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Comprehensive Multidisciplinary Management and Long-Term Care Approaches for Newborns with Birth Asphyxia: Clinical Guidelines for Healthcare Professionals

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Abstract:

Background: Birth asphyxia is a major contributor to neonatal morbidity and mortality worldwide, frequently resulting in hypoxic–ischemic encephalopathy (HIE) and multi-organ dysfunction. Optimal management requires timely diagnosis, acute intervention, and coordinated multidisciplinary care to minimize adverse outcomes.

Aim: To highlight the essential role of multidisciplinary consultations in the clinical management and long-term rehabilitation of newborns affected by birth asphyxia.

Methods: This review synthesizes current evidence and clinical guidelines on postnatal consultation strategies for infants with birth asphyxia. The focus is on the integration of neonatology, pediatric subspecialties, and allied health services to ensure comprehensive, individualized care. Literature from peer-reviewed journals and established neonatal protocols was critically analyzed.

Results: Effective management necessitates early involvement of a neonatologist for stabilization and ongoing monitoring. Pediatric neurologists provide assessment for neurological injury, particularly HIE. Cardiologists and nephrologists manage cardiac and renal complications, while pulmonologists address respiratory dysfunction. In complex cases with multi-organ involvement, pediatric intensivists or palliative care specialists are essential. Developmental pediatricians, along with physical and occupational therapists, play a crucial role in early rehabilitation and long-term developmental support. Early, coordinated intervention enhances recovery potential and reduces long-term disability.

Conclusion: A multidisciplinary consultation framework is critical for optimizing outcomes in birth asphyxia. Early, coordinated, and ongoing involvement of diverse specialties ensures comprehensive management from acute care through long-term follow-up.

Keywords: Birth asphyxia, hypoxic–ischemic encephalopathy, neonatal care, multidisciplinary team, neonatal rehabilitation, pediatric neurology

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Introduction

Perinatal asphyxia is a condition resulting from an interruption in blood flow or gas exchange to or from the fetus occurring immediately before, during, or after delivery. This disruption leads to a significant reduction in oxygen and blood supply to critical organs, most notably the brain, heart, liver, and skeletal muscles, thereby causing severe systemic and neurological consequences. Impaired placental gas exchange in the prenatal period or compromised pulmonary gas exchange after birth can lead to partial oxygen deprivation, known as hypoxia, or complete deprivation, referred to as anoxia. These conditions contribute to progressive hypoxemia and elevated carbon dioxide levels (hypercapnia). When oxygen deprivation becomes severe, the infant's metabolism shifts toward anaerobic pathways, resulting in the accumulation of lactic acid and the development of metabolic acidosis. Within this context, neonatal hypoxic-ischemic encephalopathy (HIE) is defined as the neurological injury specifically associated with perinatal asphyxia and ischemia, representing one of the most serious outcomes of this pathophysiological process [1][2].

Clinical Presentation of Neonatal Hypoxic Events

A neonatal hypoxic episode often manifests through a combination of biochemical, neurological, and systemic signs that provide critical diagnostic clues. One hallmark is the presence of metabolic acidosis, often accompanied by a significant base deficit, indicating impaired oxygen utilization and the accumulation of acidic metabolites. Newborns may present with low Apgar scores, reflecting compromised cardiorespiratory and neurological function in the immediate postnatal period. In many cases, signs of multiple organ-system dysfunction are observed, indicating that the hypoxic insult has extended beyond the central nervous system to other vital organs [1][2].

Neurological manifestations play a central role in the clinical profile of neonatal hypoxia. These may include hypotonia, abnormal oculomotor activity or pupillary reactions, diminished or absent sucking reflexes, disordered breathing patterns such as apnea or hyperpnea, and the occurrence of clinical seizures. The diagnosis of HIE requires careful exclusion of alternative explanations for the neurological findings, such as inborn metabolic defects, genetic syndromes, congenital neurological malformations, or the effects of certain medications. In addition, neuroimaging studies, particularly magnetic resonance imaging (MRI), often reveal characteristic patterns of injury associated with hypoxic-ischemic events, which serve as an important tool for confirming the diagnosis and assessing the extent of brain damage [1][2].

Etiology

Perinatal asphyxia results from any disruption in the supply of oxygenated blood to the fetus, and its etiology spans maternal, placental, and fetal factors. Maternal causes often involve systemic conditions that impair blood flow or oxygen delivery. Hemodynamic compromise, as seen in amniotic fluid embolism, sepsis, or shock, can abruptly reduce perfusion to the placenta and fetus. Severe maternal hypoxemia from respiratory or cardiovascular disorders may also limit fetal oxygen availability [4][5].

Uterine pathology can be a direct cause of acute oxygen deprivation. Uterine rupture, for example, interrupts placental attachment and circulation, leading to an immediate and profound drop in fetal oxygenation. Placental abnormalities are another major contributor. Placental abruption, where the placenta prematurely separates from the uterine wall, reduces or completely halts maternal-fetal gas exchange. Similarly, conditions affecting the umbilical cord—such as true knots, prolapse, or

sustained compression—can obstruct blood flow and rapidly induce fetal hypoxia [4][5].

Infectious processes may act either by triggering severe maternal illness that compromises systemic circulation or by directly affecting the placenta and fetal membranes, leading to inflammation and impaired function. Such infections can occur before or during labor, adding to the risk of asphyxia. The timing of perinatal asphyxia varies. The majority of cases occur during labor and delivery (intrapartum), when complications such as prolonged cord compression or placental insufficiency are most likely to develop. However, approximately 20% of cases occur before labor begins (antepartum), often linked to chronic placental pathology or maternal conditions that reduce oxygen delivery over time. A smaller proportion occurs shortly after birth (early postnatal period), typically in neonates already in a compromised state who may require immediate resuscitation [3][4][5].

Determining the underlying cause is critical for targeted management and prevention. A thorough obstetric and peripartum history—covering maternal health, labor progression, fetal monitoring records, and delivery events—provides essential clues. Despite careful evaluation, a significant number of infants diagnosed with hypoxic-ischemic encephalopathy lack a clearly identifiable sentinel event, underscoring the complexity of perinatal asphyxia and the multifactorial nature of its development [6].

Epidemiology

In high-resource countries, the incidence of perinatal asphyxia at term is estimated at approximately 2 cases per 1,000 live births. This rate increases dramatically—by nearly tenfold—in regions with limited access to comprehensive maternal and neonatal healthcare services, reflecting the critical role of timely obstetric intervention and specialized newborn care in prevention and management [7].

The prognosis for affected infants remains serious. Among neonates who experience perinatal asphyxia, between 15% and 20% die within the neonatal period. Of those who survive, up to one-quarter are left with lasting neurological impairments, including motor deficits, cognitive delays, or epilepsy, which can impose a lifelong burden on the child, family, and healthcare systems [8].

In preterm infants, establishing a clear cause for perinatal asphyxia is often challenging. Multiple perinatal and maternal factors may interact to produce hypoxic-ischemic injury, and the presentation may differ from that in term infants. The incidence in this population can be disproportionately high, particularly in low-resource settings where access to advanced obstetric monitoring, neonatal resuscitation, and intensive care is limited [9][10][11]. These disparities highlight the global inequities in maternal and newborn health and underscore the importance of strengthening healthcare infrastructure to reduce the incidence and severity of perinatal asphyxia.

Pathophysiology

The development of brain injury in hypoxic-ischemic encephalopathy (HIE) is a dynamic and multi-phase process that unfolds over a period of hours to days following the initial insult. The sequence begins with a primary neuronal injury that occurs immediately after the interruption of oxygen and glucose delivery to the brain. The severity and rapidity of this deprivation influence the brain's compensatory responses. In less acute cases, cerebral autoregulatory mechanisms can partially preserve function by redirecting blood flow toward essential regions, such as the brainstem and cerebellum, which are critical for vital functions. This selective perfusion, however, leaves watershed areas—regions between major cerebral arteries—more vulnerable to injury. In more abrupt and severe hypoxic-ischemic episodes, deep gray matter structures such as the basal ganglia are

preferentially affected due to their high metabolic demand and limited capacity for hypoxic tolerance [6].

At the cellular level, the immediate energy failure is driven by a rapid decline in adenosine triphosphate (ATP) production. ATP depletion impairs the activity of the ATP-dependent sodium-potassium pump, a key mechanism for maintaining ionic gradients across neuronal membranes. As sodium ions accumulate intracellularly, water follows osmotically, leading to cytotoxic edema and cell swelling. This loss of ionic homeostasis results in widespread neuronal depolarization and eventual cell death. Cell lysis further exacerbates the injury by releasing intracellular glutamate, a potent excitatory neurotransmitter, into the extracellular space. Elevated glutamate concentrations activate N-methyl-D-aspartate (NMDA) receptors, promoting excessive calcium influx into neurons. Intracellular calcium overload triggers a cascade of destructive processes, including activation of proteases, lipases, and endonucleases, which accelerate neuronal injury and death [6].

Following this primary phase, a latent period of approximately six hours typically ensues. During this interval, partial reperfusion of brain tissue occurs, and some neurons may recover if the injury was not irreversible. This phase represents a potential therapeutic window, as the restoration of oxygen and glucose delivery can temporarily stabilize cellular metabolism. However, pathological processes such as oxidative stress and inflammatory activation also begin during this time. Microglial activation and cytokine release initiate neuroinflammatory pathways that can contribute to delayed injury if not effectively controlled.

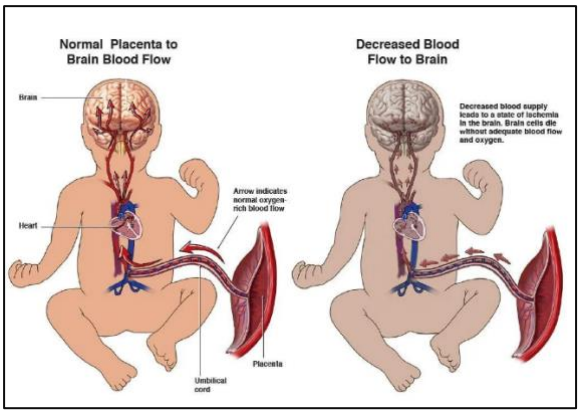

Figure-1: Birth Asphyxia.

The **secondary** injury phase unfolds over the next 24 to 48 hours and is characterized by reperfusion-related damage. As blood flow returns to injured brain regions, it carries not only oxygen and nutrients, but also toxic metabolites and excitatory neurotransmitters released from necrotic and apoptotic cells. This propagation of toxic signals extends the damage into previously uninjured or marginally affected brain tissue. Reactive oxygen species generated during reperfusion further injure cellular membranes, mitochondria, and nuclear DNA. The interplay between excitotoxicity, oxidative damage, and inflammation during this stage amplifies neuronal loss, disrupts synaptic integrity, and impairs long-term functional recovery.

This progression from primary energy failure to secondary reperfusion injury explains why clinical signs of HIE may worsen after an initial period of apparent stabilization. It also underscores the importance of early recognition and timely initiation of neuroprotective interventions, such as therapeutic hypothermia, to interrupt or mitigate the secondary injury cascade. Understanding these sequential mechanisms is essential for optimizing acute management strategies and for guiding research into novel therapies aimed at improving neurodevelopmental outcomes in affected infants [6].

History and Physical

Perinatal asphyxia produces a wide spectrum of systemic complications that can involve the central

nervous system, respiratory system, cardiovascular system, liver, and kidneys. The degree of injury is influenced by both the severity and timing of the hypoxic-ischemic event. Neurological injury is among the most significant consequences, and its clinical presentation can vary considerably. In neonates with hypoxic-ischemic encephalopathy (HIE) secondary to perinatal asphyxia, assessment of neurological function is critical for diagnosis, prognosis, and treatment planning [12].

One widely used method for clinical evaluation is the Sarnat staging system, which classifies the severity of encephalopathy into three stages based on neurological findings and autonomic function. In Sarnat stage I, representing the mildest form of injury, the neonate typically shows generalized increased sympathetic activity. Clinical signs may include hyperalertness, prolonged wakefulness, mydriasis, hyperreflexia, and increased deep tendon reflexes. Despite these abnormalities, overall neurological function remains relatively preserved, and seizures are uncommon at this stage.

In Sarnat stage II, the neurological compromise becomes more pronounced. Affected infants are often lethargic or obtunded, with decreased muscle tone and strong distal flexion. Parasympathetic activity predominates, manifesting as miosis, bradycardia, and increased secretions. Seizures are common in this stage and may occur within the first 24 hours of life. These seizures often correlate with abnormal electroencephalogram (EEG) patterns, reflecting evolving cortical injury. The combination of altered consciousness, abnormal tone, autonomic dysregulation, and seizure activity marks this as a moderate stage of encephalopathy [12].

Sarnat stage III represents the most severe form of HIE. Infants present with a markedly depressed level of consciousness, often approaching coma. Muscle tone is profoundly reduced, resulting in flaccidity, and deep tendon reflexes are markedly diminished or absent. EEG findings are severely abnormal, frequently showing patterns consistent with extensive cortical suppression. Interestingly, clinical seizures are less common in stage III than in stage II. This is due to the severity of the brain injury, which often disrupts the neuronal circuits necessary to generate and propagate observable seizure activity [12].

It is important to note that Sarnat staging has limitations, particularly in extremely preterm neonates. The neurological systems of these infants are less developed, which can alter the expected clinical presentation. For example, preterm infants are less likely to exhibit overt seizure activity, even in the presence of significant brain injury. Instead, they may show a higher prevalence of white matter injury and intraventricular hemorrhage. These differences underscore the need for careful interpretation of neurological findings in preterm infants and the importance of incorporating neuroimaging and EEG monitoring into the assessment [12].

A comprehensive history is essential to complement the physical examination. This includes details about maternal health, pregnancy complications, fetal monitoring results, timing and nature of the hypoxic event, and resuscitation measures taken at birth. Together, the history and neurological assessment form the foundation for diagnosing HIE, determining severity, and guiding immediate management strategies aimed at minimizing long-term neurological sequelae.

Table-1: Key Clinical Differences in Birth Asphyxia Severity and Recommended Management.

Severity Level	Clinical Features	Common Causes	Recommended Interventions
Mild HIE	Hyperalertness, mild	Short duration	Monitor vitals, feeding

Severity Level	Clinical Features	Common Causes	Recommended Interventions
	hypotonia, poor feeding, jitteriness	hypoxia, mild cord compression	support, prevent secondary injury
Moderate HIE	Lethargy, significant hypotonia, weak primitive reflexes, possible seizures	Prolonged hypoxia, placental insufficiency	Initiate therapeutic hypothermia (if term), seizure control, supportive care
Severe HIE	Coma, absent reflexes, severe respiratory distress, multiorgan dysfunction	Prolonged or severe hypoxia-ischemia	Aggressive supportive care, ventilation, hypothermia (term infants), prognosis counseling

Evaluation

The evaluation of a neonate with suspected perinatal asphyxia and possible hypoxic-ischemic encephalopathy (HIE) requires a systematic approach aimed at identifying the extent of multi-organ involvement and guiding immediate management. Laboratory investigations, continuous clinical monitoring, and neuroimaging play complementary roles in establishing the diagnosis and assessing prognosis [13][14].

Arterial blood gas (ABG) analysis is a key initial investigation, as it allows differentiation between respiratory and metabolic acidosis while quantifying the degree of hypoxemia. In the context of perinatal asphyxia, a significant metabolic acidosis with low pH and elevated base deficit is a strong indicator of impaired tissue oxygenation and anaerobic metabolism. ABG results also help guide ventilatory support and ongoing metabolic management. Assessment of liver function is essential, as hypoxic injury frequently extends to hepatic tissue. Measurement of serum transaminase levels, particularly alanine aminotransferase (ALT) and aspartate aminotransferase (AST), provides evidence of hepatocellular injury. Coagulation factor testing, including prothrombin time and international normalized ratio (INR), is important because liver dysfunction can impair synthesis of clotting proteins, increasing the risk of bleeding complications [14].

Myocardial injury is another possible consequence of perinatal asphyxia, and laboratory markers such as troponin and creatine kinase MB isoenzyme (CK-MB) can assist in detecting cardiac involvement. These values, combined with clinical signs such as poor perfusion or arrhythmias, can help guide cardiovascular support. Renal dysfunction is also common, and measurement of creatinine and blood urea nitrogen (BUN) provides an estimate of renal impairment, which may influence fluid and medication management [13][14][15].

Glucose monitoring is critical in the acute phase. Physiologically stressed neonates deplete glycogen stores rapidly and are at high risk for severe hypoglycemia. Hypoglycemia not only worsens brain injury but can also independently cause neurological damage. Frequent point-of-care blood glucose checks during and after resuscitation are therefore recommended to allow prompt correction. Neurological monitoring is equally important. Infants with suspected HIE require close observation for seizure activity, which may be subtle or clinically silent. If seizures are suspected or if the infant is at high risk, electroencephalography (EEG) or continuous video EEG should be initiated. These tools are valuable not only for seizure detection but also for

assessing background brain activity, which has prognostic implications [15].

Neuroimaging, particularly magnetic resonance imaging (MRI), is a cornerstone in the evaluation of hypoxic-ischemic brain injury. MRI is typically performed 5 to 10 days after the hypoxic event, when injury patterns become more clearly demarcated. The optimal timing depends on the infant's clinical stability, as transport and sedation considerations must be balanced against the need for diagnostic clarity. The distribution of injury varies depending on the duration and severity of the hypoxic insult, but evidence of brain injury is seen in most neonates with HIE, even in cases classified as mild [16]. By integrating laboratory testing, vigilant monitoring, and timely neuroimaging, clinicians can obtain a comprehensive picture of the extent of systemic and neurological injury, enabling targeted intervention and informed prognostication.

Treatment / Management

Management strategies for perinatal asphyxia and hypoxic-ischemic encephalopathy (HIE) are guided by the infant's gestational age, the severity of neurological injury, and the extent of multi-organ involvement. There is currently no specific treatment for preterm infants or for term infants with only mild HIE. In these cases, the focus remains on maintaining normothermia and providing optimal supportive care to minimize secondary complications. For term and near-term infants (≥35 weeks gestation) with moderate to severe HIE, therapeutic hypothermia is the standard of care [17]. The rationale for this intervention is rooted in the pathophysiological progression of brain injury in HIE. Following the initial primary neuronal insult, caused by the interruption of oxygen and glucose supply, there is a latent period lasting up to six hours before the onset of secondary injury. During this window, reperfusion of previously ischemic areas occurs, and damaged neurons release toxic neurotransmitters such as glutamate. These events initiate cascades of oxidative stress, inflammation, and excitotoxicity, which amplify neuronal death [18][19][20][21][22].

Therapeutic hypothermia aims to intervene during this latent period to reduce metabolic demand, slow the destructive biochemical cascades, and limit the extent of secondary injury. Cooling is achieved through selective head cooling or whole-body hypothermia, typically for a duration of 72 hours, followed by gradual rewarming. Initiation requires meeting strict eligibility criteria, including gestational age, time from birth, clinical staging, and evidence of significant asphyxia, as detailed in the companion StatPearls resource on "Neonatal Therapeutic Hypothermia" [17].

For infants who do not qualify for hypothermia—such as preterm neonates, the target is to maintain normothermia and provide meticulous supportive management across organ systems. This involves anticipating and treating complications early. Respiratory distress and persistent pulmonary hypertension of the newborn (PPHN) are common in asphyxiated infants. Management may require endotracheal intubation and mechanical ventilation to optimize gas exchange. Administration of exogenous surfactant can improve lung compliance in cases of secondary surfactant deficiency. Inhaled nitric oxide is indicated for significant pulmonary hypertension to promote selective pulmonary vasodilation and improve oxygenation.

Coagulopathy, often secondary to liver dysfunction and consumption of clotting factors, should be corrected cautiously with blood products such as fresh frozen plasma, platelets, or cryoprecipitate. This correction is essential not only for hemostasis but also for maintaining adequate oxygen-carrying capacity in the event of concurrent anemia. Myocardial dysfunction may manifest as hypotension or poor perfusion and can necessitate the use of vasopressors such as dopamine or dobutamine

to maintain systemic perfusion pressure. Renal impairment may be presented with oliguria or anuria. In such cases, judicious use of crystalloids and blood products is critical to prevent fluid overload, which can exacerbate pulmonary and cardiac compromise. Monitoring urine output and renal function tests helps guide fluid and electrolyte therapy.

Regardless of whether an infant is undergoing cooling or maintained at normothermia, continuous monitoring of systemic and neurological status is essential. Infants with birth asphyxia often compensate for metabolic acidosis by inducing hyperventilation to lower carbon dioxide levels. However, excessive hypocapnia can cause cerebral vasoconstriction, thereby reducing cerebral oxygen delivery [23]. Therefore, ventilatory settings should be adjusted to maintain appropriate carbon dioxide levels. Avoidance of hyperoxia during and after resuscitation is also a priority. Excessive oxygen administration can increase the generation of free radicals, exacerbating oxidative injury to the brain, myocardium, and other tissues [24]. Oxygen therapy should be titrated to achieve target saturations appropriate for the infant's age and condition.

Given the high metabolic demands of the neonatal brain, euglycemia must be maintained. Both hypoglycemia and hyperglycemia can worsen neurological outcomes. Frequent blood glucose monitoring is recommended, with prompt correction of any deviations from the normal range [25]. Blood pressure stability is another critical parameter. Hypotension can further compromise cerebral perfusion, while hypertension may worsen intracranial hemorrhage risk, especially in preterm infants. Vasoactive support and careful fluid management are used to maintain consistent cerebral oxygen delivery.

In all cases, management is multidisciplinary, requiring coordination between neonatologists, neurologists, respiratory therapists, and nursing staff. By combining targeted interventions such as therapeutic hypothermia in eligible term and near-term infants with vigilant supportive care for all affected neonates, the goal is to minimize further injury, optimize recovery, and improve long-term neurodevelopmental outcomes.

Differential Diagnosis

When assessing a newborn suspected of birth asphyxia, the clinical presentation may overlap with several other conditions. Accurate differentiation is essential to guide timely and effective treatment, prevent unnecessary interventions, and address the underlying cause. The following are important conditions to consider.

Brain Tumors

Although rare in neonates, congenital brain tumors such as teratomas, astrocytomas, or choroid plexus papillomas can present with signs resembling hypoxic-ischemic encephalopathy (HIE). Symptoms may include poor feeding, lethargy, abnormal muscle tone, seizures, and abnormal respiratory patterns. Neuroimaging with cranial ultrasound, CT, or MRI is critical for identification. Early diagnosis enables surgical or medical management before irreversible neurological injury occurs.

Developmental Defects

Structural brain malformations like holoprosencephaly, lissencephaly, or agenesis of the corpus callosum may mimic the neurological depression seen in perinatal asphyxia. These defects often present with hypotonia, feeding difficulties, apnea, and seizures. Antenatal ultrasound and postnatal MRI can detect these abnormalities. Unlike asphyxia, these conditions are non-progressive from birth, and the management approach focuses on supportive care and addressing specific complications rather than reversing hypoxic injury.

Methylmalonic Acidemia

This inherited metabolic disorder results from a defect in the methylmalonyl-CoA mutase enzyme or related cofactors, leading to toxic

accumulation of methylmalonic acid. Newborns may present within days after birth with hypotonia, poor feeding, vomiting, lethargy, and metabolic acidosis—findings that may be mistaken for birth asphyxia. Laboratory evaluation showing elevated methylmalonic acid levels in blood or urine confirms the diagnosis. Early treatment with vitamin B12 supplementation, dietary protein restriction, and metabolic crisis management can prevent irreversible neurological damage.

Propionic Acidemia

Caused by a deficiency of propionyl-CoA carboxylase, this disorder results in accumulation of propionic acid and related metabolites. Symptoms often appear within the first week of life and include poor feeding, vomiting, lethargy, seizures, and metabolic acidosis—closely resembling hypoxic injury. Diagnosis is made through plasma amino acid analysis, organic urine acids, and enzymatic studies. Prompt management involves protein restriction, carnitine supplementation, and aggressive treatment of metabolic decompensation.

Sepsis

Neonatal sepsis can present with nonspecific signs such as apnea, bradycardia, hypotonia, poor feeding, and seizures, all of which can be seen in birth asphyxia. Differentiating the two is vital because sepsis requires urgent antimicrobial therapy. Blood cultures, complete blood count, C-reactive protein, and lumbar puncture are essential in evaluation. Sepsis may also coexist with hypoxic injury, further complicating the presentation.

Neuromuscular Disorders, including Neonatal Myopathy

Inherited neuromuscular disorders such as congenital myopathies or spinal muscular atrophy can present at birth with profound hypotonia ("floppy infant"), weak cry, respiratory insufficiency, and feeding difficulty. These findings can be misattributed to perinatal asphyxia. Electromyography, muscle biopsy, and genetic testing help confirm the diagnosis. Management focuses on respiratory and nutritional support, with some conditions having targeted genetic therapies. Because birth asphyxia shares signs with several metabolic, infectious, structural, and neuromuscular conditions, careful history-taking, targeted laboratory tests, and neuroimaging are essential to avoid misdiagnosis. Distinguishing between these conditions ensures that infants receive specific, life-saving interventions and that families are counseled appropriately regarding prognosis and recurrence risk.

Ongoing Research:

Ongoing research in therapeutic hypothermia is focused on addressing knowledge gaps regarding its use beyond the currently established indications. While the treatment is widely accepted as effective for term and near-term infants with moderate-to-severe hypoxic–ischemic encephalopathy (HIE), evidence in other neonatal groups remains limited. Several clinical trials are underway to evaluate its potential role in preterm infants, particularly those born between 33 and 35 weeks of gestation, and in infants with mild HIE. These studies are designed to assess both safety and efficacy, with an emphasis on determining whether cooling therapy can provide meaningful neuroprotection in these populations.

The inclusion of preterm infants in hypothermia research addresses an important clinical question. Preterm neonates are at higher risk of brain injury due to the fragility of their developing neural structures and the increased vulnerability of cerebral vasculature. Hypoxic–ischemic injury in these infants often results in a combination of white matter and cortical damage, which may differ from patterns seen in term infants. While therapeutic hypothermia has been shown to mitigate secondary brain injury through the reduction of metabolic demand, inflammation, and apoptotic processes, it remains uncertain whether these mechanisms confer the same degree of

protection in preterm infants. Furthermore, cooling in preterm neonates raises additional safety concerns, such as increased susceptibility to coagulopathy, hypotension, and infection. Ongoing trials are therefore carefully monitoring both neurological and systemic outcomes to establish a risk–benefit profile.

Another important focus of current studies is the application of therapeutic hypothermia in infants with mild HIE. Traditionally, this group has not received cooling therapy due to the assumption that their risk of long-term neurological impairment is low. However, recent observational studies have suggested that even mild HIE can lead to cognitive, behavioral, and motor deficits later in childhood. As a result, randomized controlled trials are now investigating whether early intervention with hypothermia can prevent subtle but significant neurodevelopmental challenges in this group. These studies aim to clarify whether the benefits outweigh potential risks, including bradycardia, electrolyte imbalance, and impaired coagulation, which can occur even in otherwise stable infants.

In addition to safety and efficacy, ongoing research is working to refine the parameters of hypothermia therapy. Key variables under investigation include the optimal cooling temperature, duration of treatment, and rewarming protocols. Current standard practice for term infants involves cooling to 33.5°C for 72 hours followed by gradual rewarming, but these parameters may not be ideal for preterm or mildly affected infants. Adjustments to treatment intensity and timing may be necessary to maximize neuroprotection while minimizing complications.

The results of these trials have the potential to expand the clinical use of therapeutic hypothermia and reshape neonatal neurocritical care. If benefits are confirmed, cooling therapy could be extended to a broader neonatal population, offering protection to infants who currently receive only supportive care. This could lead to significant improvements in survival rates without disability and enhance long-term quality of life for affected children. Until then, careful evaluation of emerging evidence will be critical to guide safe and effective adoption in clinical practice.

Table-2: Current Evidence and Research Status for Therapeutic Hypothermia in Different Neonatal Groups.

Neonatal Group	Evidence Status	Main Findings / Limitations	Research Needs
Term infants with moderate–severe HIE	Strong evidence from multiple RCTs	Reduces mortality and neurodevelopmental impairment	Optimization of cooling duration and rewarming
Preterm (33–35 weeks) with HIE	Limited, ongoing trials	Safety and efficacy not yet confirmed	Large-scale RCTs for protocol validation
Mild HIE (term)	Insufficient evidence	Some observational studies show potential benefit	Controlled trials to assess neurodevelopment outcomes
Preterm (<33 weeks) with HIE	Very limited data	Safety concerns due to immature physiology	Safety-focused feasibility studies

Staging:

The modified Sarnat examination is used to establish the initial stage of encephalopathy and determine eligibility for therapeutic hypothermia in

neonates born after 35 weeks of gestation (see Table. Modified Sarnat Examination). In practice, the diagnosis of encephalopathy using this tool generally requires the presence of abnormalities in at least three distinct categories. In situations where findings across categories are inconclusive or evenly distributed between stages, the level of consciousness serves as the decisive factor in classification. It is important to note that this examination has not been validated for use in significant preterm infants, and its application in that group remains uncertain.

In the category of level of consciousness, infants with mild encephalopathy display excessive alertness, those with moderate encephalopathy are lethargic, and those with severe encephalopathy present in stupor or coma. For activity, a normal or only slightly reduced activity level is associated with mild encephalopathy. Markedly reduced activity corresponds to moderate encephalopathy, while the complete absence of activity indicates severe encephalopathy. Tone is also a key parameter. Increased muscle tone is seen in mild cases, decreased tone in moderate cases, and a flaccid state in severe cases.

Regarding posture, normal posture or mild distal flexion is characteristic of mild encephalopathy. Infants with moderate encephalopathy exhibit distal flexion or complete extension, while those with severe encephalopathy present with decerebrate posturing. Primitive reflexes also help guide staging. A normal suck reflex, possibly accompanied by a hyperactive Moro reflex, is consistent with mild encephalopathy. Weak suck or an incomplete Moro reflex is typical of moderate encephalopathy. Absence of both the suck and Moro reflexes indicates severe encephalopathy. The autonomic system is assessed by examining pupil reactivity, heart rate, and breathing patterns. A normal autonomic profile corresponds to mild encephalopathy. Signs of moderate encephalopathy include constricted pupils, bradycardia, or periodic breathing. Severe encephalopathy is suggested by pupils that are deviated, dilated, or unresponsive to light, variability in heart rate, or apnea.

By evaluating these parameters collectively, the modified Sarnat examination provides a structured method for determining the stage of encephalopathy and identifying neonates who may benefit from therapeutic hypothermia. Its emphasis on multiple clinical domains—neurological activity, reflex integrity, posture, tone, and autonomic function—ensures that the assessment captures both subtle and profound neurological dysfunction. The reliance on the level of consciousness as a tiebreaker reflects its central importance in gauging neurological injury severity. While its use has become standard for term and near-term infants, further research is needed to adapt and validate this staging system for preterm neonates, whose presentation and vulnerability to hypoxic–ischemic injury may differ significantly.

Prognosis

Birth asphyxia carries a substantial risk of morbidity and mortality, with outcomes that can range from relatively mild impairments to conditions that are life-threatening. Reported mortality rates exceed 30%, and most deaths occur within the first several days of life. Among survivors, a significant proportion experience persistent neurological deficits of varying severity. Some of these infants may later die from complications such as aspiration or systemic infections. Long-term follow-up studies have documented that survivors are at risk of developing disabling cerebral palsy, poor cognitive development, low psychomotor performance, recurrent seizures, blindness, and profound hearing loss [3][26].

Accurate data on the extent and nature of long-term dysfunction in preterm infants affected by birth asphyxia remain limited. Few studies provide precise estimates, and assessing prognosis in this group has been challenging. Evidence suggests that the patterns of injury in preterm infants differ from

those observed in term and near-term infants, indicating possible differences in underlying vulnerability and injury mechanisms [12][27].

Neuroimaging, particularly magnetic resonance imaging (MRI) performed shortly after birth, has shown value in predicting severe neurodevelopmental disability or mortality in infants with extensive injury. However, its predictive accuracy is lower in those with mild or moderate injury patterns [28]. This limitation underscores the complexity of early prognostication and the influence of evolving clinical factors over time.

Although several prognostic models and scoring systems have been developed, clinical examination remains the primary tool for ongoing assessment. Serial evaluations during infancy and childhood are essential for identifying emerging deficits, monitoring developmental progress, and adjusting care plans accordingly [29][30][31]. This continued observation is particularly important in cases where early imaging or initial neurological assessment does not clearly indicate the severity of injury, as subtle or progressive impairments may only become apparent with time.

Overall, prognosis following birth asphyxia depends on multiple factors, including the severity and duration of hypoxic-ischemic injury, gestational age, the timeliness and effectiveness of interventions, and the presence of associated complications. The high rate of long-term disability among survivors emphasizes the need for structured follow-up programs, early therapeutic interventions, and coordinated multidisciplinary care aimed at maximizing developmental potential and quality of life [31].

Complications

Birth asphyxia is associated with a broad spectrum of complications that can involve multiple organ systems, with the central nervous system being particularly susceptible. Hypoxic-ischemic encephalopathy (HIE) is a common neurological consequence, often leading to persistent functional impairments including cerebral palsy, developmental delays, and cognitive dysfunction. In severe cases, infants may experience seizures, hypotonia, and impaired feeding ability, which can further compromise their overall health status and survival prospects [32].

Beyond neurological injury, systemic complications are frequent and can involve critical organ systems. Renal impairment, including acute kidney injury, is a notable outcome due to the high sensitivity of renal tissues to hypoxic damage. Hepatic injury may also occur, manifesting as abnormal liver function, while cardiovascular instability can result from myocardial depression and compromised circulatory regulation [32].

Respiratory complications are another significant concern, with persistent pulmonary hypertension being one of the most serious, often requiring intensive respiratory support. Metabolic derangements such as lactic acidosis are also common, arising from anaerobic metabolism during the hypoxic episode, and can exacerbate organ dysfunction.

The combined impact of these complications can profoundly affect both immediate and long-term health outcomes, underscoring the need for early recognition, comprehensive management, and long-term follow-up of infants affected by birth asphyxia to mitigate adverse consequences and improve prognosis.

Consultations

Infants experiencing birth asphyxia typically require the coordinated involvement of a multidisciplinary care team to address the full scope of their clinical needs. A neonatologist plays a central role in the immediate resuscitation process and in directing ongoing clinical management. When there is concern for neurological injury, such as hypoxic-ischemic encephalopathy (HIE), a pediatric

neurologist is consulted to perform detailed assessments and to guide monitoring strategies aimed at detecting and mitigating further neurological compromise [32].

Specialized input from other pediatric subspecialists is frequently required to manage complications affecting various organ systems. Cardiologists may be involved to evaluate and treat cardiovascular instability or structural or functional cardiac complications, while nephrologists are consulted to address acute kidney injury or other renal dysfunctions that may arise secondary to asphyxia. Respiratory compromise often necessitates the expertise of a pediatric pulmonologist, who can optimize ventilation strategies and support long-term respiratory care when needed. In complex cases involving multiple organ systems, the involvement of a pediatric intensivist becomes crucial for advanced monitoring and management in an intensive care setting. Alternatively, for infants with severe and irreversible injury, a pediatric palliative care specialist may guide symptom management and family support, focusing on comfort and quality of life [32].

Following stabilization and discharge planning, ongoing developmental follow-up is essential. Outpatient developmental pediatricians oversee long-term monitoring for cognitive, motor, and behavioral outcomes, while physical and occupational therapists initiate early interventions to support motor skill acquisition, functional independence, and overall developmental progress. Early and coordinated engagement with these professionals ensures that rehabilitation strategies are integrated into the infant's care plan from the earliest stages, optimizing the potential for improved neurodevelopmental outcomes [32].

Enhancing Healthcare Team Outcomes

Birth asphyxia remains a significant contributor to neonatal morbidity and mortality, and its optimal management requires a highly coordinated interprofessional team approach. Such collaboration ensures that care remains patient-centered, that outcomes are improved, and that patient safety is upheld through well-structured teamwork. The complexity and urgency of this condition demand that each team member understands their role and works in concert to deliver time-sensitive, evidence-based interventions.

Neonatologists serve as the primary decision-makers in both diagnosis and treatment initiation. They lead critical interventions, including neonatal resuscitation and the initiation of therapeutic hypothermia for eligible infants, while ensuring that individualized care plans are developed in collaboration with other relevant specialists. Their role extends beyond acute management to include long-term care planning, integrating the input of subspecialists when complications such as hypoxic-ischemic encephalopathy or multi-organ dysfunction are present [32].

Advanced practitioners and nurses provide continuous bedside monitoring, promptly detecting changes in clinical status and initiating necessary interventions. They are responsible for administering medications and supportive therapies with precision, ensuring strict adherence to established protocols to prevent secondary injury. Their presence at the bedside also facilitates ongoing communication with the family, helping them understand the infant's progress and the care being provided. Pharmacists play an essential role in ensuring the safety and accuracy of medication administration during both the acute resuscitation phase and subsequent management. This includes calculating and verifying appropriate doses for critical medications such as anticonvulsants, inotropes, and sedatives, which require precise titration in neonates. Their expertise helps minimize the risk of dosing errors and adverse drug interactions in a population that is particularly vulnerable to medication-related complications [32].

The clinical team must maintain proficiency in neonatal resuscitation, the correct application of therapeutic hypothermia, and the monitoring of multi-organ function. Timely action is essential, as the window for initiating therapeutic hypothermia is within the first six hours of life. Adherence to established evidence-based protocols, including those outlined in neonatal resuscitation guidelines, is critical to achieving optimal neuroprotective effects and preventing avoidable harm.

Ethical responsibilities are a central component of care in birth asphyxia cases. The team must act in the best interests of the infant, delivering life-saving interventions when appropriate, while also providing clear and compassionate communication with the family regarding prognosis, potential risks, and expected long-term outcomes. Ethical challenges often emerge when the prognosis is poor, requiring careful consideration of quality of life, family values, and cultural factors when deciding on the extent of ongoing interventions. These discussions are best handled collaboratively, ensuring that all perspectives are considered and that decisions are made with both medical and ethical integrity. Effective interprofessional communication underpins all aspects of care delivery. Team members must consistently share updates on the infant's condition, promptly communicate any changes, and align treatment strategies to ensure continuity and accuracy in care. Clear documentation, structured handovers, and regular team huddles can reduce the risk of errors and promote a unified approach [32].

Coordinated care also involves timely specialist consultations, efficient scheduling of diagnostic procedures such as neuroimaging, and planning for rehabilitation or long-term follow-up services. This proactive planning helps ensure that infants receive the necessary interventions at every stage, from acute stabilization to ongoing developmental support. When executed effectively, this collaborative model not only addresses the immediate medical needs of the infant but also strengthens overall team performance. It promotes a culture of safety, reduces preventable complications, and enhances both short- and long-term outcomes. By combining clinical expertise, precise protocol adherence, ethical decision-making, and open communication, the interprofessional healthcare team maximizes the chances of survival and quality of life for infants affected by birth asphyxia while maintaining the highest standards of professional care [32].

Final Overview:

Therapeutic hypothermia is the only intervention with high-quality evidence demonstrating a reduction in death or major neurodevelopmental disability for term and near-term infants with moderate to severe hypoxic-ischemic encephalopathy when applied within six hours of birth. Large randomized trials and pooled analyses established the efficacy of whole-body or selective head cooling, showing improved survival free of disability at 18 to 24 months. These trials underpin contemporary practice in high-resource settings and form the basis of guideline recommendations.

International and national guideline bodies have translated trial data into operational recommendations. Guidance from pediatric and resuscitation authorities recommends initiating therapeutic hypothermia for eligible infants ≥35 weeks' gestation who meet clinical and biochemical criteria and who can begin cooling within the six-hour latent window; standard practice is cooling to approximately 33 to 34°C for 72 hours followed by controlled rewarming. These protocols emphasize strict eligibility assessment, temperature control, continuous cardiorespiratory and neurologic monitoring, and management of multisystem complications during and after cooling.

Recent trial activity has challenged and refined the boundaries of these recommendations. A major randomized controlled trial performed in low- and middle-income countries found no benefit and suggested harm from cooling in resource-limited settings where perinatal care contexts differ substantially from the original trial environments. That study highlighted how differences in etiology, timing of insult, infection burden, and supportive care capacity may modify treatment effect and safety, prompting calls for caution in wholesale adoption of cooling in such settings without contextual validation.

Research has also targeted populations previously excluded from landmark trials. Pilot randomized studies have examined hypothermia in neonates with mild HIE and in late preterm infants. Early data from a randomized pilot in mild HIE did not demonstrate clear improvement in cerebral magnetic resonance biomarkers with cooling, though sample sizes and baseline imbalances limit definitive interpretation. Trials in the 33–35 weeks gestational age group remain ongoing; until adequately powered safety and efficacy data emerge, consensus documents recommend against routine cooling outside established criteria and instead stress meticulous supportive care and enrollment in controlled studies when possible.

These developments carry practical implications for guideline implementation and research priorities. First, guideline committees should incorporate contextual modifiers, explicitly address low-resource settings and defining minimum supportive care requirements necessary to ensure safety. Second, trial design must emphasize stratified analyses by setting, etiology, and coexisting morbidities, and should include robust safety monitoring for systemic adverse effects such as coagulopathy, arrhythmia, and infection. Third, biomarker and neuroimaging endpoints may help power smaller feasibility studies, but ultimately long-term neurodevelopmental outcomes remain the gold standard for clinical effectiveness.

In summary, therapeutic hypothermia represents evidence-based standard care for appropriately selected term and near-term infants with moderate to severe HIE in well-resourced settings. Recent trials underscore that efficacy and safety are context dependent. Current global neonatal guidelines should therefore be dynamic, integrating emerging trial data, defining setting-specific prerequisites for implementation, and prioritizing randomized evaluation in preterm and mild HIE populations before broader adoption. Continued coordinated research will determine whether the therapeutic window established by earlier trials can be safely and effectively extended to other neonatal groups and care environments.

Conclusion

Birth asphyxia presents a complex clinical scenario that requires immediate and sustained multidisciplinary involvement. The acute phase demands rapid stabilization under the guidance of a neonatologist, with the prompt inclusion of relevant subspecialists according to organ systems affected. Neurological monitoring by pediatric neurologists is particularly important due to the high risk of hypoxic–ischemic encephalopathy, which can significantly influence neurodevelopmental outcomes. Cardiovascular and renal assessments, often undertaken by cardiologists and nephrologists, are essential for addressing secondary organ injury that may emerge during the neonatal period. Pulmonologists contribute to the management of respiratory compromise, which can exacerbate systemic hypoxia and further impair recovery. In severe cases with multi-organ dysfunction, pediatric intensivists provide critical care support, while pediatric palliative care specialists may be engaged to address quality-of-life considerations when prognosis is poor. Early integration of developmental pediatricians ensures that rehabilitation strategies are

initiated during the early stages of recovery, optimizing neuroplasticity and functional gains. Physical and occupational therapists form a key part of this continuum, targeting motor skills, sensory integration, and adaptive functioning. Evidence indicates that early and well-coordinated multidisciplinary engagement not only addresses immediate survival but also mitigates long-term disability through structured follow-up and tailored intervention programs. This approach fosters continuity of care, improves family engagement, and aligns treatment goals across specialties. The long-term success of newborns affected by birth asphyxia depends heavily on such collaborative care models, which bridge the gap between acute intervention and sustained developmental support.

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