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2026 Volume 11, Issue 1
Advances in Precision Medicine
ISSN: 2424-9106 (Online)
ISSN: 2424-8592 (Print)

"Evaluation-Intervention-Follow-Up" Integrated Management: Improving Long-Term Prognosis of Neonatal Hypoxic-Ischemic Encephalopathy

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Abstract: In recent years, with the continuous improvement of perinatal medicine and neonatal intensive care technology, the survival rate of high-risk infants has significantly increased. Despite this, neonatal hypoxic-ischemic encephalopathy (HIE) caused by perinatal asphyxia, which leaves behind neurological sequelae, is still frequently seen. Even if these infants receive hypothermia treatment after birth, they still have certain neurodevelopmental disorders, which affect their quality of life. The treatment of HIE should not only focus on the neonatal period but also pay attention to the risk of neurological sequelae during their growth process. Implementing precise assessment, early intervention, and rehabilitation training in the later neonatal period for the pathogenesis of HIE is of great significance in reducing the occurrence of sequelae and improving the prognosis of HIE infants. This article will systematically discuss the application of the "assessment-intervention-follow-up" integrated management plan in improving the long-term prognosis of neonatal hypoxic-ischemic encephalopathy.
Keywords: newborn; hypoxic-ischemic encephalopathy; long-term prognosis; comprehensive management

Online publication: January 26, 2026

1. Introduction

Neonatal hypoxic-ischemic encephalopathy (HIE) is a neurodevelopmental disorder caused by insufficient oxygen supply and reduced blood flow to the brain during fetal development. In developed countries, 1-2 out of every 1,000 newborns are affected by HIE. Globally, HIE claims 500,000 lives annually[1]. Affected infants face not only mortality risks but also develop severe cerebral palsy (CP). These children with severe CP often exhibit multiple neurological impairments, with their quality of life being as compromised as the condition itself. The lifelong care of HIE-induced CP patients requires substantial medical expenditures that far exceed indirect social service and educational investments, creating a heavy financial burden for families and society[2].

Hypoxia-ischemia encephalopathy (HIE) during the perinatal period significantly impacts neonatal growth and development. When the body experiences hypoxia, reduced blood flow and oxygen supply to brain tissue disrupt cellular energy metabolism. This leads to decreased adenosine triphosphate (ATP) production, mitochondrial dysfunction, and reactive oxygen species (ROS) generation. These factors compromise endogenous antioxidant defenses, induce widespread oxidative stress, and ultimately cause neuronal damage and cell death through a cascade of reactions[3]. The critical 6-hour window between primary hypoxic-ischemic injury and secondary energy depletion/cell death represents the therapeutic

“golden hour” for effective treatment. However, current understanding of this “time window” remains limited. Clinically, many physicians neglect this critical period, often resorting to prolonged drug therapy that fails to address chronic complications and imposes long-term financial burdens on families[4].

Currently, therapeutic hypothermia (TH) remains the most widely used evidence-based treatment for hypoxic-ischemic encephalopathy (HIE) in clinical practice, and is also the most effective protective measure within the “time window”.

It primarily works by reducing brain cell energy metabolism, alleviating oxidative stress, inhibiting apoptosis and inflammatory responses, thereby maintaining the structural and functional integrity of brain cells [5]. TH serves as the standardized neuroprotective treatment for moderate-to-severe HIE infants. The protocol involves initiating TH within 6 hours after birth, maintaining core body temperature between 33°C and 34°C for 72 hours[6]. Clinical studies have demonstrated that TH administered within 72 hour ssignificantly improves neurological function scores, survival rates, and long-term neurodevelopmental outcomes in affected infants. Additionally, TH reduces neonatal epilepsy incidence and enhances neurological function recovery[7]. Although TH offers significant therapeutic advantages for HIE, its efficacy depends on multiple factors including treatment initiation timing, duration of hypothermia, and the newborn’s overall condition[8]. Notably, 29% of HIE infants receiving TH still develop neurodevelopmental disorders. While TH effectively lowers mortality and disability risks, it cannot completely eliminate long-term complications such as epilepsy, motor dysfunction, and cognitive impairment associated with HIE. Research indicates persistent neuroinflammatory responses may persist even after TH treatment, potentially contributing to adverse outcomes. In regions with limited medical resources, the therapeutic effectiveness of TH remains suboptimal [9].

HIE (Hypoxic-ischemic encephalopathy) occurs during the perinatal period, yet treatment primarily focuses on the neonatal phase and continues through the child’s growth. Currently, most clinical interventions remain limited to the neonatal period, neglecting post-discharge monitoring of growth and neurological development.

Late-stage follow-up for newborns is crucial for early behavioral intervention and rehabilitation training. Research shows that the brain remains in rapid development until age 5, with the first two years being the most critical period for neural development and neuroplasticity. Early intellectual-behavioral interventions and physical rehabilitation for HIE patients during this critical window can promote brain cell repair, compensatory neural fiber growth, and the establishment of new neural pathways, significantly improving brain function and reducing long-term sequelae. The development and maturation of the nervous system require external environmental stimuli such as colors, odors, sounds, and shapes. Prolonged exposure to a stimulus-free environment inevitably leads to abnormal brain and cognitive development [10].

The detrimental effects of HIE (Hearing Impairment in Early Life) on children’s global quality of life demand urgent attention. Early objective assessment, long-term follow-up, and timely intervention for newborns with HIE are crucial for reducing disability rates, improving quality of life, and ultimately enhancing family well-being worldwide. This paper examines the impact of an integrated’ assessment-intervention-follow-up’ management approach on children affected by HIE.

2. The “evaluation” phase of integrated management: Precise assessment and risk stratification.

In recent years, with the development of follow-up medical technology, the survival rate of neonatal asphyxia has significantly improved, but the number of children with sequelae has also been increasing. Therefore, timely and effective evaluation is the key to improving the prognosis of children.

2.1. Magnetic resonance imaging (MRI)

MRI, characterized by its non-invasive nature, radiation-free operation, and high tissue resolution, has been widely adopted in the diagnosis and treatment of hypoxic-ischemic encephalopathy (HIE). In early-stage HIE, MRI can directly visualize

abnormalities in cerebral white matter fibers and track disease progression, enabling clinicians to systematically analyze hypoxic-ischemic conditions[11]. Studies reveal distinct MRI patterns across HIE severity levels. Mild-to-moderate HIE primarily involves single lesions in subcortical white matter with low myelinization risk, while severe HIE predominantly affects the precentral gyrus cortex. Within 24 hours and 24-48 hours postnatal, mild-to-moderate HIE infants demonstrate significantly lower brain injury parameters (INi, la, Bv) compared to severe cases [12]. These findings demonstrate that MRI aids in HIE severity classification and facilitates timely interventions to ensure effective treatment for affected infants.

2.2. Video electroencephalography (VEG)

Given the non-specific clinical manifestations of hypoxic-ischemic encephalopathy (HIE), early diagnosis relying solely on clinical symptoms and imaging studies presents significant challenges. As a neurophysiological monitoring method, VEG enables early detection of brain injury in HIE patients and assists clinicians in making informed judgments about injury severity and prognosis[13]. Utilizing synchronized video monitoring technology, VEG records cerebral background activity for retrospective analysis, offering advantages such as ease of operation, simplicity, and safety, making it particularly suitable for infants requiring intensive care due to hypoxia-ischemia[14]. VEG can monitor neonatal neurophysiology within 6 hours after birth, visually reflecting brain waves and epileptiform discharges. It evaluates brain injury severity through the continuity, periodicity, wavelength characteristics, and epileptic patterns of cerebral activity, aiding clinical assessment[15]. Studies demonstrate that continuous VEG monitoring within 72 hours post-birth helps identify acute-phase cerebral background activity patterns in HIE, enabling accurate injury evaluation and optimal intervention timing [16].

2.3. Color doppler ultrasound. historically

HIE was primarily diagnosed through head impact assessment, which failed to demonstrate cerebral blood flow distribution patterns or hemodynamic changes. Since cerebral hemodynamic alterations are stress responses triggered by neonatal asphyxia, which reduces cerebral blood flow and causes hypoxic-ischemic brain injury, the extreme oxygen sensitivity of cerebral blood flow makes two-dimensional ultrasound unable to reveal characteristic manifestations. Therefore, intracranial color Doppler ultrasound monitoring becomes particularly crucial [17]. This imaging technique can observe hemodynamic changes in cerebral tissue and middle cerebral artery blood flow in HIE infants [18]. Studies indicate that hyperperfusion is a key feature of HIE. In mild-to-moderate HIE cases, cerebral and middle cerebral artery blood flow peak values decrease, with reduced flow velocity and significantly elevated PI and RI, indicating hypoperfusion. As the condition progresses, cerebral and middle cerebral artery blood flow peak values increase, accompanied by rising RI levels, potentially related to prolonged and severe asphyxia[19]. These findings demonstrate that dynamic intracranial color Doppler ultrasound monitoring of cerebral hemodynamics in HIE infants provides critical guidance for brain injury assessment, early diagnosis, and timely intervention[20].

3. The “Intervention” phase in integrated management: sequential assessment-based intervention.

HIE intervention strategies have long been a subject of debate, primarily focusing on either single or combined therapies, with no consensus reached to date. To implement effective HIE measures, it is crucial to recognize that hypoxia-ischemia is a dynamic process. This necessitates adopting targeted, continuous interventions tailored to address challenges at different stages of HIE treatment – what is known as protocol-based intervention.

3.1. Acute phase neuroprotective intervention

Currently, the most effective brain-protective measure targeting the time window in clinical practice is therapeutic hypothermia (TH). Administering TH within 6 hours after birth can reduce mortality and disability risks in infants with hypoxic-ischemic encephalopathy (HIE) born at 36 weeks or later [21]. Recent studies indicate that for severe HIE cases,

initiating head hypothermia therapy within 6 hours is crucial to stabilize vital signs. During the acute phase, hyperbaric oxygen therapy may be considered after ruling out intracranial hemorrhage or pneumothorax, which can improve overall therapeutic outcomes and reduce mortality and neurological sequelae risks. Typically, this treatment lasts 5-10 days, though the duration should be adjusted according to the infant's recovery progress. Gradually incorporating gentle massage therapy during this period can effectively promote motor and cognitive development [10,22].

3.2. Adjuvant drug therapy

3.2.1. Erythropoietin (EPO)

Erythropoietin (EPO) is a glycoprotein hormone synthesized and secreted by the liver in infants. Studies have shown that neurons and astrocytes can produce endogenous EPO, which exerts neuroprotective effects through paracrine secretion. When the brain suffers from hypoxia, ischemia, or inflammation, EPO secretion increases and binds to corresponding receptors, inhibiting excessive activation of microglia and cytokine release, thereby achieving neuroprotective effects[23,24]. Currently, recombinant human erythropoietin is used to treat children with clinical hypoxic-ischemic encephalopathy (HIE). It primarily improves cerebral blood circulation and hypoxia-like conditions in HIE patients by increasing hemoglobin concentration, while also demonstrating neuroprotective[25]. Research indicates that EPO monotherapy alone shows limited improvement in HIE neurological function. When administered to HIE patients, 1000 U/kg EPO combined with 32°C hypothermia treatment for 8 hours does not significantly improve behavioral capacity. However, 5000 U/kg EPO combined with 32.5-33°C hypothermia treatment for 3 hours, or human umbilical cord blood mesenchymal therapy (2×10^6/ml, 0.5 ml), can significantly improve sensory-motor functions, behavioral scores, and reduce brain injury area in HIE patients. This suggests that optimal therapeutic outcomes for HIE require careful consideration of EPO dosage and therapeutic hypothermia temperature [26].

3.2.2. Oxygen free radical scavenger

When reactive oxygen species (ROS) exceed the capacity of endogenous antioxidant enzymes following hypoxic-ischemic encephalopathy (HIE), oxidative stress is induced. Clinical studies demonstrate that reduced glutathione, a key antioxidant, enhances antioxidant enzyme activity and inhibits the formation of oxygen free radicals and lipid peroxides, thereby exerting neuroprotective effects. Clinical trials showed that children with HIE receiving reduced glutathione (300 mg) combined with ganglioside (20 mg) for 7-14 days exhibited significant reduction in neuronal edema, improved neuronal damage, gradual recovery of consciousness, enhanced muscle tone, and decreased seizure frequency[27]. Additionally, this treatment significantly improved the neuroblastoma-associated neurofibrillary angiopathy (NBNA) score and CT values in HIE-induced cerebral white matter lesions [28].

3.2.3. Cell membrane stabilizers

Gangliosides, as a type of sphingolipid, are components of animal cell membranes and are particularly abundant in the nervous system. When the brain is injured, gangliosides (especially monosialyl gangliosides) can cross the blood-brain barrier under hypoxic conditions, inhibit NO_2 synthesis, and stabilize neuronal cell membranes. They can also correct intracellular and extracellular ion imbalances, reduce cerebral edema, promote neurological function and behavioral recovery, and lower mortality rates [29,30]. Research analysis shows that gangliosides as adjuvant therapy for HIE can significantly delay the onset of neurodevelopmental and intellectual impairments [31]. Clinical studies indicate that combining gangliosides with EPO can substantially reduce the incidence and mortality rates of HIE in affected children [32]. Additionally, they can decrease muscle tone and improve neurological damage. When combined with TH, gangliosides enhance the scores of NBNA, MDI, and PDI [33].

3.3. Studies on diversified rehabilitation interventions during recovery and long-term phases have demonstrated that immature brain tissue possesses plasticity.

Timely removal of damaging factors can facilitate partial repair of injured neurons. Current HIE treatments primarily focus on acute-phase therapies such as thrombolytic therapy (TH), free radical scavenging, and maintaining cerebral membrane stability. Implementing appropriate interventions during the recovery phase for HIE patients could yield significantly better rehabilitation outcomes [34,35].

Traditional rehabilitation training for visual, auditory, and sensory functions has been tailored to children's developmental characteristics. However, standalone approaches present limitations. Touch therapy and hydrotherapy, as comprehensive tactile stimulations, can soothe children's emotions through sustained contact while promoting personality and psychological development. The full-body movements in hydrotherapy enhance chest and abdominal muscle strength, facilitate joint extension, and support skeletal growth. Through water temperature regulation, children improve thermoregulation and environmental adaptability. Touch therapy stimulates the hypothalamic-pituitary system via neuro-humoral regulation, triggering secretion of growth hormones like human growth hormone (hGH) and adrenocorticotropic hormone (ACTH). Simultaneously, it reduces stress responses in hyperemic-ischemic encephalopathy (HIE) infants, decreases crying frequency, improves sleep quality, and ultimately accelerates growth and shortens recovery timelines [36]. When combined with visual-auditory stimulation and motor training based on developmental stages, hydrotherapy and touch therapy demonstrate synergistic effects. These combined approaches enhance cerebral cortex plasticity, strengthen synaptic activity, promote neural function recovery, expedite rehabilitation progress, and reduce neurological sequelae risks [36,37].

3.4. Individualized intervention

The neural development process follows a progressive pattern from basic to advanced stages. Therefore, neurofunctional training for HIE patients should adhere to this principle: First, correct abnormal postures and movement patterns, then gradually train them to develop normal postures and movement patterns, ultimately achieving rehabilitation goals. During the period when HIE patients exhibit peak compensatory capacity and neural plasticity, in addition to conventional comprehensive treatment, early individualized intervention becomes crucial. Individualized intervention refers to adopting different assessment methods at various HIE stages and formulating targeted plans based on individual behavioral capabilities. This approach requires not only early intervention but also close collaboration between parents and doctors. By tailoring intervention plans according to the severity and disease stage of HIE patients, and adapting them to local conditions, we can achieve optimal rehabilitation outcomes [38].

4. The "follow-up" phase in integrated management: systematic monitoring and outcomes evaluation recent

studies have revealed that **c**erebral palsy symptoms persist in 60% of HIE infants during their first six months post-discharge, when intervention effectiveness diminishes. Early detection of abnormal neurological signs through 2-3 month follow-ups after birth enables timely intervention with optimal outcomes. Therefore, monthly follow-ups are recommended within the first six months, then every three months after six months, and every six months after one year [39]. Regular monitoring serves as the cornerstone for early individualized intervention in HIE infants. A structured follow-up plan should be established for discharged HIE infants to enable continuous health monitoring, quality-of-life assessment, and timely early intervention. Early intervention for HIE requires comprehensive and sustained efforts.

After clinicians develop personalized intervention plans, long-term parental cooperation and mastery of training methods are essential for achieving optimal rehabilitation outcomes. Effective follow-up not only ensures parental engagement in early intervention but also serves as the prerequisite for its successful implementation. Only through thorough follow-up can clinicians promptly identify issues, provide timely interventions, improve prognosis, and enhance

quality of life [40] .

5. Analysis of timeliness in the integrated “assessment-intervention-follow-up” model

Many clinicians currently limit treatment for HIE (Hemiplegic Infantile Encephalopathy) patients to the neonatal period, neglecting long-term developmental outcomes. While HIE occurs during the perinatal period, its treatment spans from late infancy to lifelong care. Early assessment, rehabilitation training, and regular follow-ups are crucial for improving prognosis and quality of life, with optimal timing for intervention. Delaying intervention until motor and cognitive delays are observed yields minimal therapeutic benefits. Clinicians should communicate with families to emphasize that the brain remains in accelerated development before age 2. Regular monitoring, dynamic evaluation, and personalized interventions can reduce sequelae. Therefore, clinicians should adopt a dialectical approach based on HIE’s developmental stages, implementing targeted and continuous early interventions supported by long-term family rehabilitation programs to promote motor and cognitive development and enhance postnatal quality of life.

6. Conclusion

Currently, clinicians primarily employ hypothermia and symptomatic treatments for HIE, with no definitive cure available. Previous interventions were limited to neonatal stages, failing to comprehensively monitor disease progression or implement timely interventions. The integrated “Assessment-Intervention-Follow-up” model enhances traditional approaches by prioritizing long-term prognosis and quality of life. This framework aims to conduct systematic precision assessments, initiate early interventions, and establish long-term follow-up protocols to improve outcomes. In summary, this integrated model effectively enhances motor and cognitive development in newborn HIE patients, contributing to better long-term prognosis.

Disclosure statement

The author declares no conflict of interest.

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