

## Post-resuscitation management of asphyxiated neonate

Perinatal asphyxia (PA) is a major public health problem. As per the latest estimates, PA accounts for 9% (i.e. 0.8 million) of total Under-5 mortality (i.e. 8.8 millions) worldwide, being one of the three most common causes of neonatal deaths along with prematurity and bacterial infections.<sup>1</sup> Of a total of 2.7 million stillbirths globally, approximately 1.2 million occur during intrapartum period, largely owing to asphyxia.<sup>2</sup> NNPD (2002-2003) reported PA to be the commonest cause of still-births, accounting for 45.1% of all such cases.

As reported in NNPD (2002-2003) APGAR scores of <7 was found at 1 minute in 8.4% while 2.4 % had scores of <7 at 5 minutes of life of all intramural births at 18 neonatal units in India<sup>Error!</sup>  
Bookmark not defined. Oxygen was used as most commonly used resuscitative measure in 9.5%, bag and mask ventilation in 6.3% and chest compressions in 0.8% while use of other medications in 0.5%. PA was responsible for 28.8% of all neonatal deaths. Manifestations of hypoxic ischaemic encephalopathy (HIE) were seen in approximately 1.4% of all babies. Apart from neonatal deaths, asphyxia is responsible for life long neuromotor disability in a large number of children.

### Definitions

There is no one definition of PA (Table 1). The definition of PA is context specific and can be sensitive e.g. those given by WHO and NNPD for the purpose of deciding immediate care of newborn or a specific definition such as the one given by AAP for the purpose of giving a label or predicting the long term outcome.

Table 1: Different definitions of perinatal asphyxia

World Health Organization <sup>3</sup>	Failure to initiate and sustain breathing
NNPD Network <sup>4</sup>	<ul style="list-style-type: none"><li>Moderate PA: Slow/gasping breathing or an Apgar score of 4 to 6 at 1 minute</li><li>Severe PA: No breathing or an Apgar score of 0-3 at 1 minute of age</li></ul>
American Academy of Pediatrics and American College of Obstetrics and Gynecology <sup>5</sup>	<p>Presence of all of following criteria:</p> <ul style="list-style-type: none"><li>Profound metabolic or mixed acidemia (pH&lt; 7.00) in umbilical cord blood</li><li>Persistence of low Apgar scores less than 3 for more than 5 minutes</li><li>Signs of neonatal neurologic dysfunction (e.g., seizures, encephalopathy, tone abnormalities)</li><li>Evidence of multiple organ involvement (such as that of kidneys, lungs, liver, heart and intestine).</li></ul>

### Consequences of asphyxia

PA is a multi-organ-system disorder affecting virtually every organ-system in the body including brain, heart, lungs, kidneys and intestine. Care of asphyxiated infant therefore should be oriented towards determining the severity of dysfunction of critical organ systems and provide appropriate support to allow recovery to happen. Many of these complications are potentially fatal. In term infants with asphyxia, renal, CNS, cardiac and lung dysfunction occur in 50%, 28%,

25% and 25% cases, respectively<sup>6</sup>. The extent of organ system dysfunction determines the early outcome of an asphyxiated neonate (Table 2).

*Table 2: Organ system dysfunction in perinatal asphyxia*

CNS	Hypoxic ischemic encephalopathy, intracranial hemorrhage, seizures, long-term neurological sequelae
Cardiac	Myocardial dysfunction, valvular dysfunction, rhythm abnormalities, congestive cardiac failure
Renal	Hematuria, acute tubular necrosis, renal vein thrombosis
Pulmonary	Delayed adaptation, respiratory failure, meconium aspiration, surfactant depletion, primary pulmonary hypertension
GI tract	Necrotizing enterocolitis, hepatic dysfunction
Hematological	Thrombocytopenia, coagulation abnormalities
Metabolic	Acidosis, hypoglycemia, hypocalcemia, hyponatremia

Hypoxic ischemic encephalopathy (HIE) refers to the CNS dysfunction associated with PA, and is often the prime concern while managing asphyxiated neonate as it can kill the neonate, and carries a potential to cause serious long-term neuromotor sequelae among survivors.

A detailed classification of HIE in term neonates was proposed by Sarnat and Sarnat<sup>7</sup>. A simpler and practical classification of HIE by severity of manifestations provided by Levene et al is recommended for routine use (Table 2)<sup>8</sup>. Thomson score is based on features of HIE and it can have a maximum (worst) score of 22. A score of 15 or more has shown a positive predictive value of 92%, negative predictive value of 82%, sensitivity of 71% and specificity of 96% for abnormal outcome at 12 months of age<sup>21</sup>.

*Table 2: Classification of HIE (Levene)<sup>8</sup>*

<b>Feature</b>	<b>Mild</b>	<b>Moderate</b>	<b>Severe</b>
Consciousness	Irritable	Lethargy	Comatose
Tone	Hypotonia	Marked hypotonia	Severe hypotonia
Seizures	No	Yes	Prolonged
Sucking/respiration	Poor suck	Unable to suck	Unable to sustain spontaneous respiration

Table 3: Thomson score<sup>21</sup>

Sign	0	1	2	3
<b>Tone</b>	normal	hyper	hypo	flaccid
<b>LOC</b>	normal	hyperalert, stare	lethargic	comatouse
<b>Fits</b>	none	< 3 per day	> 2 per day	
<b>Posture</b>	normal	fisting, cyclcing	strong distal flexion	decerebrate
<b>Moro</b>	normal	partial	absent	
<b>Grasp</b>	normal	poor	absent	
<b>Suck</b>	normal	poor	absent ± bites	
<b>Respir</b>	normal	hyperventilation	brief apnea	IPPV (apnea)
<b>Fontanell</b>	normal	full, not tense	tense	

### Evolution of HIE changes

HIE evolves gradually beginning from the time of insult to hours and days later. The initial hypoxic-ischemic event results in infarction of the brain tissue (primary energy failure). The subsequent injury (secondary injury) is mediated by reperfusion and free radicals in an area surrounding the necrotic area (penumbra). The penumbra undergoes a programmed neuronal death (apoptosis) even after the hypoxic insult is over. The time gap between these two phases could be 6 hr to 24 hr, and provides a window to institute specific therapeutic intervention.

### Clinical features of severe HIE in time frame

Birth to 12 hours	Depressed level of alertness, periodic breathing or respiratory failure, intact pupillary and oculomotor responses, hypotonia, seizures
12 to 24 hours	Variable change in level of alertness, more seizures, apnoeic spells, jitteriness, weakness in proximal limbs, upper>lower (full term), hemiparesis (full term), lower limbs (premature)
24 to 72 hours	Stupor or coma, respiratory arrest, brain stem pupillary and oculomotor disturbances, catastrophic deterioration with severe intraventricular haemorrhage and periventricular haemorrhagic infarction (premature)
After 72 hours	Persistent yet diminishing stupor, disturbed sucking, swallowing, gag and tongue movements, hypotonia>hypertonia, weakness in proximal limbs, upper>lower (full term), hemiparesis (full term), lower limbs or hemiparesis (premature)

## Management of a neonate with perinatal asphyxia

As of today, the management of asphyxiated babies is mainly supportive and involves maintaining optimum oxygenation, ventilation, perfusion, metabolic milieu and control of seizures (Figure 1).

### Delivery room care

- Obtain arterial cord blood for analysis: After cutting the cord apply additional clamp on umbilical cord on placental side keeping a cord segment of 10 to 15 cm between two clamps.
- Take a heparinized syringe and puncture the cord (clamped segment, once placenta is out; and resuscitation is over) to take blood sample from umbilical artery.

Presence of metabolic acidosis (pH <7.00 and base deficit greater than 16 mmol/L) indicates relatively long standing asphyxia (many minutes to hours), while presence of respiratory acidosis in absence of metabolic acidosis indicates presence of acute asphyxia (minutes) as in cord prolapse, acute abruption of placenta etc.

What is evidence?

A recent meta-analysis has shown a good correlation of Cord ABG abnormalities (pH <7.00 and base deficit  $\geq 16$  mmol/l) with short term (mortality, HIE, IVH or PVL) and long term prognosis (cerebral palsy).

Low arterial cord pH was significantly associated with neonatal mortality (odds ratio 16.9, 95% CI 9.7 to 29.5), HIE (OR: 13.8, 95% CI-6.6 to 28.9), IVH or PVL (OR: 2.9, 95% CI- 2.1 to 4.1), and cerebral palsy (OR: 2.3, 95% CI: 1.3 to 4.2).<sup>17</sup>

Transfer the infant to NICU if

- Apgar score 0-3 at 1 minute
- Prolonged bag and mask ventilation (60 seconds or more )
- Chest compression

Even babies transferred to mother should be monitored frequently in the first 48-72 hours for development of any features suggestive of HIE.

### NICU care

#### 1. Maintain normal temperature

- After drying, place the baby under the radiant warmer
- Maintain normal body temperature of the baby
- Avoid Hyperthermia<sup>9</sup>

#### 2. Maintain normal oxygenation and ventilation

- Assess the infant for adequacy of oxygenation and ventilation and provide support as needed
- Keep under oxygen hood in case of adequate spontaneous breathing

- Assisted ventilation is required if there is apnea, or spontaneous respiration is inadequate or there is continuing hypoxia or hypercarbia,
  - Maintain saturations between 90% and 95% and avoid any hypoxia or hyperoxia
  - Measure arterial blood gas if any respiratory or perfusion abnormalities are present (maintain pO<sub>2</sub> between 60 torr and 90 torr and pCO<sub>2</sub> at 35 to 45 torr). Avoid hypocarbia, as this would reduce the cerebral perfusion, and hypercarbia, which can increase intracranial pressure and predispose the baby to intracranial bleed.
3. *Maintain normal tissue perfusion*
- Ensure normal perfusion i.e. normal blood pressure, capillary refill time of less than 3 seconds, normal urine output, and absence of metabolic acidosis
  - Start intravenous fluid in all infants with Apgar scores <4 at 1 minute or <7 at 5 minutes of age or a baby that is not well- having respiratory problems, encephalopathy or abnormal tone.
  - In sick babies, place arterial line for guiding management of blood pressure. BP should be tightly maintained in upper normal range according to gestation and postnatal age specific BP charts avoiding wider fluctuation.<sup>11</sup>
  - If the tissue perfusion is inadequate, infuse normal saline (or Ringer's lactate) 10 mL/kg over 5-10 min
  - Administer dobutamine (preferred) or dopamine to maintain adequate cardiac output, as required.
  - Do not restrict fluid as this practice may predispose the babies to hypoperfusion. Restrict fluid only if there is hyponatremia (Sodium <120 mg%) secondary to syndrome of inappropriate secretion of ADH (SIADH) or if there is renal failure. Do echocardiography In infants needing inotropic support and also to assess contractibility and the asphyxial injury to the heart. It helps to guide appropriate management strategy<sup>20</sup>.
4. *Maintain normal hematocrit and metabolic milieu*
- Check blood glucose levels and maintain blood glucose levels between 75 mg/dL and 100 mg/dl.
  - Check hematocrit. Correct Anemia and maintain hematocrit between 45% and 55%. If the venous hematocrit in a baby is above 65%, bring it down to 55% by partial exchange transfusion using normal saline.
  - Check blood gases to detect metabolic acidosis as needed and maintain pH above 7.30.
  - In case of severe asphyxia, provide calcium in a maintenance dose of 4 mL/kg/day (of 10% calcium gluconate) for 1-2 days as a continuous infusion or as 1:1 diluted boluses, slowly under cardiac monitoring and maintain serum calcium concentration in the normal range.
5. *Treat seizures*
- Refer to seizure protocol.
6. *Nutrition: Start oral feeding once baby is hemodynamically stable, off vasopressors and normal abdominal examination (no distension, passing stool and normal bowel sounds).*
7. *Miscellaneous*
- Administer Vitamin K (1 mg IM) to all infants with perinatal asphyxia

## Role of special investigations

Electroencephalography (EEG):

EEG is not indicated routinely in all asphyxiated babies but it helps in the diagnosis and management of seizures and prognosticating the babies for long term outcomes. The prognosis is likely to be poor if the EEG shows:

- 1) Long periods of inactivity (more than 10 seconds)
- 2) Brief period of bursts (less than 6 seconds) with small amplitude bursts
- 3) Interhemispheric asymmetry and asynchrony
- 4) Isoelectric and low voltage (less than 5 microvolts) 25

Amplitude-integrated electroencephalography (aEEG) is simplified form and can be performed on continuous basis in NICU. Following abnormalities would indicate poor prognosis:

- Wide fluctuations in the amplitude with the baseline voltages dropping to near zero
- Peak amplitudes under 5 mV
- Seizure spikes

While a normal aEEG may not necessarily mean that the brain is normal, a severe or moderately severe aEEG abnormality may indicate brain injury and poor outcome. The time of onset of sleep wake cycling (SWC) has a prognostic value. If SWC returns before 36 hours then outcome is good<sup>22</sup>.

*Cranial ultrasound (US):*

Cranial US is not good for detecting changes of HIE in the term babies. However, hypoechoic areas can be seen in very severe cases (having large areas of infraction).

In preterm babies, US can pick up periventricular leukomalacia and intraventricular-periventricular hemorrhage by serial cranial US during the first week of life.

*Computed tomography (CT):*

In acute stage of HIE in term babies generalized low attenuation of brain parenchyma. CT is more useful after a traumatic delivery and suspected of having an extra-axial haemorrhage

*Magnetic resonance imaging (MRI):*

Abnormalities of thalami and basal ganglia in term infants and that of white and grey matter at term equivalent age in preterm infants and an altered signal at the level of the posterior limb of the internal capsule are strong predictors of subsequent risk of poor neurodevelopmental outcome.<sup>13,14,24</sup>

Second most common pattern of injury is injury to the watershed regions. Diffusion weighted MRI can pick up abnormalities within days after birth, though more pronounced in later during the first week. MRI is preferred over CT as it has a greater inter observer agreement and no radiation exposure.

## Newer modes of therapy

### 1. Therapeutic hypothermia

Institution of moderate therapeutic hypothermia (TH; (33°C to 34°C) in infants of at least 36 wk gestation (not preterm) with moderate to severe encephalopathy (not mild) in intensive care unit settings initiated within 4- 6 hr and continued for 72 hr of age has shown to reduce mortality and neuro-morbidity by 18 months of age.<sup>10,12</sup> TH can be instituted by selectively cooling the head or the whole body. It is a safe modality in settings where intensive care facilities to manage sickest neonates are available.

TH has become standard of care in developed countries. However, in low to middle income countries where the patient profile is different (concomitant IUGR, infection and nutritional deficiencies), and there is a paucity of intensive care, and many births occur out of hospital, small studies have shown that there may be increase in mortality with TH. The true value of TH in low to middle income countries is yet to be tested<sup>18</sup>.

Therapeutic hypothermia : What is evidence?

A cochrane review (8 RCTs; 638 term infants with moderate/ severe encephalopathy and evidence of intrapartum asphyxia) showed that TH reduced combined outcome of mortality or major neurodevelopmental disability by 24% to 18 months of age.

### 2. Prophylactic phenobarbitone

Some interest has been generated in the protective role of prophylactic phenobarbitone in newborns with perinatal asphyxia. A dose of 40 mg/kg administered prophylactically was associated with a better neuro-developmental outcome at 3 years of age.<sup>15</sup> However the Cochrane review database systematic review by Evans et al (2007) that included the 5 RCTs derived no difference in the risk of death, neurodisability.<sup>16</sup> Another study using 40 mg/kg within 1<sup>st</sup> hour showed a significant reduction in HIE with no difference in complications.<sup>19</sup> Recommendation for use of prophylactic phenobarbitone still awaits further studies.

What is evidence?

The systematic review by Evans DJ showed no significant difference in the risk of the combined outcome of death or severe neurodevelopmental disability (typical RR 0.78, 95% CI 0.49, 1.23).

### 3. Drugs under investigation

A large number of drugs are under investigation for neuro-protection in HIE. These need to be used in the early period of hypoxic ischemic injury. They act by causing blockade of free radical generation (allopurinol, oxypurinol), scavenging of oxidants (superoxide dismutase, glutathione, N-acetyl cysteine and alpha tocopherol), calcium channel blockade (flunarizine, nimodipine),

blockage of NMDA receptors (magnesium, MK801, dextromethorphan) and blockage of inflammatory mediators (phospholipase A<sub>2</sub>, indomethacin). Corticosteroids have no role on the treatment of HIE. Likewise, the current evidence does not support the use of mannitol in the management of HIE.

#### Follow up

Follow all the neonates with the moderate and severe asphyxia, especially those with stage II and III HIE staging. They should have a complete neurological assessment and intervention if needed during the follow up. A formal psychometric assessment at 18 months should be performed in all these babies.

#### Long term outcome

Among the infants who survive severe HIE, the sequelae include mental retardation, epilepsy, and cerebral palsy of varying degrees. The latter can be in the form of hemiplegia, paraplegia, or quadriplegia. Such infants need careful evaluation and support. They may need to be referred to specialized clinics capable of providing coordinated comprehensive follow-up care.

The incidence of long-term complications depends on the severity of HIE. Up to 80% of infants who survive severe HIE develop serious complications, 10-20% develop moderately serious disabilities, and up to 10% are normal. Among the infants who survive moderately severe HIE, 30-50% may suffer from serious long-term complications, and 10-20% with minor neurological morbidities. Infants with mild HIE tend to be free from serious CNS complications.

#### Predictors of mortality and neurological morbidity after perinatal hypoxic ischaemic insult

- Extended very low APGAR scores (at 20 minutes)
- Time to establish spontaneous respiration (for 30 or more minutes)
- Neonatal neurological examination (severe HIE)
- Brain imaging (USG, MRI)
- Other investigations (EEG, amplitude integrated EEG, Evoked potentials like BERA)

Research question	Subjects	Study design	Intervention	Outcomes to be measured
Does fluid restricted in asphyxiated babies improve short term morbidities and long term prognosis?	Neonates with perinatal asphyxia with any HIE	RCT	Comparison of 2/3 maintenance and full maintenance fluid	<ul style="list-style-type: none"> <li>• Worst HIE stage</li> <li>• Incidence of hyponatremia, renal failure, shock</li> <li>• Neurological examination at discharge</li> <li>• Neurological outcome at 18 months</li> </ul>

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