such as sucking and Moro reflexes), and signs of autonomic dysfunction (e.g., abnormal pupillary responses, respiratory distress, or bradycardia), meet the clinical criteria for therapeutic hypothermia. The occurrence of seizures is a significant marker of encephalopathy and may serve as a basis for eligibility after meeting demographic and

biochemical criteria [1,13,14]. Newborns meeting the above criteria are eligible for therapeutic hypothermia treatment [1,13]. Neuroimaging techniques play a supplementary role but their diagnostic value is limited during the first 24 hours of life. On transcranial ultrasound, lesions usually appear after 24-48 hours, whereas diffusion-weighted imaging (DWI) may reveal abnormalities earlier, although the full extent of the damage becomes apparent at a later stage [1].

Criteria Group	Specific Criteria
Demographic	gestational age ≥36 weeks birth weight ≥1800 g ability to initiate treatment within ≤6 hours of life
Biochemical	pH ≤7.0 or BE ≥16 mmol/L (within the first hour of life)
Biochemical (borderline)	pH 7.0–7.15 or BE 10–15.9 mmol/L + (Apgar score ≤5 at 10 minutes or mechanical ventilation ≥10 minutes)
Clinical	Symptoms of moderate or severe HIE
Additional	Seizures as a marker of encephalopathy

Table 2. Eligibility criteria for therapeutic hypothermia [1,13,14].

3.5. Protocol and Clinical Course of Therapeutic Hypothermia

Therapeutic hypothermia (TH) is administered according to a protocol comprising three phases: cooling, rewarming and normothermia [15]. During the cooling phase, the body temperature is maintained at 33.5 °C for 72 hours. Treatment should be initiated within the first 6 hours of life [14,15,16]. During this period newborns often require analgosedation, most commonly with opioids (morphine or fentanyl) sometimes in combination with midazolam. A significant proportion of patients also require respiratory support, including mechanical ventilation [15,17] After the cooling phase ends, gradual rewarming at a controlled rate occurs for approximately 12-15 hours until normothermia is achieved, which constitutes the final stage of therapy [15]. It has been demonstrated that the use of therapeutic hypothermia reduces the risk of death or severe neurodevelopmental disability in children assessed at 18 months of age [14].

3.6. Preterm Infants (≤35 Weeks of Gestation)

In preterm infants born between 33 and 35 weeks of gestation, the efficacy of therapeutic hypothermia has not been conclusively demonstrated. This is due to differences in neurological maturity and the greater susceptibility of the brain's white matter to damage [18,19]. Studies indicate no significant reduction in mortality or severe neurodevelopmental disorders in this group, while simultaneously increasing the risk of complications such as coagulopathy, seizures, hypotonia, intracranial hemorrhage, metabolic acidosis and thrombocytopenia, as well as a high rate of moderate and severe developmental disorders [18,19,20].

3.7. Therapeutic hypothermia in mild hypoxic-ischemic encephalopathy

Mild hypoxic-ischemic encephalopathy (HIE) is not a completely benign clinical condition and may be associated with an increased risk of brain damage and neurodevelopmental disorders, including cognitive and language difficulties or autism spectrum disorders. The course of neonatal encephalopathy is dynamic, so the mild form of the disease may progress [2]. To date, no clear definition of mild HIE or standards for its treatment has been established, as newborns with this form of the disease were not included in key randomized trials on therapeutic hypothermia. Nevertheless, this therapy is sometimes used in some centers, a phenomenon referred to as "therapeutic creep," resulting mainly from concerns about disease progression and the loss of the therapeutic window [2]. Amplitude-integrated EEG (aEEG) can complement the neurological assessment, although its predictive value is limited in the first hours of life and increases after 24-48 hours [2,21]. Studies indicate that some newborns with mild HIE show abnormalities on neuroimaging or in neurodevelopmental assessments and approximately 16% of children develop developmental disorders in the first years of life [2,21,22]. Clinical trials are currently underway (including COMET and COOL-PRIME) to evaluate the efficacy of this therapy in newborns with mild HIE [23].

3.8. Extended, Delayed, and Deeper Therapeutic Hypothermia

In newborns with moderate or severe hypoxic-ischemic encephalopathy (HIE), delayed initiation of therapeutic hypothermia (TH) between 6 and 24 hours of life, its continuation for 96 hours, and deeper hypothermia (32.0°C) did not show a significant effect on mortality or

disability [1,24,25]. The adjusted relative risk of death was higher in the group cooled for 120 hours than in the group cooled for 72 hours [25].

3.9. Neurophysiological and neuroimaging diagnostics

Amplitude-integrated EEG (aEEG) and conventional EEG (cEEG) allow for the prediction of neurological development in newborns treated with therapeutic hypothermia, particularly when the recordings are analyzed between 48 and 72 hours of life. Seizures may occur both during hypothermia and after the rewarming phase and a high number of seizures is associated with a poorer neurological prognosis [1]. Magnetic resonance imaging (MRI) is the primary method for assessing brain damage in newborns with encephalopathy, including those treated with therapeutic hypothermia. T1 - and T2 - weighted sequences and diffusion-weighted imaging (DWI) are used in the diagnosis. The examination performed between the 4th and 6th day of life, immediately after the end of hypothermia, has the greatest diagnostic value. MRI abnormalities are found in over 90% of newborns with encephalopathy and seizures, most commonly in the basal ganglia and thalamus [3,26,27]. Magnetic resonance spectroscopy (MRS) provides additional prognostic information by allowing for the assessment of brain metabolites. The concentration of N-acetylaspartate (NAA) and the lactate/NAA ratio within the basal ganglia demonstrate particularly high prognostic value [1,28]. MRI scans performed later in life show reduced volumes of white and gray matter, as well as structures such as the hippocampus and thalamus in children with HIE, which correlates with cognitive and motor functions. Abnormalities in the mammillary bodies observed in approximately 35-38% of patients are associated with memory and cognitive impairments [1,29,30].

3.10. Adverse effects

The most common cardiovascular complications include sinus bradycardia, arterial hypotension, and cardiac arrhythmias, including QT prolongation [31]. The severity of bradycardia correlates with a decrease in body temperature and amounts to approximately 15 beats/min for every 1°C drop in temperature [31,32]. Intraventricular hemorrhage was observed in approximately 0.9-9% of newborns; however, in most cases, it was mild and showed no significant association with neurodevelopmental outcomes at 18-26 months of age [1,33,34]. Respiratory complications include impaired oxygenation associated with pulmonary vasoconstriction and transient neonatal pulmonary hypertension, which in some cases requires the use of inhaled nitric oxide [31]. Hypothermia also affects metabolic and electrolyte balance,

leading to disorders such as hypokalemia, hyponatremia, hypomagnesemia, and hypophosphatemia [31]. Glycemic disturbances are common during treatment; therefore, monitoring via continuous glucose monitoring (CGM) is recommended [35]. Normoglycemia was observed in 15-57.4% of newborns, hypoglycemia in 13.6-20.0%, and hyperglycemia in 10.8-37% of patients [36,37]. Both glycemic disturbances increase the risk of death [34]. Hypothermia may also lead to coagulation disorders associated with platelet dysfunction, transient renal dysfunction, elevated liver enzymes, and increased susceptibility to infection [31]. In some school-aged children (6-8 years), motor and cognitive impairments persist. [38] The relative risk of cerebral palsy in children treated with hypothermia is approximately 0.6 [39]. All children with cerebral palsy had an intelligence quotient (IQ) <70; however, reduced intelligence test scores are also more frequently observed in patients without cerebral palsy compared to the general population [39-41].

System	**Adverse effects**
Cardiovascular	Sinus bradycardia Arterial hypotension Arrhythmias (including QT prolongation)
Central nervous	Intraventricular hemorrhage
Respiratory	Decreased oxygenation Transient pulmonary hypertension of the newborn (PPHN)
Metabolic and electrolyte	Hypokalemia Hyponatremia Hypomagnesemia Hypophosphatemia Hypoglycemia Hyperglycemia
Hematologic	Coagulation disorders (platelet dysfunction)
Urinary	Transient renal dysfunction
Digestive	Elevated liver enzymes
Immunological	Increased susceptibility to infection

Table 3. Adverse effects [1, 31-41].

3.11. New areas of research and combination therapies

Recombinant erythropoietin (rEPO) is an alternative therapy being evaluated in newborns with hypoxic-ischemic encephalopathy (HIE), demonstrating potential neuroprotective and neuroregenerative effects as well as a favorable safety profile, particularly when administered during the early latent phase. However, its efficacy requires confirmation in Phase III trials [1,2]. The HEAL trial demonstrated that adding erythropoietin to therapeutic hypothermia did not improve outcomes and was associated with a higher incidence of adverse events [1,42,43]. A meta-analysis of studies conducted in low- and middle-income countries showed a reduction in the risk of death or disability from 49.7% to 27.6% in newborns treated with erythropoietin alone, where therapeutic hypothermia could not be used [44].

4. DISCUSSION

Therapeutic hypothermia significantly improves the prognosis in newborns with moderate and severe HIE; however, its efficacy in mild HIE remains unclear. The phenomenon of "therapeutic creep" indicates an expansion of indications beyond the populations included in randomized trials. Despite a good safety profile, TH may cause transient multisystem complications: bradycardia, hypotension, metabolic and coagulation disorders, pulmonary hypertension, glycemic disturbances, as well as neurological complications such as MPD or reduced IQ. Knowledge of potential risks allows for early intervention and patient monitoring. The narrow therapeutic window (up to 6 hours) requires rapid assessment of demographic, biochemical, and neurological criteria. Early monitoring of blood glucose (CGM), EEG, and MRI enhances safety and enables the prediction of long-term outcomes. Research on combined neuroprotective therapies, such as recombinant erythropoietin, is ongoing and may improve treatment efficacy in the future. However, the results of studies to date are mixed and require further randomized clinical trials.

5. CONCLUSIONS

Therapeutic hypothermia remains the standard of care for newborns with moderate to severe hypoxic-ischemic encephalopathy, significantly reducing the risk of death and long-term neurodevelopmental impairment. Its effectiveness depends on early initiation, optimal duration and strict adherence to established treatment protocols. Current evidence does not support

extending the duration of therapy, increasing the depth of hypothermia or delaying its initiation beyond the recommended therapeutic window. In addition, the use of therapeutic hypothermia in mild cases of hypoxic-ischemic encephalopathy and in preterm infants remains controversial and requires further investigation. Accurate clinical assessment, including the use of the Sarnat classification and adjunctive neurophysiological and neuroimaging tools, is essential for appropriate patient selection and monitoring. Despite its proven benefits, therapeutic hypothermia is associated with potential adverse effects, highlighting the need for careful clinical supervision. Future research should focus on optimizing patient selection, refining treatment protocols and exploring adjunctive neuroprotective strategies to further improve neurological outcomes.

Disclossure

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Conflict of Interest Statement

The authors deny any conflict of interest

Declaration of the use of AI:

In preparing this work, the authors used ChatGPT to improve the language, readability, and text formatting. After using this tool, the authors reviewed and edited the content as necessary and accept full responsibility for the substantive content of the publication.

References

1. Chakkarapani E, de Vries LS, Ferriero DM, Gunn AJ. Neonatal encephalopathy and hypoxic-ischemic encephalopathy: the state of the art. Pediatric Research 2025;98(7):2444-2458. https://doi.org/10.1038/s41390-025-03986-2.
2. McDouall A, Wassink G, Bennet L, Gunn AJ, Davidson JO. Challenges in developing therapeutic strategies for mild neonatal encephalopathy. Neural Regeneration Research 2022;17(2):277-282. https://doi.org/10.4103/1673-5374.317963.
3. Weeke LC, Groenendaal F, Toet MC, Benders MJ, Nievelstein RA, van Rooij LG, de Vries LS. The aetiology of neonatal seizures and the diagnostic contribution of neonatal

cerebral magnetic resonance imaging. Developmental Medicine and Child Neurology 2015;57(3):248-256. https://doi.org/10.1111/dmcn.12629.

4. Tsuda K, Shibasaki J, Isayama T, Takeuchi A, Mukai T, Sugiyama Y, Ioroi T, Takahashi A, Yutaka N, Iwata S, Nabetani M, Iwata O. Three-year outcome following neonatal encephalopathy in a high-survival cohort. Scientific reports 2022;12(1):7945. https://doi.org/10.1038/s41598-022-12091-x.
5. Greco P, Nencini G, Piva I, Scioscia M, Volta CA, Spadaro S, Neri M, Bonaccorsi G, Greco F, Cocco I, Sorrentino F, D'Antonio F, Nappi L. Pathophysiology of hypoxic-ischemic encephalopathy: a review of the past and a view on the future. Acta Neurologica Belgica 2020;120(2):277-288. https://doi.org/10.1007/s13760-020-01308-3.
6. Namusoke H, Nannyonga MM, Ssebunya R, Nakibuuka VK, Mworozi E. Incidence and short term outcomes of neonates with hypoxic ischemic encephalopathy in a peri-urban teaching hospital, Uganda: a prospective cohort study. Maternal Health, Neonatology and Perinatology 2018;4:6. https://doi.org/10.1186/s40748-018-0074-4.
7. Ezenwa BN, Olorunfemi G, Fajolu I, Adeniyi T, Oleolo-Ayodeji K, Kene-Udemezue B, Olamijulo JA, Ezeaka C. Trends and predictors of in-hospital mortality among babies with hypoxic ischaemic encephalopathy at a tertiary hospital in Nigeria: a retrospective cohort study. Plos One 2021;16(4):e0250633. https://doi.org/10.1371/journal.pone.0250633.
8. Gunn AJ, Laptook AR, Robertson NJ, Barks JD, Thoresen M, Wassink G, Bennet L. Therapeutic hypothermia translates from ancient history into practice. Pediatric Research 2017;81(1-2):202-209. https://doi.org/10.1038/pr.2016.198.
9. Douglas-Escobar M, Weiss MD. Hypoxic-ischemic encephalopathy: a review for the clinician. JAMA Pediatrics 2015;169(4):397-403. https://doi.org/10.1001/jamapediatrics.2014.3269.
10. Chiang MC, Lien R, Chu SM, Yang PH, Lin JJ, Hsu JF, Fu RH, Lin KL. Serum lactate, brain magnetic resonance imaging and outcome of neonatal hypoxic ischemic encephalopathy after therapeutic hypothermia. Pediatrics and Neonatology 2016;57(1):35-40. https://doi.org/10.1016/j.pedneo.2015.04.008.
11. Mrelashvili A, Russ JB, Ferriero DM, Wusthoff CJ. The Sarnat score for neonatal encephalopathy: looking back and moving forward. Pediatric Research 2020;88(6):824-825. https://doi.org/10.1038/s41390-020-01143-5.

12. Widłak K, Wójtowicz A, Ściślak R, Drankowska J, Kos M, Szuster A, Tarkowska A, Szponar E, Furmaga-Jabłońska W. Ischemic Stroke As a Rare Cause of Seizures in a Newborn- Case Report. Journal Education Health Sport 2019,9, 76-84. http://dx.doi.org/10.5281/zenodo.3265753
13. Vesoulis ZA, Liao SM, Rao R, Trivedi SB, Cahill AG, Mathur AM. Re-examining the arterial cord blood gas pH screening criteria in neonatal encephalopathy. Archives of Disease in Childhood - Fetal and Neonatal Edition 2018;103(4):F377-F382. https://doi.org/10.1136/archdischild-2017-313078.
14. Branagan A, Hurley T, Quirke F, Devane D, Taneri PE, Badawi N, Sinha B, Bearer C, Bloomfield FH, Bonifacio SL, Boylan G, Campbell SK, Chalak L, D'Alton M, de Vries LS, El Dib M, Ferriero DM, Gale C, Gressens P, Gunn AJ, Kay S, Maeso B, Mulkey SB, Murray DM, Nelson KB, Nesterenko TH, Pilon B, Robertson NJ, Walker K, Wusthoff CJ, Molloy EJ; Steering Group for DEFiNE. Consensus definition and diagnostic criteria for neonatal encephalopathy: study protocol for a real-time modified Delphi study. Pediatric Research 2025;97(1):430 436. https://doi.org/10.1038/s41390-024-03303-3.
15. Sutin J, Vyas R, Feldman HA, Ferradal S, Hsiao CH, Zampolli L, Pierce LJ, Nelson CA, Morton SU, Hay S, El-Dib M, Soul JS, Lin PY, Grant PE. Association of cerebral metabolic rate following therapeutic hypothermia with 18-month neurodevelopmental outcomes after neonatal hypoxic ischemic encephalopathy. EBioMedicine 2023;94:104673. https://doi.org/10.1016/j.ebiom.2023.104673.
16. Koryszko K, Pokrywka N, Suwała D, Polak M, Hetnar P, Kiper S, Fortuna M, Toczek S, Tomala M, Jastrowicz-Chęć, K. Therapeutic Hypothermia As a Treatment Strategy for Neonates Born in Asphyxia - a Review of the Current State of Knowledge. Quality of Sport 2025, 43, 61418 https://doi.org/10.12775/QS.2025.43.61418
17. Vega-Del-Val C, Arnaez J, Caserío S, Gutiérrez EP, Castañón L, Benito M, Garcia-Alix A; Grupo ARAHIP. Adherence to hypothermia guidelines in newborns with hypoxic-ischemic encephalopathy. Anales de Pediatria (English Edition) 2022;97(1):30-39. https://doi.org/10.1016/j.anpede.2021.07.007.
18. Herrera TI, Edwards L, Malcolm WF, Smith PB, Fisher KA, Pizoli C, Gustafson KE, Goldstein RF, Cotten CM, Goldberg RN, Bidegain M. Outcomes of preterm infants treated with hypothermia for hypoxic-ischemic encephalopathy. Early Human Development 2018;125:1-7. https://doi.org/10.1016/j.earlhumdev.2018.08.003.

19. Faix RG, Laptook AR, Shankaran S, Eggleston B, Chowdhury D, Heyne RJ, Das A, Pedroza C, Tyson JE, Wusthoff C, Bonifacio SL, Sánchez PJ, Yoder BA, Laughon MM, Vasil DM, Van Meurs KP, Crawford MM, Higgins RD, Poindexter BB, Colaizy TT, Hamrick SEG, Chalak LF, Ohls RK, Hartley-McAndrew ME, Dysart K, D'Angio CT, Guillet R, Kicklighter SD, Carlo WA, Sokol GM, DeMauro SB, Hibbs AM, Cotten CM, Merhar SL, Bapat RV, Harmon HM, Sewell E, Winter S, Natarajan G, Mosquera R, Hintz SR, Maitre NL, Benninger KL, Peralta-Carcelen M, Hines AC, Duncan AF, Wilson-Costello DE, Trembath A, Malcolm WF, Walsh MC; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Whole-body hypothermia for neonatal encephalopathy in preterm infants 33 to 35 weeks' gestation: a randomized clinical trial. JAMA Pediatrics 2025;179(4):396-406. https://doi.org/10.1001/jamapediatrics.2024.6613.
20. Rao R, Trivedi S, Vesoulis Z, Liao SM, Smyser CD, Mathur AM. Safety and short-term outcomes of therapeutic hypothermia in preterm neonates 34-35 weeks gestational age with hypoxic-ischemic encephalopathy. The Journal Pediatrics 2017;183:37-42. https://doi.org/10.1016/j.jpeds.2016.11.019.
21. Prempunpong C, Chalak LF, Garfinkle J, Shah B, Kalra V, Rollins N, Boyle R, Nguyen KA, Mir I, Pappas A, Montaldo P, Thayyil S, Sánchez PJ, Shankaran S, Laptook AR, Sant'Anna G. Prospective research on infants with mild encephalopathy: the PRIME study. Journal of Perinatology 2018;38(1):80-85. https://doi.org/10.1038/jp.2017.164.
22. Finder M, Boylan GB, Twomey D, Ahearne C, Murray DM, Hallberg B. Two-year neurodevelopmental outcomes after mild hypoxic ischemic encephalopathy in the era of therapeutic hypothermia. JAMA Pediatrics 2020;174(1):48-55. https://doi.org/10.1001/jamapediatrics.2019.4011.
23. Garegrat R, Montaldo P, Burgod C, Pant S, Mazlan M, Palanisami B, Chakkarapani E, Woolfall K, Johnson S, Grant PE, Land S, Mahmoud M, Brady T, Cornelius V, Adams E, Dorling J, Aladangadi N, Fleming P, Pressler R, Shennan A, Petrou S, Soe A, Basset P, Shankaran S, Thayyil S. Whole-body hypothermia in mild neonatal encephalopathy: protocol for a multicentre phase III randomized controlled trial. BMC Pediatrics 2024;24(1):460. https://doi.org/10.1186/s12887-024-04935-4.
24. Laptook AR, Shankaran S, Tyson JE, Munoz B, Bell EF, Goldberg RN, Parikh NA, Ambalavanan N, Pedroza C, Pappas A, Das A, Chaudhary AS, Ehrenkranz RA, Hensman AM, Van Meurs KP, Chalak LF, Khan AM, Hamrick SEG, Sokol GM, Walsh MC, Poindexter BB, Faix RG, Watterberg KL, Frantz ID 3rd, Guillet R, Devaskar U,

Truog WE, Chock VY, Wyckoff MH, McGowan EC, Carlton DP, Harmon HM, Brumbaugh JE, Cotten CM, Sánchez PJ, Hibbs AM, Higgins RD; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Effect of therapeutic hypothermia initiated after 6 hours of age on death or disability among newborns with hypoxic-ischemic encephalopathy: a randomized clinical trial. JAMA 2017;318(16):1550-1560. https://doi.org/10.1001/jama.2017.14972.

25. Shankaran S, Laptook AR, Pappas A, McDonald SA, Das A, Tyson JE, Poindexter BB, Schibler K, Bell EF, Heyne RJ, Pedroza C, Bara R, Van Meurs KP, Huitema CMP, Grisby C, Devaskar U, Ehrenkranz RA, Harmon HM, Chalak LF, DeMauro SB, Garg M, Hartley-McAndrew ME, Khan AM, Walsh MC, Ambalavanan N, Brumbaugh JE, Watterberg KL, Shepherd EG, Hamrick SEG, Barks J, Cotten CM, Kilbride HW, Higgins RD; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Effect of depth and duration of cooling on death or disability at age 18 months among neonates with hypoxic-ischemic encephalopathy: a randomized clinical trial. JAMA. 2017;318(1):57-67. https://doi.org/10.1001/jama.2017.7218.
26. Ouwehand S, Smidt LCA, Dudink J, Benders MJNL, de Vries LS, Groenendaal F, van der Aa NE. Predictors of outcomes in hypoxic-ischemic encephalopathy following hypothermia: a meta-analysis. Neonatology 2020;117(4):411-427. https://doi.org/10.1159/000505519.
27. Chakkarapani E, Poskitt KJ, Miller SP, Zwicker JG, Xu Q, Wong DS, Roland EH, Hill A, Chau V. Reliability of early magnetic resonance imaging and necessity of repeating MRI in noncooled and cooled infants with neonatal encephalopathy. Journal of Child Neurology 2016;31(5):553-559. https://doi.org/10.1177/0883073815600865.
28. Mitra S, Kendall GS, Bainbridge A, Sokolska M, Dinan M, Uria-Avellanal C, Price D, McKinnon K, Gunny R, Huertas-Ceballos A, Golay X, Robertson NJ. Proton magnetic resonance spectroscopy lactate/N-acetylaspartate within 2 weeks of birth accurately predicts 2-year outcomes in neonatal encephalopathy after therapeutic hypothermia. Archives of Disease in Childhood - Fetal and Neonatal Edition 2019;104(4):F424-F432. https://doi.org/10.1136/archdischild-2018-315478.
29. Spencer APC, Lee-Kelland R, Brooks JCW, Jary S, Tonks J, Cowan FM, Thoresen M, Chakkarapani E. Brain volumes and functional outcomes in children without cerebral

palsy after therapeutic hypothermia. Developmental Medicine and Child Neurology 2023;65(3):367-375. https://doi.org/10.1111/dmcn.15369.

30. Spencer APC, Lequin MH, de Vries LS, Brooks JCW, Jary S, Tonks J, Cowan FM, Thoresen M, Chakkarapani E. Mammillary body abnormalities and cognitive outcomes in children cooled for neonatal encephalopathy. Developmental Medicine and Child Neurology 2023;65(6):792-802. https://doi.org/10.1111/dmcn.15453.
31. Geisinger R, Rios DR, McNamara PJ, Levy PT. Asphyxia, therapeutic hypothermia, and pulmonary hypertension. Clinics in Perinatology 2024;51(1):127-149. https://doi.org/10.1016/j.clp.2023.11.007.
32. Acun C, Ali M, Liu W, Karnati S, Fink K, Aly H. Effectiveness and safety of dexmedetomidine in neonates with hypoxic ischemic encephalopathy undergoing therapeutic hypothermia. The Journal of Pediatric Pharmacology and Therapeutics 2024;29(3):232-240. https://doi.org/10.5863/1551-6776-29.3.232.
33. Odd D, Sabir H, Jones SA, Gale C, Chakkarapani E. Risk factors for infection and outcomes in infants with neonatal encephalopathy: a cohort study. Pediatric Research 2024;96(3):785-791. https://doi.org/10.1038/s41390-024-03157-9.
34. Lakatos A, Kolossváry M, Szabó M, Jermendy Á, Barta H, Gyebnár G, Rudas G, Kozák LR. Neurodevelopmental effect of intracranial hemorrhage in hypoxic ischemic brain injury in hypothermia-treated neonates. BMC Pediatrics 2019;19(1):430. https://doi.org/10.1186/s12887-019-1777-z.
35. Puzone S, Diplomatico M, Caredda E, Maietta A, Miraglia Del Giudice E, Montaldo P. Hypoglycaemia and hyperglycaemia in neonatal encephalopathy: a systematic review and meta-analysis. Archives of Disease in Childhood - Fetal and Neonatal Edition 2023;109(1):18-25. https://doi.org/10.1136/archdischild-2023-325592.
36. Mietzsch U, Wood TR, Wu TW, Natarajan N, Glass HC, Gonzalez FF, Mayock DE, Comstock BA, Heagerty PJ, Juul SE, Wu YW; HEAL Study Group. Early glycemic state and outcomes of neonates with hypoxic-ischemic encephalopathy. Pediatrics. 2023;152(4):e2022060965. https://doi.org/10.1542/peds.2022-060965.
37. Ali MAM, Farghaly MAA, El-Dib I, Karnati S, Aly H, Acun C. Glucose instability and outcomes of neonates with hypoxic ischemic encephalopathy undergoing therapeutic hypothermia. Brain and Development 2024;46(8):262-267. https://doi.org/10.1016/j.braindev.2024.05.003.

38. Mess E.A., Rybakiewicz A., Pawelak A., Lisowska A., Ornat M. Assessment of the Level of Anxiety of Caring for Disabled. Pedagogy and Psychology of Sport 2019, 5, 165-182. http://dx.doi.org/10.5281/zenodo.2561188
39. Pappas A, Shankaran S, McDonald SA, Vohr BR, Hintz SR, Ehrenkranz RA, Tyson JE, Yolton K, Das A, Bara R, Hammond J, Higgins RD; Hypothermia Extended Follow-up Subcommittee of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Cognitive outcomes after neonatal encephalopathy. Pediatrics. 2015;135(3):e624-e634. https://doi.org/10.1542/peds.2014-1566.
40. Lee-Kelland R, Jary S, Tonks J, Cowan FM, Thoresen M, Chakkarapani E. School-age outcomes of children without cerebral palsy cooled for neonatal hypoxic-ischaemic encephalopathy. Archives of Disease in Childhood - Fetal and Neonatal Edition 2020;105(1):8-13. https://doi.org/10.1136/archdischild-2018-316509.
41. Robb TJ, Tonks J, Spencer APC, Jary S, Whitfield CK, Thoresen M, Cowan FM, Chakkarapani E. Communication skills in children aged 6-8 years without cerebral palsy cooled for neonatal hypoxic-ischemic encephalopathy. Scientific Report 2022;12(1):17757. https://doi.org/10.1038/s41598-022-21723-1.
42. Wisnowski JL, Monsell SE, Bluml S, Goodman AM, Li Y, Comstock BA, Heagerty PJ, Juul SE, Wu YW, McKinstry RC, Mathur AM; HEAL Consortium. Brain injury outcomes after adjuvant erythropoietin neuroprotection for moderate or severe neonatal hypoxic-ischemic encephalopathy. Developmental Neuroscience 2024;46(5):285-296. https://doi.org/10.1159/000534618.
43. Wu YW, Comstock BA, Gonzalez FF, Mayock DE, Goodman AM, Maitre NL, Chang T, Van Meurs KP, Lampland AL, Bendel-Stenzel E, Mathur AM, Wu TW, Riley D, Mietzsch U, Chalak L, Flibotte J, Weitkamp JH, Ahmad KA, Yanowitz TD, Baserga M, Poindexter BB, Rogers EE, Lowe JR, Kuban KCK, O'Shea TM, Wisnowski JL, McKinstry RC, Bluml S, Bonifacio S, Benninger KL, Rao R, Smyser CD, Sokol GM, Merhar S, Schreiber MD, Glass HC, Heagerty PJ, Juul SE; HEAL Consortium. Trial of erythropoietin for hypoxic-ischemic encephalopathy in newborns. The New England Journal of Medicine 2022;387(2):148-159. https://doi.org/10.1056/nejmoa2119660.
44. Ivain P, Montaldo P, Khan A, Elagovan R, Burgod C, Morales MM, Pant S, Thayyil S. Erythropoietin monotherapy for neuroprotection after neonatal encephalopathy in low-to-middle income countries: a systematic review and meta-analysis. Journal of Perinatology 2021;41(9):2134-2140. https://doi.org/10.1038/s41372-021-01132-4.