NEONATAL HYPOXIC–ISCHEMIC ENCEPHALOPATHY: PATHOPHYSIOLOGY, MULTIMODAL DIAGNOSIS, AND CONTEMPORARY NEUROPROTECTIVE STRATEGIES

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Abstract

Background: Neonatal hypoxic–ischemic encephalopathy (HIE) is a major cause of early neurological dysfunction and later neurodevelopmental disability. Although therapeutic hypothermia improves outcomes in appropriately selected term and near-term infants, residual injury and uncertainty in diagnosis and prognosis remain important challenges.

Objective: To critically synthesize current evidence on the mechanisms of hypoxic–ischemic brain injury, multimodal diagnostic assessment, established neuroprotection, and emerging therapeutic approaches.

Methods: This narrative review draws on the author's monograph framework and selected landmark randomized trials, international guidance, and peer-reviewed literature available through October 2026. It is not a systematic review or an original patient cohort; no pooled effect estimates or new clinical data were generated.

Results: HIE evolves through primary energy failure, a latent phase, secondary injury involving excitotoxicity, oxidative stress, inflammation and mitochondrial dysfunction, and subsequent repair or maladaptive remodeling. Clinical examination, continuous electroencephalography, magnetic resonance imaging, and targeted laboratory testing provide complementary rather than interchangeable information. Controlled cooling initiated within six hours and maintained at approximately 33.5–34.5°C for 72 hours remains the principal evidence-based neuroprotective intervention for infants born at or beyond 36 weeks with moderate-to-severe HIE. Recent randomized evidence does not support routine cooling at 33–35 weeks, while adjunctive erythropoietin failed to improve outcomes and increased serious adverse events.

Conclusion: High-quality HIE care depends on timely recognition, protocolized cooling in eligible infants, integrated neuromonitoring and imaging, prevention of secondary physiological insults, and structured long-term follow-up. Future studies should prioritize safe adjunctive treatments, validated prognostic models, and equitable implementation.

Keywords: neonatal hypoxic–ischemic encephalopathy; therapeutic hypothermia; neonatal seizures; magnetic resonance imaging; neuroprotection; neurodevelopment.

1. Introduction

Neonatal encephalopathy denotes disturbed neurological function in the newborn and may have hypoxic–ischemic, vascular, infectious, metabolic, genetic, or other causes. HIE should therefore not be inferred from a low Apgar score or a single abnormal laboratory result alone. Establishing a plausible hypoxic–ischemic mechanism requires consideration of the perinatal history, neurological examination, biochemical findings, and alternative diagnoses [1,2].

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The clinical relevance of HIE extends beyond the neonatal intensive care unit. Survivors may experience cerebral palsy, epilepsy, cognitive or language difficulties, and behavioral or learning problems, even when early neurological signs improve. This review addresses the transition from injury mechanisms to bedside diagnosis, acute neuroprotection, and developmental surveillance [1,3].

2. Review approach and evidence boundaries

The article is a focused narrative synthesis organized around five themes used in the underlying monograph: disease mechanisms, diagnostic assessment, international clinical evidence, treatment, and neonatal care. Priority was given to pivotal randomized controlled trials, a contemporary American Academy of Pediatrics (AAP) clinical report, and International League Against Epilepsy (ILAE) recommendations. The literature was not searched or screened according to a preregistered systematic-review protocol. Consequently, the article does not claim exhaustive retrieval, quantitative meta-analysis, or formal certainty grading.

3. Pathophysiology of hypoxic–ischemic injury

A reduction in cerebral oxygen delivery and blood flow compromises oxidative phosphorylation and adenosine triphosphate production. Failure of energy-dependent ion pumps causes depolarization, intracellular calcium accumulation, glutamate-mediated excitotoxicity, and cytotoxic edema. After reperfusion, a transient latent interval may precede secondary deterioration involving mitochondrial dysfunction, reactive oxygen species, inflammatory signaling, and cell death. The relative contribution of these mechanisms varies with developmental maturity, injury severity, and timing [3,4].

These phases help explain why intervention is time-sensitive. Therapeutic hypothermia is intended to modify evolving secondary injury, rather than reverse established primary necrosis. Mechanistic studies support multiple candidate targets—including mitochondrial preservation and modulation of inflammation—but biological plausibility does not establish clinical efficacy. New treatments require adequately powered trials with meaningful neurodevelopmental endpoints [3,4].

4. Multimodal diagnosis and prognosis

Serial neurological examination remains central to identifying moderate or severe encephalopathy. Standardized assessment considers consciousness, spontaneous activity, posture, tone, primitive reflexes, autonomic function, and seizures. Sarnat-based classifications are useful but can evolve during the first hours of life; they must be interpreted alongside perinatal and biochemical findings [1,5].

Continuous conventional EEG is preferred for detecting electrographic seizures and characterizing background activity; amplitude-integrated EEG may supplement monitoring where resources are limited. The absence of visible convulsions does not exclude electrographic seizures. The ILAE recommends phenobarbital as the usual first-line antiseizure medication when treatment is required, with specific exceptions such as suspected channelopathies [2,6].

Magnetic resonance imaging, including diffusion-weighted sequences, can characterize injury distribution and extent, particularly in basal ganglia–thalamic and watershed patterns. MRI is valuable for counseling and follow-up planning, but scan timing, treatment exposure, and clinical context influence interpretation. Prognostic conclusions should combine neurological examination, EEG evolution, imaging, and longitudinal developmental assessment rather than rely on any isolated marker [2,7].

Blood gases, glucose, electrolytes, lactate, and organ-function tests support acute stabilization and assessment of associated systemic injury. They may inform the overall probability of hypoxic–ischemic

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injury but are not individually diagnostic. Differential diagnosis should remain active when the clinical course or imaging is atypical [1,2].

5. Therapeutic hypothermia: established benefits and boundaries

For appropriately selected neonates born at ≥36 weeks with moderate-to-severe HIE, therapeutic hypothermia initiated within six hours of birth and maintained at 33.5–34.5°C for 72 hours reduces death or major neurodevelopmental impairment. Controlled rewarming and comprehensive intensive care are integral to the treatment protocol. The 2026 AAP clinical report emphasizes standardized eligibility assessment, transport pathways, continuous temperature control, neurophysiological monitoring, MRI, and longitudinal follow-up [2,8,9].

Evidence must not be extrapolated uncritically to other populations. In a randomized trial enrolling 168 infants born at 33–35 weeks, Bayesian analysis suggested a higher probability of death or disability with cooling; routine extension of the term-infant protocol to this gestational group is therefore not supported. The 2026 AAP report also identifies insufficient evidence for routine cooling in mild HIE; decisions in borderline circumstances require specialist assessment and documentation [2,10].

6. Adjunctive neuroprotection and supportive care

Several agents have been investigated as additions to hypothermia. In the multicenter HEAL trial, 501 infants with moderate-to-severe HIE were randomized to erythropoietin or placebo alongside standard cooling. The primary outcome of death or neurodevelopmental impairment occurred in 52.5% versus 49.5%, respectively, with more serious adverse events in the erythropoietin group. These results do not support routine high-dose erythropoietin as an adjunctive neuroprotective treatment [11].

Clinical management should also limit preventable secondary insults. Priorities include stable oxygenation and perfusion, avoidance of hyperthermia, careful glucose and electrolyte management, prompt detection and treatment of seizures, and surveillance for multiorgan dysfunction. Specific targets and drug regimens should follow local neonatal intensive care protocols and specialist judgment; no single supportive intervention should be represented as independently proven to prevent long-term disability [2,6].

7. Long-term outcomes and implementation

Neurodevelopmental follow-up should assess motor, cognitive, language, hearing, vision, and behavioral domains over time. An apparently reassuring early examination does not exclude later difficulties. Coordination among neonatology, pediatric neurology, developmental services, rehabilitation professionals, and families facilitates early identification of needs [2,7].

For health systems with uneven access to cooling centers, the immediate implementation priorities are staff training, rapid recognition and referral, safe transport, protocolized temperature monitoring, EEG access, and reliable follow-up. Local feasibility and quality-improvement studies are needed before assuming that benefits observed in specialized trial settings will transfer unchanged to every setting [2].

8. Research priorities and limitations

Important questions include whether validated combinations of EEG, MRI, clinical variables, and biomarkers can improve individualized prognosis; which adjunctive treatments are both safe and effective; and how high-quality care can be delivered across different resource settings. Future investigations should predefine outcomes, account for gestational age and disease severity, and include long-term follow-up.

This article has limitations inherent to narrative reviews: selective source inclusion, no formal risk-of-bias assessment across all included literature, and no independent patient-level analysis. Mechanistic

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conclusions and clinical recommendations have different evidentiary foundations and should not be treated as equivalent.

9. Conclusion

Neonatal HIE is a dynamic brain injury syndrome requiring rapid, coordinated clinical decisions. Multimodal assessment improves diagnostic confidence and supports prognostic counseling, while therapeutic hypothermia remains the best-established disease-modifying treatment for eligible infants born at ≥36 weeks with moderate-to-severe HIE. Recent evidence cautions against routine cooling of more premature infants and against unproven adjunctive erythropoietin. Consistent neurocritical care and sustained developmental follow-up are essential components of an evidence-informed care pathway.

Declarations

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