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The impact of therapeutic hypothermia in neonates with hypoxic-ischemic encephalopathy: a narrative review.

Wiktoria Matyszkiewicz[1], Aleksandra Wąż[2], Nadia Żurek[3], Martyna Miśkiewicz[4], Gabriela Kawa[5], Jolanta Renata Bartoń-Kowalska[6], Julia Dymalska[7], Małgorzata Kapsa[8], Julianna Cyganik[9]

Medical University of Silesia, Katowice, Poland, ORCID: 0009-0005-8905-2257[1]
Medical University of Silesia, Katowice, Poland, ORCID: 0009-0000-4889-5083[2]
Medical University of Silesia, Katowice, Poland, ORCID: 0009-0001-0432-3144[3]
Medical University of Silesia, Katowice, Poland, ORCID: 0009-0004-4505-8983[4]
Poznań University of Medical Sciences, Poznań, Poland, ORCID: 0009-0005-9217-3965[5]
Healthcare Complex in Dąbrowa Tarnowska, Poland, ORCID: 0009-0002-1895-2598[6]
Poznań University of Medical Sciences, Poznań, Poland, ORCID: 0009-0004-8185-5242[7]
Poznań University of Medical Sciences, Poznań, Poland, ORCID: 0009-0001-9805-0895[8]
Poznań University of Medical Sciences, Poznań, Poland, ORCID: 0009-0002-5138-7834[9]

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ABSTRACT

Hypoxic-ischemic encephalopathy (HIE) remains a primary cause of permanent neurological deficits in neonates. Therapeutic hypothermia (TH) is currently the only intervention with proven neuroprotective efficacy, and the aim of this study is to analyze its impact on the clinical prognosis of patients. Based on a literature review, it has been demonstrated that the implementation of a cooling protocol (33.5°C for 72 hours) within the first 6 hours of life reduces the risk of death and disability by approximately 25% (RR 0.75). TH significantly reduces the incidence of cerebral palsy and improves psychomotor outcomes at school age. Despite the occurrence of adverse effects such as bradycardia or thrombocytopenia, the method is characterized by an acceptable safety profile. Magnetic resonance imaging (MRI) (days 4-10) and biomarker analysis (S100B, NSE) are of critical importance in prognosticating outcomes. Hypothermia currently constitutes the gold standard of care, and the further development of neuroprotection is associated with the implementation of adjuvant therapies.

Introduction

Hypoxic-ischemic encephalopathy (HIE) is a syndrome of neurological disorders resulting from restricted oxygen supply and impaired blood flow to the neonatal brain during the peripartum period [1]. In extreme cases, this hypoxia leads to sudden cardiac arrest (SCA), defined as the total cessation of mechanical

cardiac activity and blood flow, requiring immediate cardiopulmonary resuscitation. While SCA is a discrete event, HIE represents an evolutionary process in which primary cellular damage initiates a biochemical cascade leading to secondary neuronal death [2].

Despite advances in perinatal care, peripartum hypoxia remains a significant public health issue. It is estimated that in high-income countries, the incidence of HIE ranges from 1 to 3 per 1000 live births, whereas in low- and middle-income countries, this rate may be up to tenfold higher [1], [5]. The clinical consequences are profound: before the introduction of routine hypothermia, approximately 25% of neonates with moderate or severe HIE died during the neonatal period, and another 20–30% developed permanent neurological deficits, such as cerebral palsy (CP), intellectual disability, epilepsy, and visual or hearing impairments [3], [4].

The concept of utilizing low temperatures for therapeutic purposes dates back to antiquity; however, its scientific foundations in neonatology began to take shape only in the mid-20th century. A breakthrough occurred in the early 21st century with the publication of results from key multicenter trials, such as the NICHD trial and the TOBY study [2], [3]. These studies provided incontrovertible evidence that controlled reduction of the neonate's body temperature to 33.5°C significantly improves survival without major neurological deficits. Following these discoveries, therapeutic hypothermia ceased to be regarded as an experimental intervention and became a recognized standard of care in neonatal intensive care units (NICUs) worldwide [1].

The aim of this narrative review is to summarize and critically analyze the current knowledge available in the PubMed database regarding the impact of therapeutic hypothermia in neonates with HIE and after SCA. This work focuses on assessing the clinical efficacy of the method in preventing long-term neurodevelopmental complications and analyzing its safety profile based on the latest guidelines and meta-analyses.

Pathophysiology of hypoxic-ischemic injury

Neonatal brain injury in the course of HIE is a dynamic process, referred to in the literature as the "evolution of injury," which can be divided into three key stages [6]. The first of these, the primary phase, results directly from energy failure caused by the cessation of oxygen and glucose supply, leading to the collapse of oxidative phosphorylation and a rapid decline in adenosine triphosphate (ATP) concentration. This lack of energy results in the dysfunction of ion pumps (Na^+/K^+-ATPase), cellular depolarization, cytotoxic edema, and a massive influx of calcium (Ca^{2+}) into the neurons, which initiates immediate necrotic death [6], [7]. Following successful resuscitation and return of spontaneous circulation (ROSC), the latent phase follows, typically lasting from one to six hours and constituting the so-called "therapeutic window." Although biochemical parameters may appear stable during this interval, pro-apoptotic pathways are initiated at the cellular level [7]. Delaying the implementation of hypothermia beyond the sixth hour of life significantly reduces its efficacy, as the injury cascade becomes an irreversible process after this time [1], [8]. The final stage, the secondary phase, occurs between the 6th and 72nd hour after the primary incident. Despite adequate blood oxygenation, secondary energy failure, excitotoxicity resulting from excessive glutamate release, intense oxidative stress (production of free radicals), and an inflammatory response occur, resulting in programmed cell death (apoptosis) in areas significantly more extensive than the primary necrotic foci [6], [8].

Therapeutic hypothermia does not act on a single specific receptor but exhibits a multifaceted neuroprotective effect, modifying the course of the latent and secondary phases. Through these

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mechanisms, hypothermia effectively inhibits the destructive cascade in the latent phase, preventing the development of the full secondary phase, which serves as the foundation for protecting the neonate's neurological functions [1], [8].

Table 1. Neuroprotective mechanisms.

Neuroprotective mechanism	**Action at the cellular level**	**Result for brain tissue**
Reduction of cerebral metabolism	Reduction of metabolic rate by 5-7% for every 1°C drop in body temperature.	Decreased demand for oxygen and ATP; protection of cells during the critical period.
Inhibition of excitotoxicity	Limitation of extracellular glutamate concentration (the primary excitatory neurotransmitter).	Prevention of massive neuronal destruction due to overstimulation.
Membrane stabilization	Inhibition of calcium (Ca^{2+}) influx into neurons and stabilization of the blood-brain barrier.	Limitation of the development of cytotoxic and vasogenic cerebral edema.
Anti-inflammatory and anti-apoptotic action	Inhibition of pro-inflammatory cytokine release and blockade of caspase activation.	Disruption of the programmed cell death (apoptosis) cascade.

Qualification criteria for treatment

Proper qualification of the neonate for therapeutic hypothermia (TH) is crucial to maximize the benefits of neuroprotection while limiting the exposure of patients with mild injury to potential adverse effects. This process is based on a three-tier verification: biochemical, clinical, and neurological [2], [9].

The first step is to confirm a severe hypoxic incident in the immediate peripartum period. According to the guidelines, the neonate must meet at least one of the following objective criteria:

- A pH value < 7.0 in umbilical cord blood gas or arterial/capillary blood collected within the first hour of life [2].
- A base deficit (BE ≤ −16 mmol/l) in blood gas analysis [9].
- If blood gas parameters are unavailable, an additional criterion is the occurrence of an "acute perinatal event" (e.g., placental abruption, cord prolapse) combined with an Apgar score ≤ 5 at the 10th minute of life or the necessity of continued mechanical ventilation/resuscitation for at least 10 minutes [2], [10].

After establishing the biochemical markers of hypoxia, it is necessary to confirm the presence of encephalopathy. The Sarnat classification remains the gold standard, allowing for the assessment of the degree of central nervous system damage [11]. In clinical classification, Grade II (moderate encephalopathy) manifests as, among others, lethargy, hypotonia, impaired reflexes, and miosis (pupillary constriction). In contrast, Grade III (severe encephalopathy) is characterized by stupor or coma, lack of response to stimuli, muscular flaccidity, and apnea [11]. Most clinical trials (including the NICHD protocol) exclude neonates with Grade I (mild encephalopathy-hyperalertness, jitteriness), in whom the risks associated with TH outweigh the potential benefits [2].

Amplitude-integrated EEG (aEEG) has become an indispensable tool in the early diagnosis of HIE. It allows for continuous monitoring of the bioelectrical activity of the brain at the patient's bedside before the decision to initiate cooling is made. The literature emphasizes that an aEEG recording with an abnormal background (e.g., low-amplitude recording, burst-suppression, or continuous seizure activity) possesses

high prognostic value in identifying children who will develop severe injury [10], [12]. The use of aEEG allows for the objectification of the clinical assessment, particularly in ambiguous situations or when the physical examination is hindered by the administration of sedative medications [12].

Methodology of implementing therapeutic hypothermia

Modern neonatology has developed two primary approaches to implementing therapeutic hypothermia (TH), which differ in the method of cold distribution but are based on the same neuroprotective principles.

Table 2. Comparison of therapeutic hypothermia methods.

Feature	Selective Head Cooling (SHC)	Whole-Body Cooling (WBC)
Technique	Utilization of a specialized cap with circulating cool water; reduction of cerebral temperature.	Utilization of cooling mattresses or blankets (servo-controlled systems).
Target temperature	Systemic temperature maintained at approximately 34.5°C.	Deep (rectal/esophageal) temperature maintained at 33.5°C.
Advantages and evidence	Efficacy confirmed in the *CoolCap* trial, particularly in neonates with severe aEEG changes.	Simplicity of use, more uniform core temperature reduction; currently the more frequently selected method.
Limitations	Technically more difficult to maintain; limited access to the patient's head (e.g., hindered cranial ultrasound).	Requires rigorous hemodynamic monitoring due to systemic effects of cooling.
Clinical conclusions	A method of proven efficacy, but logistically more demanding.	Facilitates easier monitoring and nursing care while maintaining identical neuroprotective efficacy.

The efficacy of therapeutic hypothermia is strictly dependent on rigorous adherence to the time-temperature parameters validated in key clinical trials. In the case of whole-body cooling, the objective is to maintain a constant rectal or esophageal temperature at 33.5°C (range 33°C - 34°C), while in selective head cooling, the systemic temperature is typically 34.5°C [2], [13]. The standard duration of the cooling phase is 72 hours. This period coincides with the duration of the secondary neuronal injury phase, allowing for the attenuation of apoptotic and inflammatory processes [1], [14].

The final stage of therapy, rewarming to normothermia, is a critical period requiring special attention. Excessive rapid rewarming may lead to hemodynamic destabilization, recurrence of seizures, or exacerbation of cerebral edema [15]. According to protocols, this process must be slow and controlled. The standard rewarming rate is 0.5°C per hour. The entire process of returning to a temperature of 36.5°C typically takes approximately 6 hours [14], [15]. During rewarming, continuous aEEG monitoring is essential, as this is a period of increased cerebral susceptibility to seizure activity.

Clinical impact and efficacy

The analysis of therapeutic hypothermia (TH) efficacy is based on the evaluation of two primary endpoints: neonatal survival and the quality of subsequent neurodevelopment. Data from the last two decades clearly confirm that TH is an intervention that alters the natural course of the disease.

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The most comprehensive Cochrane meta-analysis, including 11 randomized controlled trials (n = 1505 neonates), demonstrated that therapeutic hypothermia significantly reduces the risk of death or moderate/severe disability at 18-24 months of age [1]. The relative risk (RR) value for the combined adverse outcome is approximately 0.75 (95% CI: 0.68-0.83). This means that TH prevents death or permanent disability in one out of every four treated infants who would otherwise have been at risk [4], [16].

The efficacy of TH extends beyond survival alone, as the reduction of severe disability is of key importance. Long-term studies, such as the follow-up of the NICHD and TOBY trials, have provided evidence that the benefits of treatment persist into school age (6-7 years) [16]. The application of therapeutic hypothermia is associated with a statistically significant reduction in the incidence of cerebral palsy (RR approx. 0.66); thus, cooled children present severe forms of spastic paresis less frequently [1], [16]. Simultaneously, although the impact on isolated blindness and deafness is less frequently reported as a separate endpoint, aggregate data indicate an overall improvement in psychomotor and cognitive test scores (e.g., Bayley Scales), which translates to better sensory and social functioning [3], [16].

The specifics of management for neonates following full SCA (e.g., Apgar score 0 at 1 and 5 minutes, prolonged resuscitation) is a topic requiring particular attention. These patients represent the group at the highest risk of therapeutic failure. TH should be the standard for every neonate after successful cardiopulmonary resuscitation, provided they meet the remaining qualification criteria [17]. Neonates requiring chest compressions and adrenaline administration have a statistically worse prognosis. However, TH still improves their chances of "intact survival" (survival without deficits) compared to care in normothermia [17], [18]. In this group, hemodynamic monitoring is critical, as blood pressure instability occurs more frequently following SCA and during TH, necessitating precise administration of catecholamines [18].

Safety and possible complications

Despite its high neuroprotective efficacy, therapeutic hypothermia (TH) induces a series of physiological changes that require strict monitoring within the neonatal intensive care unit (NICU). Most observed complications are predictable and result directly from the impact of low temperature on metabolism and organ function [19].

The most frequently reported cardiovascular symptom is sinus bradycardia. This is a physiological response to the reduction in temperature (a decrease of approximately 10-15 beats/min for every 1°C drop in core temperature). As long as cardiac output remains stable and peripheral perfusion is maintained, this bradycardia does not require medical intervention [19], [21]. A more significant challenge is arterial hypotension, which may affect up to 30-50% of cooled neonates. It can result both from the pathophysiology of HIE itself (myocardial dysfunction following hypoxia) and the effect of TH on vascular resistance, which often necessitates the use of inotropic support (e.g., dopamine, dobutamine) [19], [21].

The impact of TH on the hematopoietic system manifests primarily as thrombocytopenia, resulting from splenic platelet sequestration and the inhibition of their production in the bone marrow. Furthermore, low temperature may impair the coagulation cascade by inhibiting the activity of proteolytic enzymes and platelet function, leading to a prolongation of prothrombin time (PT) and activated partial thromboplastin time (aPTT) [20]. Although clinically significant hemorrhages are rare, particular vigilance regarding central nervous system (CNS) or pulmonary hemorrhage should be maintained in neonates following SCA [21].

Temperature changes exert a significant influence on carbohydrate and electrolyte metabolism, leading, among others, to hypoglycemia. This results from limited glycogen reserves in neonates with HIE and TH-induced impairment of glycogenolysis, requiring precise intravenous glucose administration [1]. Simultaneously, electrolyte imbalances, such as hypokalemia, hypomagnesemia, and hypocalcemia, are frequently observed during therapy. Strict control of potassium levels is particularly crucial during the rewarming phase, when rapid ionic shifts occur between the intra- and extracellular compartments [15], [21].

Subcutaneous fat necrosis (SCFN) is a rare but highly characteristic complication of TH. It manifests as the appearance of firm, erythematous nodules in the subcutaneous tissue (typically on the back, buttocks, or arms) several days or weeks after the conclusion of treatment [22]. Although SCFN usually resolves spontaneously, it requires monitoring due to the risk of severe hypercalcemia, which can lead to renal damage [22].

In summary, the safety profile of TH is acceptable, and most complications are reversible. The key to success is an experienced medical team capable of interpreting these changes not as therapeutic errors, but as inherent features of the cooling process [19], [21].

Monitoring and prognosis during therapy

Monitoring a neonate undergoing TH extends beyond the control of vital parameters and includes the search for objective indicators allowing for early neurodevelopmental prognosis. Combining advanced imaging with the analysis of biochemical biomarkers allows for a precise assessment of the degree of CNS injury.

Magnetic resonance imaging (MRI) is currently recognized as the "gold standard" in assessing structural brain damage in neonates with HIE. Although cranial ultrasound examinations are helpful in excluding intracranial hemorrhages, their sensitivity in detecting hypoxic changes is limited [23]. The literature emphasizes the importance of the timing of the examination. The optimal period is between the 4th and 10th day of life, following the completion of the rewarming phase [23], [24]. Key parameters evaluated in MRI include diffusion-weighted imaging (DWI), which allows for early detection (as early as day 2.33) of areas of cytotoxic cerebral edema, although it may undergo the phenomenon of so-called "pseudonormalization" after the first week [24]. The poorest prognosis is associated with injury to the basal ganglia and thalamus (BGT). Changes in these areas are strongly correlated with the subsequent occurrence of dyskinetic cerebral palsy [23]. Watershed injuries (vascular border zones) correlate instead with cognitive deficits [24].

Given that the full extent of injuries on MRI appears with a delay of several days, there is an intensive search for serum biomarkers that would allow for the assessment of TH efficacy during its implementation. One such marker is the S100B protein, found primarily in glial cells (astrocytes). Its elevated concentration in serum or urine in the first hours after birth is a sensitive indicator of blood-brain barrier damage and correlates with the severity of encephalopathy [25], [26]. Concurrently, an important role is played by neuron-specific enolase (NSE), which is released into the bloodstream upon neuronal destruction. Studies indicate that NSE concentrations measured at 12 and 24 hours of life have high prognostic value in predicting unfavorable neurodevelopmental outcomes in children treated with hypothermia [25]. Currently, increasing attention is being paid to modern markers, such as glial fibrillary acidic protein (GFAP) and neurofilament light chains (NfL), which demonstrate promising specificity in monitoring the progression of hypoxic injuries under the influence of cooling [26]. Despite their significant potential, serum biomarkers are currently treated primarily as research tools, and clinical decisions continue to rely on a combination of the clinical picture, aEEG recordings, and MRI results [23], [25].

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Conclusions

Therapeutic hypothermia is currently the only method with proven neuroprotective efficacy in neonates with moderate and severe hypoxic-ischemic encephalopathy and following sudden cardiac arrest. Its clinical effectiveness, manifesting as a reduction in the risk of death or disability by approximately 25%, is strictly dependent on the rigorous maintenance of protocol parameters, including cooling to a temperature of 33.5°C for 72 hours before the sixth hour of life. In long-term observations, this therapy significantly limits the incidence of cerebral palsy and improves neurodevelopmental outcomes in school-aged patients. Despite the risk of adverse effects such as bradycardia, thrombocytopenia, or hypoglycemia, the safety profile of the method remains acceptable, and the disturbances themselves are predictable and reversible within the neonatal intensive care unit. The gold standard for monitoring and prognosis is based on magnetic resonance imaging performed between the fourth and tenth day of life and the analysis of serum biomarkers, such as S100B protein and neuron-specific enolase. Future directions for the development of this field focus on the implementation of combination therapies, in which hypothermia is supported by adjuvant pharmacotherapy, creating an opportunity for further improvement in the prognosis of neonates with the most severe degrees of central nervous system injury.

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