# Birth asphyxia

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Birth asphyxia

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Birth Asphyxia

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Birth asphyxia refers to an impairment of the normal exchange of respiratory gases during parturition, and the ensuing adverse effects on the fetus. It is an important cause of fresh stillbirth and early neonatal death. The condition of a newborn infant is determined by a complex interaction of maternal, placental, uterine and fetal factors extending through pregnancy to delivery. At the core of the feto-maternal unit is the process of placental exchange whereby oxygen from the maternal circulation and carbon dioxide from the fetal circulation passively diffuse across the placental membrane. During normal uterine contractions placental exchange is abolished when the uterine pressure exceeds 10 mm Hg. Studies using infra-red spectroscopic techniques during normal labor show that many infants undergo intermittent hypoxia during the process of delivery. Despite this hypoxic stress most infants are born in good condition. The fetus who experiences significant asphyxia episode is at risk of developing hypoxic ischemic encephalopathy or other end organ damage.

Certain terms that are commonly used during evaluation of a baby at risk for brain injury in the perinatal period:

**Neonatal Depression:**

Neonatal depression is a general term used to describe infants who have a prolonged transition from intrauterine to extraterine environment and usually have low APGAR scores.

**Neonatal Encephalopathy:**

Neonatal encephalopathy is a clinical term used to describe an abnormal neurobehavioral state that consists of a decreased level of consciousness. It characteristically begins within the first postnatal day and may be associated with seizure like activity, hypoventilation or apnoea, depressed primitive reflexes and the appearance of brain stem reflexes. It does not imply a specific aetiology, nor does it imply irreversible neurological injury.
Hypoxic Ischemic Encephalopathy:

Hypoxic Ischemia encephalopathy is an abnormal neurobehavioural state in which the predominant pathogenetic mechanism is impaired cerebral blood flow.

Hypoxic Ischemic Brain Injury:

Hypoxic ischemic brain injury refers to the neuropathology attributable to hypoxia/ischemia as evidenced by biochemical or post-mortem abnormalities.

BIRTH ASPHYXIA DEFINITION:

The major difficulty in collecting accurate epidemiological data on birth asphyxia is the lack of a common definition of the condition. Most studies have been conducted in hospital settings in developed countries and may not be representative of the situation at community level in developing countries.

The 1996 guidelines from the AAP (American Academy of Pediatrics) and ACOG (American College of Obstetricians and Gynaecologists)¹ for hypoxic-ischemic encephalopathy (HIE) indicate that all of the following must be present for the designation of perinatal asphyxia, severe enough to result in acute neurological injury:

- Profound metabolic or mixed acidemia (pH < 7) in an umbilical artery blood sample, if obtained
- Persistence of an Apgar score of 0-3 for longer than 5 minutes
- Neonatal neurologic sequelae (eg, seizures, coma, hypotonia)
- Multiple organ involvement (eg, kidney, lungs, liver, heart, intestines)

AAP and ACOG indicate that all of the following must be present for the designation of perinatal asphyxia

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- Persistence of an Apgar score of 0-3 for longer than 5 minutes
- Neonatal neurologic sequelae (eg, seizures, coma, hypotonia)
- Multiple organ involvement (eg, kidney, lungs, liver, heart, intestines)

However, for field workers (Manual – Basic newborn resuscitation: a practical guide) birth asphyxia is defined as failure to initiate and sustain breathing at birth or an APGAR less than 7 at 1 minute. The practical utility of this definition is that it helps identify infants which would need resuscitation and further care. However, specificity and predictive value of this definition for death and neurological damage are very limited. It tends to overestimate by 8 fold² the number of cases as opposed to the definition based on observation of neonatal encephalopathy. The International Classification of Diseases (10th revision) classifies birth asphyxia² reference to Apgar scores at one minute of age (Apgar 1 = 4-7: mild/moderate birth asphyxia, Apgar 1 < 3: severe birth asphyxia). The National Neonatology Forum of
India has defined asphyxia as “gasping or ineffective breathing or lack of breathing at one minute of life”.

Amongst all the definitions the one specified by ACOG is closest to the defining the etiology and terminology (the controversies in the definition are being discussed under heading APGAR and cord blood gases). The term “asphyxia” should not be used unless the neonate meets all of the conditions mentioned in the ACOG definition. To label an infant with hypoxic-ischemic encephalopathy from birth asphyxia without these criteria may not only cause one to miss the real cause of a neurologic problem, such as infections or metabolic abnormalities, but also unfairly incriminate a colleague.

APGAR and birth asphyxia:

APGAR score (Table 1) was devised by Virginia Apgar, an obstetric anaesthesiologist in 1952 to express the early postnatal condition of the newborn. It was designed to be a guide to the resuscitation of the newborn. Over time the universality of the Apgar score led many investigators to adopt it as a marker for birth asphyxia. Most commonly a one minute Apgar less than or equal to three, or a five minute Apgar less than seven have been taken to indicate birth asphyxia. The problems with using APGAR score as a marker of birth asphyxia are: 1) Apgar score may be low because of causes other than birth asphyxia e.g prematurity, maternal sedation, neuromuscular disorder etc. 2) APGAR score has a poor correlation with the long term outcome. However, the extended Apgar score recorded 20 minutes after birth has much better specificity for the prediction of both early death and disability.

<table>
<thead>
<tr>
<th>Sign</th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>Absent</td>
<td>Below 100</td>
<td>Above 100</td>
</tr>
<tr>
<td>Respiratory effort</td>
<td>Absent</td>
<td>Slow, irregular</td>
<td>Good, crying</td>
</tr>
<tr>
<td>Muscle tone</td>
<td>Flaccid</td>
<td>Some flexion of extremities</td>
<td>Active motion</td>
</tr>
<tr>
<td>Reflex, irritability</td>
<td>No response</td>
<td>Grimace</td>
<td>Vigorous cry</td>
</tr>
<tr>
<td>Color</td>
<td>Pale</td>
<td>Cyanotic</td>
<td>Completely pink</td>
</tr>
</tbody>
</table>

Table 1: APGAR Score
Cord blood gases and birth asphyxia:
The normal cord blood gas values of the fetus are important to know to interpret gases after delivery (Table 2). During the course of normal labor, the PaO2 drops, the PaCO2 rises, and the base deficit rises. Severe acidemia is when the pH is below 7 and there is a base deficit of more than 12 mMol/L. Metabolic acidosis in isolation also proved to be a poor predictor of significant perinatal brain injury. The sensitivity and positive predictive value of a low pH for adverse outcome are 21% and 8%, respectively. Cord blood lactate levels are no better at 12% and 5%, respectively. Some studies suggest that neurologic injury is more likely to occur in an infant who is depressed but has a normal pH.

<table>
<thead>
<tr>
<th></th>
<th>pH</th>
<th>PaO2 (mm Hg)</th>
<th>PaCO2 (mm Hg)</th>
<th>HCO (mEq/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Umbilical artery</td>
<td>7.27 ± 0.08</td>
<td>25 ± 19</td>
<td>45 ± 10</td>
<td>22 ± 3.7</td>
</tr>
<tr>
<td>Umbilical vein</td>
<td>7.34 ± 0.07</td>
<td>36 ± 10</td>
<td>40 ± 6</td>
<td>23 ± 2.2</td>
</tr>
</tbody>
</table>

Table 2: Normal blood gases values at the time of birth

INCIDENCE:
Each year 4 million neonates in the world die due to asphyxia which represents 38% of all deaths under 5 years. The frequency of perinatal asphyxia is approximately 1% to 1.5% of live births in western hemisphere and is inversely related to gestational age and birth weight. It occurs in 0.5% of live born infants >36 weeks gestation and accounts for 20% of perinatal deaths. According to the National Neonatal Perinatal Database of India, 23% of all neonatal deaths in our country are related to asphyxia. 25-30% of all stillbirths occur intrapartum. In absolute numbers, this translates into between 2,50,000 to 3,50,000 deaths due to asphyxia and contributes to as many as 300,000 to 400,000 stillbirths annually. To add to this, there is an unaccounted disability related to asphyxia in the developing countries. Because of the limited availability of data, and despite its enormous magnitude, available figures are likely to underestimate the real proportion of the problem.

CLINICAL MANIFESTATIONS:
Neurological syndrome: the occurrence of a neonatal neurological syndrome, indeed, is a sine qua non for attributing subsequent brain injury to intrapartum insults. The brain syndrome in HIE is often described in terms of time after the insults.
Birth to 12 hours: in the first hours after the insult, signs of presumed bilateral cerebral hemispherical disturbance predominate. The severely affected infant is either deeply stuporous or in coma. Periodic breathing or respiratory irregularity is prominent. Severely affected ones may exhibit marked hypoventilation or respiratory failure. Majority of infants at this stage are markedly hypotonic with minimal spontaneous or elicited movement. Less affected ones, have preserved tone and is more likely with prominent involvement of basal ganglia.

12 to 24 hours after insult: during this time the infants neurological status changes in a variable manner. Infants with severe disease remain stuporous and those with less severe disease often begin to exhibit some degree of improvement in alertness. Infants with injury to basal ganglia often exhibit an increase in their hypertonia, especially in response to their handling. Full term infants often exhibit weakness in the hip shoulder distribution, with more impressive involvement of proximal extremities. Seizures often occur during this time.

24 to 72 hours: during this time, the severely affected infant’s level of consciousness often deteriorates further and deep stupor or coma ensues. Babies who die with HIE most often do so at this time. Preterm babies may have intraventricular haemorrhages, and term babies often demonstrate signs of major cerebral necrosis.

After 72 hours: infants who survive to this extent usually improve over the next few days or weeks. Although the level of consciousness improves, mild to moderate stupor continues. Disturbances of feeding are common. Generalized hypotonia is common but hypertonia may be seen in babies who have had significant basal ganglia involvement.

Grading of HIE: In 1976 Samat and Samat (Table 3) published a combined clinical and EEG study of 21 term infants who displayed evidence of fetal distress(7). They described a syndrome of neurological and electro-encephalogram (EEG) features that they labelled neonatal encephalopathy following fetal distress.

In their original study the syndrome was divided into three stages, with severely affected infants typically progressing from grade 1 to grade 3.
<table>
<thead>
<tr>
<th></th>
<th>State 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of Consciousness</td>
<td>Hyperalert</td>
<td>Lethargic or obtunded</td>
<td>Stuporous</td>
</tr>
<tr>
<td>Neuromuscular Control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle tone</td>
<td>Normal</td>
<td>Mild hypotonia</td>
<td>Flaccid</td>
</tr>
<tr>
<td>Posture</td>
<td>Mild distal flexion</td>
<td>Strong distal flexion</td>
<td>Intermittent decerebration</td>
</tr>
<tr>
<td>Stretch reflexes</td>
<td>Overactive</td>
<td>Overactive</td>
<td>Decreased or absent</td>
</tr>
<tr>
<td>Segmental myoclonus</td>
<td>Present</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Complex Reflexes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suck</td>
<td>Weak</td>
<td>Weak or absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Moro</td>
<td>Strong; low threshold</td>
<td>Weak; incomplete; high threshold</td>
<td>Absent</td>
</tr>
<tr>
<td>Oculovestibular</td>
<td>Normal</td>
<td>Overactive</td>
<td>Weak or absent</td>
</tr>
<tr>
<td>Tonic neck</td>
<td>Slight</td>
<td>Strong</td>
<td>Absent</td>
</tr>
<tr>
<td>Autonomic Function</td>
<td>Generalized sympathetic</td>
<td>Generalized parasympathetic</td>
<td>Both systems depressed</td>
</tr>
<tr>
<td>Pupils</td>
<td>Mydriasis</td>
<td>Miosis</td>
<td>Variable; often unequal; poor light reflex</td>
</tr>
<tr>
<td>Heart Rate</td>
<td>Tachycardia</td>
<td>Bradycardia</td>
<td>Variable</td>
</tr>
<tr>
<td>Bronchial and Salivary Secretions</td>
<td>Sparse</td>
<td>Proluse</td>
<td>Variable</td>
</tr>
<tr>
<td>Gi Motility</td>
<td>Normal or decreased</td>
<td>Increased; diarrhoea</td>
<td>Variable</td>
</tr>
<tr>
<td>Seizures</td>
<td>None</td>
<td>Common; focal or multifocal</td>
<td>Uncommon (excluding decerebration)</td>
</tr>
<tr>
<td>EEG Findings</td>
<td>Normal (awake)</td>
<td>Early; low-voltage continuous delta and theta. Later; periodic pattern (awake) Seizures: focal 1 to 1 Hz spike-and-wave</td>
<td>Early: periodic pattern with isopotential phases Later: totally isopotential</td>
</tr>
<tr>
<td>Duration</td>
<td>1-3 days</td>
<td>2-14</td>
<td>Hours to weeks</td>
</tr>
</tbody>
</table>

Table 3. Sarnat Clinical Stages of Perinatal Hypoxic Ischemic Brain Injury

This scheme was later modified by Fenichel et al. (Table 4), who grouped the clinical features of what he termed hypoxic ischemic encephalopathy (HIE) into three different patterns (mild, moderate and severe). The asphyxiated infant was not considered to progress through the grades but rather to exhibit the characteristic
features and time course (of either deterioration or resolution) consistent with a particular grade.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Grade 1 (mild)</th>
<th>Grade 2 (moderate)</th>
<th>Grade 3 (severe)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conscious level</td>
<td>irritable/hyperalert</td>
<td>lethargic</td>
<td>comatose</td>
</tr>
<tr>
<td>Tone</td>
<td>either mildly abnormal</td>
<td>moderately abnormal</td>
<td>severely abnormal</td>
</tr>
<tr>
<td></td>
<td>(hypo/hyper)</td>
<td>(hypotonic or dissociated)</td>
<td>(hypotonia)</td>
</tr>
<tr>
<td>Suck</td>
<td>normally abnormal</td>
<td>poor</td>
<td>absent</td>
</tr>
<tr>
<td>Primitive reflexes</td>
<td>exaggerated</td>
<td>depressed</td>
<td>absent</td>
</tr>
<tr>
<td>Seizures</td>
<td>absent</td>
<td>present</td>
<td>present</td>
</tr>
<tr>
<td>Brain stem reflexes</td>
<td>normal</td>
<td>normal</td>
<td>impaired</td>
</tr>
<tr>
<td>Respiration</td>
<td>tachypneic</td>
<td>occasional apneas</td>
<td>severe apnea</td>
</tr>
</tbody>
</table>

Adapted from Fenichel(10).
The features in **bold** are the main requirements for each grade.
Features not in bold may be present but are essential for syndrome assignment.
a/b: either abnormal tone or abnormal suck should accompany altered conscious level to assign grade 1.

**Table 4:** Fenichel Grading for Hypoxic ischemic encephalopathy. The features in the bold are the main requirements for each grade. Features not in bold may be present but are essential for syndrome assignment. a/b: either abnormal tone or abnormal suck should accompany altered conscious level to assign grade 1.

For usage in clinical studies and for well equipped centres, Samat and Sarnat staging is mostly used but Fenichel grading may be of use in resource constrained settings since it is based only on clinical criteria alone.

Multiorgan involvement is a hallmark of hypoxic-ischemic encephalopathy. Organ systems involved following a hypoxic-ischemic events include the heart, lungs, kidney, liver & blood.

Multiorgan involvement is a hallmark of hypoxic-ischemic encephalopathy. Systems involved following a hypoxic-ischemic events include the following:

Heart (43-78%): May present as reduced myocardial contractility, severe hypotension, passive cardiac dilatation, and tricuspid regurgitation.

Lungs (71-86%) may have severe pulmonary hypertension requiring assisted ventilation.

Renal (46-72%) failure presents as, during recovery, as high-output tubular failure, leading to significant water and electrolyte imbalances.

Liver (80-85%): Elevated liver function test results, hyperammonemia and coagulopathy can be seen. This may suggest possible Gl dysfunction. Poor
peristalsis and delayed gastric emptying are common.; Intestinal injuries may not be apparent in the first few days of life or until feeds are initiated.

Hematologic: (32-54%) include increased nucleated RBCs, neutropenia or neutrophilia, thrombocytopenia, and coagulopathy. Severely depressed respiratory and cardiac functions and signs of brainstem compression suggest a life-threatening rupture of the vein of Galen (ie, great cerebral vein) with a hematoma in the posterior cranial fossa.

**Differential diagnosis of neonatal encephalopathy:**

These include:

- (i) perinatal hypoxia-ischemia; (ii) ; (iii) ; (iv) hyperbilirubinemia; (v) trauma; (vi) hemorrhage; (vii) cerebral infarction; (viii) metabolic disorders; (ix) neuromuscular disease; and (x) dysmorphic syndromes.

**PATHOLOGY OF HIE:**

There is no single distinct or uniform pathological appearance of the brain following hypoxia – ischemia. Cell death will occur when the metabolic demand fails to be met by the substrate delivery via the blood. The pattern of injury depends upon the severity of asphyxia insult, its timing and duration.

**Observed patterns of injury following hypoxia ischemia**

*Cerebral edema:* may occur within 24 hours of the injury. It arises through two mechanisms: cytotoxic, when membrane pump failure leads to intracellular fluid accumulation, and vasogenic, when the impaired blood brain barrier permits capillary leak and interstitial fluid accumulation.

Selective neuronal necrosis: is the most commonly observed pathology following hypoxia-ischemia in term infants, affecting neurons in a scattered fashion and often widely distributed throughout the grey matter. The cerebral cortex layers III and IV and the hippocampus appear particularly vulnerable.

Basal ganglia and brainstem: in animal models this type of injury is seen following total asphyxia rather than chronic partial asphyxia and is responsible for the dyskinetic type of cerebral palsy seen in survivors of hypoxia-ischemia, and abnormal signal intensity on the MRI is a common finding. If the child survives the initial period, then an abnormal myelination occurs which is detectable on MRI. This is responsible for the marble-like appearance of the basal ganglia seen at post mortem known as status marmoratus.

*Parasagittal injury:* this is an ischemic injury affecting the cerebral cortex and subcortical white matter in the vascular watersheds between the anterior, middle
and posterior cerebral arteries, giving rise to a parasagittal distribution and is often symmetrical. This type of injury is characteristic of the full term infant with perinatal asphyxia. This results in shoulder girdle hypotonia and neck hypotonia pattern seen in some term babies. These lesions are better picked up on the MRI; CT scans till commonly used in evaluation of such infants, is not so sensitive for detection of this lesion because the axial images often fail to detect the superficial cortical subcortical lesions of parasagittal injury.

*Periventricular leukomalacia or the white matter injury.* This refers to necrosis of white matter in a characteristic distribution, i.e., in the white matter dorsal antrolateral to the external angles of the lateral ventricles, and less severe injury to the white matter peripheral to these focal necrosis.

End result of periventricular leukomalacia, of course depends on the size of the initial lesion and the time after the acute insult. With focal periventricular lesions, some degree of tissue dissolution is often apparent macroscopically after 1-3 weeks. These lesions may initially be visible on USG scan as cavities in the brain but eventually constrict and coalesce and no longer visible on USG. Ischemia insults in preterm infants produce periventricular leukomalacia. When it occurs in term babies, it usually results in subcortical leukomalacia. This survivors of this type of injury show multicystic leukoencephalopathy (Figure 1).

![Figure 1: Pathophysiology of periventricular leukomalacia](image)
Focal and multifocal cerebral infarction: Infarction of a major cerebral artery, most commonly the left middle cerebral artery, has in the past been reported in association with asphyxia, but it is now realized that this lesion occurs most commonly in babies with no evidence of intrapartum asphyxia (67%).

The major manifestation of asphyxia results from a combination of hypoxia and ischemia of the brain and other vital organs. The cerebral hemodynamics in term infants with acute encephalopathy are deranged in the first few days after perinatal asphyxia. These occur with a combination of vasodilatation and vasoparalysis. Acute hypoxic ischemic insult results in an increase in cerebral blood volume, a reduction in its response of cerebral blood volume (CBVR) to changes in arterial carbon dioxide PaCO₂ tension, and an increase in cerebral blood flow. Possible mechanisms for the coupled response of vasodilation and abolished CBVR include a disturbance in prostanoid metabolism following brain injury and an increased production of nitric oxide. It is also noted that cerebral edema may actually peak after 36 to 48 hours of the asphyxia event, that the hypoxic-ischemic brain damage may be an evolving process, which begins during the insult and extends into the recovery period after resuscitation (reperfusion interval).

At the cellular level, cerebral hypoxia-ischemia initiates a cascade of biochemical events starting with a shift from oxidative to anaerobic metabolism (glycolysis)(12) (Figure 2). Metabolism results in accumulation of nicotinamide-adenine-dinucleotide (NADH), flavin-adenine-dinucleotide (FADH), and lactic acid with H⁻ ions. Anaerobic glycolysis cannot keep pace with the cellular energy demands, resulting in a depletion of high-energy phosphate reserves, including ATP. Transcellular ion pumping fails, leading to an accumulation of intracellular Na⁺, Ca²⁺, Cl⁻, and water (cytotoxic edema). Hypoxia-ischemia also stimulates release of excitatory amino acids (glutamate) from axon terminals. The glutamate release, in turn, activates glutamate cell-surface receptors, resulting in an influx of Na⁺ and Ca²⁺ ions. Within the cytosol, free fatty acids accumulate from increased membrane phospholipid turnover and, thereafter, undergo peroxidation by oxygen-free radicals that arise from the reductive process within mitochondria and as byproducts in the synthesis of prostaglandins, xanthine, and uric acid. Ca²⁺ accumulate within the cytosol as a consequence of increased plasma (cellular) membrane influx via voltage-sensitive and agonist-operated calcium channels and of decreased efflux across the plasma membrane combined with release from mitochondria and the endoplasmic reticulum. Nitric oxide, a free-radical gas, is generated via Ca²⁺ in selected neurons and diffuses to adjacent cells that are susceptible to nitric oxide toxicity. The combined effects of cellular energy failure, acidosis, glutamate, and

The combined effects of cellular energy failure, acidosis, glutamate and nitric oxide neurotoxicity, free-radical formation, Ca²⁺ accumulation, and lipid peroxidation serve to disrupt structural components of the cell with its ultimate death.
nitric oxide neurotoxicity, free-radical formation, Ca\textsuperscript{2+} accumulation, and lipid peroxidation serve to disrupt structural components of the cell with its ultimate death (Figure 3).

![Flowchart](image)

**Figure 2:** Cellular mechanisms leading to brain injury following asphyxia

![Flowchart](image)

**Figure 3:** Pathogenic mechanism of immediate and delayed brain cell death
LABORATORY STUDIES:

These are nonspecific tests to confirm or exclude a diagnosis of hypoxic-ischemic encephalopathy (HIE) because the diagnosis is made based on the history, physical and neurological examinations, and laboratory evidence. Many of the tests are performed to assess the severity of brain injury and to monitor the functional status of systemic organs. As always, the results of the tests should be interpreted in conjunction with the clinical history and the findings from physical examination.

Many of the tests are performed to assess the severity of brain injury and to monitor the functional status of systemic organs. As always, the results of the tests should be interpreted in conjunction with the clinical history and the findings from physical examination.

Laboratory studies should include the following:

**Serum electrolyte levels and Renal function Test:** In severe cases, daily assessment of serum electrolytes is valuable until the infant’s status improves. Markedly low serum sodium, potassium, and chloride levels in the presence of reduced urine flow and excessive weight gain may indicate acute tubular damage or syndrome of inappropriate antidiuretic hormone (SIADH) secretion, particularly during the initial 2-3 days of life. Serum creatinine levels, creatinine clearance, and BUN levels suffice in most cases.

**Cardiac and liver enzymes:** These values are an adjunct to assess the degree of hypoxic-ischemic injury to these other organs. These findings may also provide some insight into injuries to other organs, such as the bowel.

**Blood gas Monitoring:** Blood gas monitoring is used to assess acid-base status and to avoid hyperoxia and hypoxia as well as hypercapnia and hypocapnia.

**Neuroimaging:**

Neuroimaging has become increasingly important in the evaluation of neonatal encephalopathy, and may provide information regarding the type and timing of brain injury. Various modalities have been used to evaluate infant brains with neonatal encephalopathy, including cranial sonography (CS), computed tomography (CT) and magnetic resonance imaging (MRI) with MR spectroscopy. Head MR imaging techniques yield the most useful information, though the resources necessary for transporting, monitoring, and supporting sick babies during this procedure are not always readily available.
Cranial sonography:

Head sonography has a low sensitivity (50%) for the detection of anomalies associated with hypoxic-ischemic encephalopathy. Findings include global increase in cerebral echogenicity and obliteration of cerebrospinal fluid (CSF) containing spaces suggestive of cerebral edema. Increase in the echogenicity of deep gray matter structures may also be identified, typically when ultrasonography is performed after 7 days of life. Cranial sonography has a high sensitivity and specificity for locating hemorrhages and defining ventricular size.

Head CT:

CT scan of the head can be useful to confirm cerebral edema (obliteration of cerebral ventricles, blurring of sulci), manifested as narrowness of the lateral ventricles and flattening of gyri. Areas of reduced density that indicate evolving zones of infarction may be present. Evidence of hemorrhage in the ventricles or in the cerebral parenchyma may also be seen.

Head MRI, MR spectroscopy and diffusion-weighted imaging (DWI) techniques:

MRI is the imaging modality of choice for the diagnosis and follow-up of infants with moderate-to-severe hypoxic-ischemic encephalopathy (HIE). Early MRI (and particularly after day 4), conventional images may accurately demonstrate the injury pattern as area of hyperintensity. DWI allows earlier identification of injury patterns in the first 24-48 hours. The MRI sequence identifies areas of edema and, hence, injured areas. DWI changes peak at 3-5 day and pseudonormalizes by the end of the first week. MRS allows for quantification of intracellular molecules. Proton MRS allows identification of cerebral lactate, which persist for weeks following a significant hypoxic-ischemic injury.

Electroencephalography:

Amplitude-integrated electroencephalography (aEEG):

A single-channel aEEG performed within a few hours of birth can help evaluate the severity of brain injury in the infant with hypoxic-ischemic encephalopathy. The abnormalities seen in infants with moderate-to-severe hypoxic-ischemic encephalopathy include the following:
a) Discontinuous tracing characterized by a lower margin below 5 mV and an upper margin above 10 mV.

b) Burst suppression pattern characterized by a background with minimum amplitude (0-2 mV) without variability and occasional high voltage bursts (>25 mV).

c) Continuous low voltage pattern characterized by a continuous low voltage background (< 5 mV).

d) Inactive pattern with no detectable cortical activity.

e) Seizures, usually seen as an abrupt rise in both the lower and upper margin.

Note that considerable training is required for conducting and properly interpreting the aEEG findings. aEEG can accurately predict poor outcome with a sensitivity of 91% (95% CI, 87-95).

**Standard EEG** Traditional, multichannel EEG is an integral part of the evaluation of infants diagnosed with hypoxic-ischemic encephalopathy. It is a valuable tool to assess the severity of the injury and evaluate for subclinical seizures.

Generalized depression of the background rhythm and voltage, with varying degrees of superimposed seizures, are early findings. EEG characteristics associated with abnormal outcomes include

1. background amplitude of less than 30 mV
2. interburst interval of more than 30 seconds
3. electrographic seizures
4. absence of sleep-wake cycle at 48 hours.

Serial EEGs should be obtained to assess seizure control and evolution of background abnormalities. Improvement in the EEG findings over the first week, in conjunction with improvement in the clinical condition, may help predict a better long-term outcome.

**MANAGEMENT OF THE BABY:**

The management of the post asphyxiated infant begins before the actual time of delivery of asphyxiated infant, involves the management at the time of birth and extends into the neonatal period. Failure to initiate appropriate therapy at any stage may exacerbate ongoing injury.

**Before delivery management:**

*Identification of risk factors:* Birth asphyxia may result from multiple factors and conditions in the mother or the fetus some of which may be unavoidable and others difficult to detect or treat. Identification of conditions associated with higher
likelihood of having birth asphyxia would atleast make the resuscitation team aware to the possibility and take appropriate steps. The conditions are listed in the Table 5.

<table>
<thead>
<tr>
<th>Pre-pregnancy factors</th>
<th>Antenatal factors</th>
<th>Fetal factors</th>
<th>Intrapartum factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Socioeconomic status</td>
<td>Bleeding</td>
<td>Multiple pregnancy</td>
<td>Infection</td>
</tr>
<tr>
<td>Family history of seizures</td>
<td>Hypertensive disorders</td>
<td>Chromosomal anomaly</td>
<td>Placental bleeding</td>
</tr>
<tr>
<td>Family history of neurological disease</td>
<td>Abnormal placentaion</td>
<td>Congenital abnormality</td>
<td>Feto-maternal hemorrhage</td>
</tr>
<tr>
<td>Fertility treatment</td>
<td>Viral illness</td>
<td>Fetal growth restriction</td>
<td>Bleeding from vasa praevia</td>
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<tr>
<td>Maternal thyroid disease</td>
<td>Bacterial infection</td>
<td>Prematurity</td>
<td>Uterine rupture</td>
</tr>
<tr>
<td>Maternal obesity</td>
<td>Coagulation disorders</td>
<td>Coagulation disorders</td>
<td>Cord accident</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Postmaturity</td>
<td>Maternal collapse</td>
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<td></td>
<td></td>
<td>Breech presentation</td>
<td>Prolonged labour</td>
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<tr>
<td></td>
<td></td>
<td>Male Sex</td>
<td>Oxytocin abuse</td>
</tr>
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</table>

Table 5: Risk factor for delivering an asphyxiated baby

Minimising intrauterine infection/inflammation: Cytokines are the final common mediators of brain injury that is initiated by hypoxia/ischemia, reperfusion, and infection. Presence of maternal fever and clinical chorioamnionitis has been associated with poor neurological outcome. Adequate precautions to reduce an abnormally elevated maternal temperature and to treat suspected infection are required to reduce the vulnerability of both the preterm and term brain from hypoxic injury.

Intrapartum fetal monitoring: the data regarding the use of fetal monitoring by CTG in prevention of HIE has been conflicting. The NICE guidelines on this issue suggest that use of electronic fetal monitoring is not associated with improved outcome and results in increased operative deliveries, although it decreases the number of babies admitted in NICU because of neonatal depression. Although the sensitivity of these electronic fetal monitoring abnormalities for the identification of intrapartum asphyxia is 93% the positive predictive value is only 3%–18%.

Liberal use of caesarean section: Except in cases of term babies with breech presentation (the term breech trial) and meconium babies with fetal heart abnormalities, liberal use of C section has not been shown to improve neurological
Delivery room management:

There have been recent changes to the resuscitation program. Oxygen during resuscitation: Given the importance of oxygen free radicals in the pathogenesis of HIE, there is always a debate whether resuscitation should be initiated with 100% oxygen or a lower concentration of oxygen. The changes which have been suggested to the resuscitation guidelines as regards the oxygen management are concerned include—

Pulse oximeter is recommended that oximetry be used when resuscitation can be anticipated, when positive pressure is administered for more than a few breaths, when cyanosis is persistent, or when supplementary oxygen is administered. The probe should be attached to a predual site (ie, the right upper extremity, usually the wrist or medial surface of the palm). Need for supplemental oxygen should be determined by the percentile charts of oxygen saturation included in the new guidelines.

It is recommended that the goal in babies being resuscitated at birth, whether born at term or preterm, should be an oxygen saturation value in the interquartile range of predual saturations (Figure X) measured in healthy term babies following vaginal birth at sea level. These targets may be achieved by initiating resuscitation with air or a blended oxygen and titrating the oxygen concentration to achieve Sp O2 in the target range as described above using pulse oximetry. If blended oxygen is not available, resuscitation should be initiated with air. If the baby is bradycardic (HR <60 per minute) after 90 seconds of resuscitation with a lower concentration of oxygen, oxygen concentration should be increased to 100% until recovery of a normal heart rate.

<table>
<thead>
<tr>
<th>Targeted predual SpO2 after birth</th>
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<tbody>
<tr>
<td>1 min</td>
<td>60-65%</td>
</tr>
<tr>
<td>2 min</td>
<td>65-70%</td>
</tr>
<tr>
<td>3 min</td>
<td>70-75%</td>
</tr>
<tr>
<td>4 min</td>
<td>75-80%</td>
</tr>
<tr>
<td>5 min</td>
<td>80-85%</td>
</tr>
<tr>
<td>10 min</td>
<td>85-95%</td>
</tr>
</tbody>
</table>

**Table 6:** Predual SpO2 after birth in relation to time after delivery.
Management of baby born by meconium stained liquor:

The changes regarding the baby delivered through meconium stained liquor include suctioning of the oropharynx before delivery of the shoulders was considered routine but is no longer considered important as it has not shown to be of any benefit in a larger RCT.

In the absence of randomized, controlled trials, there is insufficient evidence to recommend a change in the current practice of performing endotracheal suctioning of nonvigorouss babies with meconium stained amniotic fluid. However, if attempted intubation is prolonged and unsuccessful, bag-mask ventilation should be considered, particularly if there is persistent bradycardia.

End expiratory pressure: Many experts recommend administration of continuous positive airway pressure (CPAP) to infants who are breathing spontaneously, but with difficulty, following birth, although its use has been studied only in infants born preterm. Nevertheless, PEEP is likely to be beneficial and should be used if suitable equipment is available. PEEP can easily be given with a flow-inflating bag or T-piece resuscitator, but it cannot be given with a self inflating bag unless an optional PEEP valve is used.

Chest compressions: There is evidence from animals and non-neonatal studies that a compression ratio of 15:2 or even 30:2 may be more effective when the arrest is of primary cardiac etiology. It is recommended that a 3:1 compression to ventilation ratio be used for neonatal resuscitation where compromise of ventilation is nearly always the primary cause, but rescuers should consider using higher ratios (eg, 15:2) if the arrest is believed to be of cardiac origin.

Temperature in the delivery room in the management of the asphyxiated infant:

Hyperthermia during resuscitation and reperfusion caused increased neuronal injury and release of oxygen free radicals and excitatory amino acids, such as glutamate, in the animal model. In the clinical setting, case control studies suggested that maternal fever is associated with an increased risk for newborn encephalopathy, as well as an increased risk for cerebral palsy. There is no documented benefit to keeping core temperature above normal at birth for asphyxiated infants. Perinatal hyperthermia should be avoided in the delivery room and during transport to a perinatal center by switching off the warmer during resuscitation and avoiding overwrapping a the child during transport.

Additional warming techniques are recommended (eg, prewarming the delivery room to 26°C, covering the baby in plastic wrapping (food or medical grade, heat-
resistant plastic), placing the baby on an exothermic mattress, and placing the baby under radiant heat may be required for babies less than 1500g as these babies are likely to suffer from uncontrolled hypothermia. The goal is to achieve normothermia and avoid iatrogenic hyperthermia.

Management in the neonatal unit:

Fluid balance: The kidney is one of the most frequently damaged organs in the asphyxiated, full term infant. The asphyxiated newborn is prone to develop prerenal or acute renal failure. Urine output should be measured with a urine collection bag or with an indwelling catheter. A decrease in urine output with oliguria (< 1ml/kg/h) or anuria indicates incipient acute renal failure. However, 60% percent of infants with acute renal failure following severe asphyxia have normal urine output.

The asphyxiated newborn is prone to develop prerenal or acute renal failure. A decrease in urine output with oliguria (< 1ml/kg/h) or anuria indicates incipient acute renal failure.

Type and amount of fluids to start with: Fluids used for initial period should be 10% dextrose as giving sodium as long as one is sure of the urine output can be detrimental. 5% dextrose should never be used as this is a hypotonic fluid and can result in worsening of cerebral edema. Fluid restriction is mostly been recommended in standard textbooks for the fear of congestive cardiac failure and SIADH, there are no randomised controlled trials to guide this practice. Fluid restriction may lead to decreased cerebral perfusion and hence worsening of the outcome and hence should not be practiced to 2/3rd level as is commonly recommended as long as one is not dealing with SIADH or CCF in asphyxiated neonates.

Fluids used for initial period should be 10% dextrose as giving sodium if one is unsure of the urine output can be detrimental.

Recognition of SIADH: electrolytes should be assessed in every asphyxiated baby within 12 hours of starting treatment. SIADH should be suspected if serum sodium is less than 130 mEq/L, and urine osmolality is more than serum osmolality. The diagnosis of SIADH cannot be made if the patient is on diuretics or has documented renal failure. In cases of confirmed SIADH, fluid should be restricted to 80% of the normal and in cases of sodium levels less than 120mEq/L, use of 3% saline can be considered.

SIADH should be suspected if serum sodium is less than 130 mEq/L, and urine osmolality is more than serum osmolality. In SIADH, fluid should be restricted to 80% of the normal.

Checking for other electrolytes: Serum potassium should be monitored carefully as asphyxia results in tissue damage and presence of renal failure in many asphyxiated neonates may result in dangerous hyperkalemia. Hypocalcemia and hypomagnesemia may also be seen in babies
with asphyxia.

**Blood glucose:** An adequate supply of glucose is critical for the neonatal brain and the heart during the recovery from an asphyxial insult. However, it is also recognized that excessively high levels of glucose may have an adverse effect on the brain by inducing local lactic acidosis, in that the damaged areas of the brain may be unable to completely metabolize glucose. Generally it is recommended that adequate glucose infusion be initiated promptly in the asphyxiated infant to avoid hypoglycemia, while preventing hyperglycemia due to an excessive exogenous glucose load.

**Treatment of Metabolic acidosis:** The use of sodium bicarbonate remains controversial even in severe birth asphyxia. The primary potential benefits of sodium bicarbonate therapy in the presence of severe metabolic acidosis would include improved myocardial performance with secondary improvement in perfusion of vital organs, and theoretically a reduction in tissue ischemia with the possibly of improved long-term outcome. Hazards of bicarbonate infusion include a sudden increase in serum osmolarity with risk of hemorrhage (particularly in the brain), sudden increase in venous pressure with reduction in CSF pressure, reduction in cerebral blood flow, and a transient increase in PCO$_2$ (dependent upon the ventilatory status of the infant). It is apparent that with effective cardiopulmonary resuscitation, the metabolic and respiratory acidosis which accompany birth asphyxia will generally resolve over 20-40 minutes. However, the washout phenomena secondary to improved perfusion and transiently increased lactic acid levels may lead to worsening in the acidosis temporarily. This should correct spontaneously if oxygenation and ventilation are adequate and cardiac and circulatory support are maintained. Although bicarbonate has not been proven to be of benefit in neonatal resuscitation, most clinicians will employ sodium bicarbonate as a slow infusion over at least 5 - 10 minutes in the presence of documented severe metabolic acidosis.

**MANAGEMENT OF OTHER ORGAN INVOLVEMENTS:**

**Brain:**

**Control of seizures:** The clinical course and manifestations of postasphyxial seizures are probably dependent of the severity and nature of the insult. Between 50-90% of postasphyxial seizures begin within 12 hours of birth; however, the factors determining their postnatal onset remain poorly understood in
most cases. Although any type of seizures (tonic, clonic, myoclonic and subtle seizures can occur in the asphyxiated newborn, a combination of seizure types is more common in the individual cases. Seizures may be clinically silent, especially in severely encephalopathic infants and after the administration of anticonvulsant drugs. In these cases, the only clinical evidence of seizures may be abrupt autonomic changes, such as hypertension, tachycardia and papillary dilation. Therapy begins with careful serial observations to detect clinical seizure activity which may exacerbate the ongoing brain injury. Seizures may occur due to dyselectrolyemia, hypoglycemia (which needs to be checked) or the asphyxia insult. Seizure due to asphyxia generally occur between 6-24 hours of the insult.

Phenobarbitone is the most common drug used for control of seizures in asphyxiated neonates. It is given in loading dose of 20mg/kg IV. A maintainence dose of 3-5 mg/kg should be started 12-24 hours after loading dose. If the seizures are not controlled after 20mg/kg of phenobarbitone, then some people give another 10mg/kg as a mini bolus but because of impaired hepatic and renal clearance we switch to phenytoin 20 mg/kg. In many centers, fosphenytoin is used in place of parent drug (phenytoin) because the risk of hypotension is less and extravasation has no adverse effects.

If seizures are not controlled after maximal doses of conventional anticonvulsants, there is little utility in eliminating every twitch or electrographic seizure unless there is cardiopulmonary compromise from the seizures. Because of the risk of apoptosis by phenobarbitone, some neonatologist prefer to use midazolam for the first seizure and use phenobarbitone if the seizures are recurrent. There is no recommendation to guide this practice as of now. Once seizures are controlled, phenytoin should be discontinued before discharge and if the neurological examination in normal, some even stop phenobarbitone before discharge especially if there was only one seizure.

Prophylactic anticonvulsants: The potential benefits of preventing further neuronal injury associated with seizures following asphyxia has prompted the widespread use of anticonvulsants, and barbiturates in particular, for the prevention of seizures. In addition to their anticonvulsant activity, barbiturates are known to decrease CNS metabolic rate when given in high doses, reduce calcium entry post-ischaemia and
scavenge free radicals. A meta-analysis combining five studies comparing barbiturates with conventional therapy following perinatal asphyxia demonstrated no difference in risks of death, severe neurodevelopmental disability, or the combined outcome of death or severe neurodevelopmental disability. At the present time, anticonvulsant therapy to term infants in the immediate period following perinatal asphyxia cannot be recommended for routine clinical practice, other than in the treatment of prolonged or frequent clinical seizures.

Control of brain swelling: The frequency of raised ICP is relatively low; in one study of 32 asphyxiated neonates, ICP > 10 mm Hg occurred only in 22%. There is no role of osmotic diuretics like mannitol or glucocorticoids in the management of cerebral edema documented on USG in babies with asphyxia.

Heart: In asphyxia, there is a myocardial dysfunction and hence it is necessary to measure the blood pressure invasively so to maintain a proper cerebral perfusion pressure. It is important to maintain systemic blood pressure in the normal range because cerebral autoregulation is often absent in term infants after a major hypoxic-ischemic insult. Hypotension should be treated with fluid resuscitation or inotropes as clinically indicated. Hypotension that is unresponsive to inotropic agents may respond to steroid therapy.

Kidney: After hypoxia or ischemia, renal adenosine acts as a vasoconstrictive metabolite that contributes to a decrease in the glomerular filtration rate. The vasoconstriction that is caused by adenosine can be inhibited by the nonspecific adenosine receptor antagonist, theophylline. In a recent, randomized, controlled trial of 51 asphyxiated, term infants, a single dose of 8 mg/kg theophylline administered prophylactically in the first hour was associated with a decrease in serum creatinine and improvement in creatinine clearance. Further studies are needed to evaluate this promising intervention.

Lung: babies who suffer asphyxia may have pulmonary hypertension, asphyxial lung injury resulting in secondary surfactant deficiency. A recent meta-analysis
showed that surfactant administration decreased the number of infants treated with extracorporeal membrane oxygenation in those with meconium aspiration syndrome that led to moderate to severe respiratory failure⁻. A recent meta-analysis noted that inhaled nitric oxide improved the outcome in term and near term infants with hypoxia, by reducing the incidence of death or need for extra corporeal membrane oxygenation(19). avoid further worsening of pulmonary hypertension, one should keep the SpO2 close to 95% in term babies with intermittent monitoring of ABG’s to avoid hyperoxia. Besides, asphyxia babies may have depressed breathing and often require supportive ventilation. Whether permissive hypercapnia is of any benefit or not in asphyxiated newborns is not clear but hypocapnia with pCO2 < 30 mm Hg is definitely associated with reduced cerebral blood flow and increased risk of periventricular leucomalacia.

**Neuroprotection:**

Many therapies have been tried and suggested for reducing the extent of brain injury following HIE. We are going to review their current status in the management of asphyxiated newborn.

**NMDA receptor antagonists:** Because of possible cardiovascular and neurobehavioral side effects and potential for teratogenic effects, NMDA receptor antagonists are not recommended in the clinical setting in neonates with asphyxial injury.

**Calcium channel blockers:** a human study of the use of the calcium channel blocker nicardapine in four severely asphyxiated, newborn infants.³⁰ Continuous infusion of nicardapine was administered at 5 to 10 mg/kg/h with incremental increases to a total of 40 mg/kg/h for total duration of 12 hours. There was marked hypotension in three infants concurrent with a decrease in cerebral blood flow velocity. Calcium channel blockers may cause systemic hypotension and cerebral hypoperfusion because cerebral autoregulation is impaired in these infants.
Magnesium: may be protective because of activity at different levels of the cascade of events following experimental injury. In term infants, a phase I study was initiated to evaluate two doses of magnesium sulphate (250 mg/kg and 400 mg/kg) in 15 full term infants with severe, acute asphyxial injury. The lower dose was not associated with hypotension, but was associated with respiratory depression. The higher dose was followed by an unacceptable risk for hypotension\textsuperscript{11}. As such there is no current role of magnesium in the management of asphyxiated newborn.

Hypothermia: Modest reductions of brain temperature, on the order of 2 to 4\textdegree{}C, seem to be the most promising of the specific, neuroprotective therapies that have emerged over the past 10 to 15 years. The pilot studies found no evidence of harm from prolonged moderate hypothermia particularly when body temperature was closely controlled; when temperature control was less accurate cardiovascular complications such as hypotension or severe bradycardia occurred. This is a single important intervention which has been shown to improve the overall intact survival in asphyxiated newborns and hence would be discussed in detail here. At present the cost of equipment is prohibitive but efforts are on way to devise cheaper methods to cool the brain after delivery.

Mechanisms of benefit: For every 1\textdegree{}C lowering of the core temperature cerebral metabolism is reduced by approximately 7\%, with consequently a lower glucose and oxygen demand. A reduction of 3–4 \textdegree{}C core temperature is associated with a reduction in free radicals and glutamate levels, protecting mitochondrial function and maintaining cerebral high energy phosphate levels. Apoptosis is considered to be a major cause of progressive neuronal injury following neonatal hypoxia ischaemia; moderate hypothermia is associated with morphologic evidence of decreased apoptosis. The efficacy of modest hypothermia as a neuroprotective regimen in adult animals is influenced by the time of initiation and duration and depth of hypothermia can be demonstrated across the developmental span from fetus to adult and can be achieved when cooling is initiated at an interval up to 5.5 hours after an hypoxic-ischemic event.

The neuroprotective mechanisms are not completely understood. Possible mechanisms include:

Reduced metabolic rate and energy depletion.
Decreased excitatory transmitter release.
Reduced alterations in ion flux.
Reduced apoptosis due to hypoxic-ischemic encephalopathy.
Reduced vascular permeability, edema, and disruptions of blood-brain barrier functions.

Evidence supporting benefit: No of large multicentric trials have been done in the world in the developed world using either head cooling or body cooling as intervention in asphyxiated infants. Metaanalysis of three trials comprising 767 infants followed to 18 months shows highly significant improvements in neurological outcomes. Therapeutic hypothermia reduces the combined rate of death and disability (the primary outcome of all the studies) with a number needed to treat of just 9 (95% confidence interval 5–25) and increases the rate of intact survival. Amongst survivors, therapeutic hypothermia reduces the rates of severe disability, cerebral palsy, and both mental and psychomotor developmental index < 70 (2 SD below mean).

Survival following hypoxic ischaemic encephalopathy is increased in infants allocated hypothermia compared with the control infants in 10 trials comprising 1320 infants, with a number needed to treat of 14, (95% confidence interval 8 to 47) but there is some heterogeneity of the included subjects. Overall the evidence is quite robust as far as incorporating hypothermia in the routine management of asphyxiated newborns is concerned. None of the large randomized trials reported clinically significant complications attributed to hypothermia. Despite this evidence some uncertainties remain regarding hypothermia: effect on neurodevelopmental outcome at age beyond 18 months is not clear and secondly, very little data is available from the developing world where the incidence of asphyxia is quite high. Of concern is the small pilot study from Uganda where there was an increased mortality in the treatment group, but this may have been due chance allocation in a small study of more infants with severe encephalopathy to the treatment group. Criteria from the larger trials (NICHD, CoolCap, and TOBY) are summarized as follows:

1. Near-term infants born at 36 weeks' gestation or more with birth weight of 1800-2000 g or more, younger than 6 hours at admission.
2. Evidence of acute event around the time of birth
   Apgar score of 5 or less at 10 minutes after birth
   Severe acidosis, defined as pH level of less than 7 or base deficit of 16 mmol/L or less (cord blood or any blood gas obtained within 1 h of birth)
   Continued need for resuscitation at 10 minutes after birth
Evidence of moderate to severe encephalopathy at birth: At least 2 of the following:

a) Lethargy, stupor, or coma
b) Abnormal tone or posture
c) Abnormal reflexes [suck, grasp, Moro, gag, stretch reflexes
d) Decreased or absent spontaneous activity
e) Autonomic dysfunction [including bradycardia, abnormal pupils, apneas]
f) Clinical evidence of seizures.

4. Moderately or severely abnormal amplitude-integrated electroencephalography (aEEG) background or seizures (CoolCap and TOBY)

Many theoretical concerns surround hypothermia and its side effects, which include coagulation defects, leukocyte malfunctions, and pulmonary hypertension, worsening of metabolic acidosis, and abnormalities of cardiac rhythm, especially during rewarming. Although all these traits suggest, cooling is well tolerated and not associated with any increase in death or serious adverse events.

Procedure of Hypothermia:

**Indication:** As above in the criteria mentioned

**Initiation Time:** Cooling must begin early, within 6 hours of injury. However, experimental evidence strongly suggest that the earlier the better.

**Duration of hypothermia therapy:** The optimal duration of brain cooling in the human newborn has not been established. In most the clinical trials, it is for 72 hours.

**Methods:**

Two methods have been used in clinical trials:

- Selective head cooling.
- Whole body cooling.

In selective head cooling, a cap (CoolCap) with channels for circulating cold water is placed over the infant's head, and a pumping device facilitates continuous circulation of cold water. Nasopharyngeal or rectal temperature is then maintained at 34-35°C for 72 hours.

In whole body hypothermia, a cooling blanket wrapped around the baby is necessary for keep the core temperature in the desired range.

The relative merits and limitations of these 2 methods have not been established.

In resource constrained setting like ours, few feasibility trials of achieving hypothermia with ice packs have been tried but those have to undergo rigorous safety studies to test their efficacy and safety.
Rewarming method: Rewarming is a critical period. In clinical trials, rewarming was carried out gradually, over 6-8 hours.

Conclusion: Therapy should be conducted under strict protocols and reserved to regional referral centres offering comprehensive multidisciplinary care and planning to conduct long-term neurodevelopmental follow-up. Therapeutic hypothermia compared with usual care was associated with a significant reduction in the combined primary end-point of death or moderate to severe neurodevelopmental disability. is the only effective neuroprotective therapy currently available for treatment of HIE and is safe and easy to administer.

EXPERIMENTAL THERAPIES:

Despite the promise hypothermia seems to show, the composite adverse outcome reduces from 58% to 47% with cooling. Thus approximately half the infants who receive therapeutic hypothermia still have an abnormal outcome. Research is now being focused on other drugs which are still in the pre-clinical stage, which act synergistically or additively with hypothermia to improve intact survival.

Approximately half the infants who receive therapeutic hypothermia still have an abnormal outcome. Research is now being focused on other drugs which are still in the pre-clinical stage, which act synergistically or additively with hypothermia to improve intact survival.

Xenon: Xenon is a non-competitive antagonist of the N-methyl-D-aspartate (NMDA) subtype of the glutamate receptor which is one of the pathways by which the apoptosis of the brain cells occurs. Xenon is neuroprotective following hypoxia–ischaemia in neonatal rats and is effective even when administration is delayed for some hours. Data from experimental animals demonstrate a synergy when xenon is administered in combination with mild therapeutic hypothermia. A clinical trial (TCBYXe; NCT00934700) is being planned in Europe where the efficacy of the combination of hypothermia and xenon will be tested against cerebral magnetic resonance biomarkers and clinical outcomes. A disadvantage of xenon is its cost and the need for a closed circuit ventilator for delivery and re-use.

Allopurinol: Free radical play a major role in damage after HIE and the primary source of these free radicals is xanthine oxidase enzyme released during ischemia by a calcium-triggered proteolytic attack on xanthine dehydrogenase. Allopurinol is a xanthine-oxidase inhibitor; in high concentrations allopurinol also scavenges hydroxyl radicals. Metaanalysis of three small trials has not suggested any benefit of postnatal administration of allopurinol but it suggested that larger trials are needed which should assess allopurinol as an adjunct to therapeutic hypothermia. Allopurinol can be transferred across placenta and taking advantage of that fact, a
ALLO –trial has been planned in Holland where pregnant women at term in whom the fetus is suspected of intrauterine hypoxia would either receive 500 mg of allopurinol IV or placebo.

N-acetyl cysteine: is an attractive neuro-protective substance as it has low toxicity, is able to cross the placenta and blood brain barrier. Its profile as a glutathione (GSH) precursor, antioxidant, anti-apoptotic, and anti-inflammatory agent makes it an interesting substance acting at multiple sites. Fetal rat studies have shown that combination of NAC and hypothermia is neuro-protective than hypothermia alone.

Melatonin: is a potent free radical scavenger and additionally induces antioxidant enzymes. Melatonin readily crosses the blood brain barrier, binds to specific brain receptors and is selectively concentrated in the brain and its subcellular compartments. A clinical trial of melatonin administration in premature infants is currently running in the UK called the MIND trial. The potential benefit of post-insult administration of melatonin combined with therapeutic hypothermia is currently being studied in the University college London piglet model.

Erythropoetin: besides controlling hematopoiesis it also has neuroprotective effects through different mechanisms such as direct neurotrophic effect, decreased susceptibility to glutamate toxicity, induction of anti-apoptotic factors, decreased inflammation, decreased nitric oxide-mediated injury, direct antioxidant effects, and protective effects on glia. The dosage for neuroprotection (1000–30,000 U/kg) is above the range used in anaemia. A recent randomized controlled study in 167 infants reported that repeated low dose (300 or 500 U/kg) rEpo was safe and resulted in improved neurological outcome in moderate to severe neonatal encephalopathy at 18 months of age. Recombinant Epo was administered every other day for 2 weeks, starting 48 h after birth. Outcomes were not different between the 2 Epo doses. Subgroup analyses indicated that Epo improved long-term outcomes only for infants with moderate HIE and not those with severe HIE. No negative hematopoietic side effects were observed.

Anticonvulsants: Presence of seizures during HIE is known to increase the extent of brain damage in HIE. Phenobarbitone which is the most common drug used in the treatment of neonatal seizures, has been shown to cause apoptosis of brain cells in the experimental animals. Two new drugs levetiracetam and topiramate which are used for seizure control in older children and adults, have been shown to be neuroprotective especially topiramate in experimental animal models of hypoxia ischemia but as of now there are no pre clinical studies to shown benefit.

Stem cells: Recent advances in regenerative medicine suggest that stem cell transplantation may improve repair of the damaged brain. Regenerative effects of stem cell transplantation are likely to involve both replacement of damaged cells by exogenous cells as well as improvement of endogenous repair processes by releasing trophic factors, however, there are still hurdles to overcome before clinical application of stem cell transplantation can safely be considered.
PROGNOSIS:

Prognosis of an individual patient is difficult to define with accuracy in cases of HIE, but certain clinical and laboratory parameters would suggest a bad prognosis.

Clinical criteria which suggest bad prognosis are:

Urine output: if an infant had good urine output, the chances of mortality and neurologic injury are 5% and 10%, respectively, whereas oliguria beyond 24 hours resulted in rates of mortality and neurologic injury of 33% and 67%, respectively. Acute tubular necrosis has not been shown to be of good prognostic value.

Severity and duration of encephalopathy: Grading schemes for the severity of HIE have been used as predictors of long term neurological function. Almost all infants with mild encephalopathy have a good outcome. The outcome of infants with moderate encephalopathy is less predictable and upto 75% of infants may make a normal recovery. Persistence of stage 2 for more than 7 days or stage 3 at any time is associated with later neurologic impairment or death. When the neurologic syndrome was severe, 80% of infants died and the remaining 20% had significant sequelae.

Persistent seizures: If the seizures are persistent or recalcitrant to anticonvulsant medications, they are nearly uniformly associated with death or significant neurologic deficits.

Discharge neurological examination: if a newborn’s neurologic examination returns to normal by 1 to 2 weeks, the infant likely will be normal at follow-up.

Laboratory finding which suggest poor prognosis:

EEG: EEG has proved to be a more reliable predictor of outcome than the early neurological examination. Conventional and amplitude integrated EEG have been used to predict long term neurological outcome in asphyxiated infants. At any time, a burst-suppression (especially when it is unreactive to stimuli) or an isoelectric pattern is associated with poor outcome. If there is only mild depression early, there can be normal outcome. If there is depression after 12 days, poor outcome is expected. A normal EEG at 7 days predicts normal outcome. Data suggests that EEG recording may be less sensitive to certain patterns of brain injury and are therefore less reliable outcome measures in such cases. Specifically, because surface EEG recording are measures of electrical activity from the surface of brain, infants with neurological injury to the deeper brain stem structures may have relatively normal neonatal EEG findings despite a poor neurological outcome.
stem structures may have relatively normal neonatal EEG findings despite a poor neurological outcome.\textsuperscript{31}

Evoked potentials: Visual- and somatosensory-evoked potentials have been reported to predict outcome and can be done within 6 hours of birth. If there is a normal response, there will likely be normal outcome. If there is a delayed response, there will likely be sequelae. If there is no response, death is the likely outcome.\textsuperscript{34}

CT scan: Presence of cystic encephalomalacia on follow up at 3-4 weeks on CT scan is suggestive of a very poor outcome. Also if there is marked diffuse hypoattenuation, infants are rarely normal at follow-up.

MRI imaging: The optimal timing of MRI scans for maximal prognostic power remains unresolved. This is in large part because of the natural evolution of brain tissue injury and its changing appearance on MRI studies. Because cerebral edema usually peaks around 3 days after birth and gradually resolved over the subsequent week, some authors have favoured MRI studies at 72 hours for prognostic purposes. Specifically, a normal MRI scan at 72 hours is predictive of a favourable outcome even after a severe insult where as diffuse edema with impaired cortical grey white differentiation or lesions in the dorsolateral thalamus or dorsal putamen are reliable predictors of poor outcome, even after a relatively benign acute course.\textsuperscript{35,36} Other authorities have suggested that as well as the phenomenon of plasticity optimal prognostic information is obtained from studies delayed beyond the first week. The relatively uncommitted structure function relationship in the immature brain, as well as the phenomenon of plasticity make the accurate prediction of specific deficits more difficult in asphyxiated infants than in adults. One study reported that an abnormal signal in the posterior limb of the internal capsule alone predicts poor neurologic status at follow-up.\textsuperscript{37} The extent of injury to the basal ganglia and thalamic injury on MRI studies has emerged as important predictor of outcome. An MRI scan after the first week of life which is essentially normal or shows mild basal ganglia/thalamic injury is associated with a favourable subsequent outcome where as more severe injury to these regions is likely to results in subsequent cerebral palsy, microcephaly and severe global delay.\textsuperscript{38} When deep nuclear lesions occur in combination with brain stem injury, the outcome is particularly poor, with prominent disturbances in speech, sucking and swallowing.

Several studies have evaluated the prognostic utility of the newer MRI techniques discussed previously. Preliminary reports suggest that DWI (diffusion weighted
images) and proton MR spectroscopy may provide useful predictors of long term outcome even within first few hours of life\textsuperscript{39,40}. In the asphyxiated infants, absence of elevated cerebral lactate is generally predictive of a favourable neurodevelopmental outcome\textsuperscript{50} whereas elevated cerebral lactate levels are predictive of poor outcome\textsuperscript{49}. Early regions of restricted diffusion by DW are predictive of later regions of injury by conventional MRI. These early DWI changes are sensitive indicators of later outcome but lack specificity.
Reference List


