Section 2

Central nervous system

7. **Post-resuscitation management of asphyxiated neonates**
8. **Seizures**
9. **Preterm brain injury**

7 Post-resuscitation Management of Asphyxiated Neonates

Perinatal asphyxia (PA) is a major cause of neonatal and under-5 mortality, particularly in developing countries. As per the latest estimates, PA accounts for 9.4% (i.e, 0.72 million) of total under-5 child mortality worldwide. Along with prematurity and systemic infections, PA is one of the three most common causes of neonatal deaths.[1,2] It is also an important cause of still births – of the total 2.7 million stillbirths that occur globally, about 1.2 million occur during the intrapartum period, largely due to asphyxia.[3] The National Neonatal Perinatal Database (NNPD; 2002-2003) reported PA to be the commonest cause of still-births, accounting for 45.1% of all such cases.[4] Almost all (98.2%) asphyxia-related deaths occur in first week of life, with 73% occurring within 24 hours of birth.[5]

Incidence

As per the NNPD (2002-2003), the incidence of PA – defined as Apgar score of <7 at 1 minute of life – was 8.4% of all live births. Oxygen was the most commonly used resuscitative measure in 9.5%, bag and mask ventilation in 6.3%, chest compressions in 0.8%, and use of medications in 0.5%. PA was responsible for 28.8% of all neonatal deaths. Manifestations of hypoxic ischemic encephalopathy (HIE) were seen in approximately 1.4% of live births.[4] Asphyxia is also responsible for life long neuromotor disability in a large number of children.

Definitions

There is no single, well-accepted definition of PA (Table 7.1). The definition 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 specific (such as the one given by AAP for the purpose of giving a label or predicting the long-term outcome).

Table 7.1: Definitions of perinatal asphyxia

	Definition
World Health Oragnization[6]	Failure to initiate and sustain breathing
NNPD Network	• Moderate PA: Slow/gasping breathing or an Apgar score of 4 to 6 at 1 minute • Severe PA: No breathing or an Apgar score of 0-3 at 1 minute of age
American Academy of Pediatrics and American College of Obstetrics and Gynecology[7]	Presence of all of following criteria: • Profound metabolic or mixed acidemia (pH< 7.0) in umbilical cord blood • Persistence of low Apgar scores less than 3 for more than 5 minutes • Signs of neonatal neurologic dysfunction (e.g., seizures, encephalopathy, tone abnormalities) • Evidence of multiple organ involvement (such as that of kidneys, lungs, liver, heart and intestine).

Consequences of asphyxia

PA is a multi-organ disorder affecting virtually every organ-system in the body including brain, heart, lungs, kidneys and intestine. Care of asphyxiated neonates therefore should be oriented towards determining the severity of dysfunction of critical organ-system and providing appropriate support to allow recovery to happen. Many of these complications are potentially fatal. In term neonates with asphyxia, renal, CNS, cardiac and lung dysfunction occur in 50%, 28%, 25% and 25% respectively.[8] The extent of organ-system dysfunction determines the early outcome of an asphyxiated neonate (Table 7.2).

Hypoxic ischemic encephalopathy (HIE) refers to the CNS dysfunction associated with PA. It is often the prime concern while managing asphyxiated neonates because it is not only associated with high risk of mortality but also carries a significant risk of serious long-term neuromotor sequelae among survivors.

A detailed classification of HIE in term neonates was proposed by Sarnat and Sarnat.[9] A simpler and practical classification of

HIE, by severity of manifestations, provided by Levene is recommended for routine use.[10] Recent addition to this list is the Thompson score, which is based on features of HIE and has 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.[11]

Table 7.2: 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

Evolution of HIE changes

HIE evolves gradually beginning from the time of insult to hours and days later (Table 7.3). 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 programmed neuronal death (apoptosis) even after the hypoxic insult is over. The time gap between these two phases could be 6 to 24 hours and provides a window to institute specific therapeutic intervention.

Management of a neonate with perinatal asphyxia

Management of asphyxiated neonates is mainly supportive and involves maintaining optimum oxygenation, ventilation, perfusion, metabolic milieu and control of seizures.

Table 7.3: Clinical features of severe HIE and the time frame

Time frame	Clinical features
Birth to 12 hours	• Decreased alertness and tone • Convulsions • Periodic breathing or respiratory failure • Intact pupillary and oculomotor responses
12 to 24 hours	• Change in alertness level • Apneic spells • Increase in convulsions • Jitteriness • Weakness in proximal limbs • In term neonates, upper limbs more involved than lower limbs; in preterm, lower limbs more involved
24 to 72 hours	• Further decrease in alertness • Pupillary and oculomotor disturbances • Respiratory arrest • In preterm neonates, intraventricular hemorrhage and periventricular hemorrhagic infarction
After 72 hours	• Persistent and diminishing stupor • Abnormal sucking, swallowing, gag and tongue movements • Hypotonia more common than hypertonia • Weakness in proximal limbs

Delivery room care

- For neonates born at term and near term (35 weeks) gestation, resuscitation should start with 21% oxygen.
- For preterm neonates born at less than 35 weeks of gestation, resuscitation should start with 21% to 30% oxygen; further oxygen concentration should be titrated to achieve target saturations.[12]
- For non-vigorous neonates born through meconium stained amniotic fluid, the 2015 Neonatal Resuscitation Program (NRP) does not recommend routine intubation at birth for suctioning of meconium.[12]
- 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 (in the 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 (minutes to hours), while presence of respiratory acidosis in absence of metabolic acidosis indicates acute asphyxia (minutes) as in cord prolapse, acute abruption of placenta, etc.

Cord blood gas in asphyxia: what is the evidence?
A recent meta-analysis has shown good association of cord ABG abnormalities (pH<7.0 and base deficit 16 mmol/l) with short-term (mortality, HIE, IVH or PVL) and long-term adverse outcomes (cerebral palsy).[13]

NICU care

Transfer the neonate to NICU, if

- Apgar score at 1 minute is 3
- Required prolonged bag and mask ventilation (60 seconds or more)
- Required chest compressions

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

Care in NICU

1. *Maintain normal temperature*

- After drying, place the baby under the radiant warmer
- Maintain normal body temperature
- Avoid hyperthermia[14]

2. *Maintain normal oxygenation and ventilation*

- Assess the infant for adequacy of oxygenation and ventilation and provide support as needed
- Keep under oxygen hood, if needed; maintain saturations between 90% and 95%; avoid hypoxia and hyperoxia
- Assisted ventilation is required if there is apnea, or spontaneous respiration is inadequate or there is continuing hypoxia or hypercarbia
- Measure arterial blood gas, if any respiratory or perfusion abnormalities are present (maintain pO_2

between 60 and 90 mm Hg and pCO_2 at 35 to 45 mm Hg). Avoid both hypocarbia (reduces cerebral perfusion) and hypercarbia (increases cerebral perfusion and intracranial pressure and predisposes to intracranial bleed)

3. *Maintain normal tissue perfusion*

- Ensure normal perfusion i.e. capillary refill time of less than 3 seconds, absence of tachycardia and metabolic acidosis, normal blood pressure, and adequate urine output
- Start intravenous fluids in all neonates with Apgar scores <4 at 1 minute or <7 at 5 minutes of age or if the neonate is sick (respiratory distress, encephalopathy or abnormal tone)
- In sick neonates, 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 wide fluctuations.[15]
- If tissue perfusion is inadequate, infuse normal saline or Ringer's lactate at 10 mL/kg over 5-10 min
- Administer dobutamine (preferred) or dopamine to maintain adequate cardiac output, as required.
- Do not restrict fluids routinely because it may predispose to hypoperfusion; restrict fluids only if there is hyponatremia (sodium <120 mEq/L) secondary to syndrome of inappropriate secretion of ADH (SIADH) or if there is renal failure.
- Do echocardiography in neonates requiring ionotropic support to evaluate decreased contractility due to asphyxia related cardiogenic shock. This helps to guide appropriate management strategy.[16]

4. *Maintain normal hematocrit and metabolic milieu*

- Check blood glucose 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 is above 65%, bring it down to 55% by partial exchange transfusion using normal saline.

- Check blood gases to detect metabolic acidosis; maintain pH above 7.30
- In case of severe asphyxia (see AAP criteria in Table 1), 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; maintain serum calcium concentration in the normal range.

5. *Treat seizures*

- Refer to protocol on 'Neonatal seizures'

6. *Nutrition*

- Start oral feeding once the neonate is hemodynamically stable, off vasopressor support, and has normal abdominal examination findings (no distension and normal bowel sounds)

Role of special investigations

The role of special investigations is to provide information on long-term prognosis.

Electroencephalography (EEG)

EEG is not indicated routinely in all asphyxiated neonates, but it helps in diagnosis and management of seizures as well as inand prognosticating the long term outcomes. The prognosis is likely to be poor, if the EEG shows any one of the following:

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)[17]

Amplitude-integrated electroencephalography (aEEG) is a simple, reliable, non-invasive technique which can be applied at the bedside in NICU for monitoring EEG continuously. Following abnormalities in aEEG 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) also has a prognostic value. If SWC returns before 36 hours of age, the prognosis is likely to be good.[18]

Cranial ultrasound (USG)

Cranial USG is not good for detecting changes of HIE in term neonates. However, hypoechoic areas can be seen in very severe cases (having large areas of infarction).

In preterm neonates, USG can detect periventricular leukomalacia and intraventricular hemorrhage during the first week of life. USG is more useful than CT in providing adjunct prognostic information in preterm neonates.

Computed tomography (CT)

CT has a role in initial evaluation, if MRI is not readily accessible. In acute stage of HIE, CT in term nenates show generalized low attenuation of brain parenchyma. However, several weeks after asphyxial insult, CT readily picks up diffuse cortical neuronal injury, injury to basal ganglia and thalamus, focal and multifocal ischemic brain injury as well as periventricular leukomalacia. CT has a limited role in identification of parasagittal cerebral injury.

Magnetic resonance imaging (MRI)

MRI is the best imaging modality for determining prognosis in term neonates. Diffusion weighted MRI can detect abnormalities within 24 to 48 hours after birth (optimal time is 2 to 3 days), whereas conventional MRI can show abnormalities in the first 3 to 4 days (though optimal time is later during the first week of life). An altered signal at the level of posterior limb of the internal capsule and abnormalities of thalami and basal ganglia

in term neonates and that of white and grey matter at term equivalent age in preterm neonates are strong predictors of subsequent risk of poor neurodevelopmental outcome.[19] Another common pattern of injury is injury to the watershed regions.

Prognostic test in neonates with asphyxia: what is the evidence?

In a recent meta-analysis of 29 studies describing 13 prognostic tests in 1306 term neonates with hypoxic-ischemic encephalopathy, aEEG in the first 6 hours showed maximum sensitivity and specificity (93% and 90%, respectively)[20].

Specific management

1. Therapeutic hypothermia (TH)

Institution of moderate therapeutic hypothermia (33^0C to 34^0C) initiated within 4- 6 hr and continued for 72hr of age in ICU has been shown to reduce mortality and neuro-morbidity by 18 months of age in infants of at least 35 weeks' gestation with moderate to severe encephalopathy.[21] 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 now become the standard of care in developed countries. However,this is not the case in low to middle income countries (LMIC), where the patient profile is different (higher risk of IUGR, infection and nutritional deficiencies), there is a paucity of intensive care, and many births occur at home. Indeed, a few studies have shown increased mortality following TH in these settings.[22] But recent studies from India showed that with proper monitoring and optimal supportive care, TH is feasible using indigenous cooling methods like gel-packs. The studies even reported better long term neurological outcomes.[23]

What is the evidence?

The Cochrane review (8 RCTs; 638 term neonates with moderate/ severe encephalopathy and evidence of intrapartum asphyxia) showed that TH reduced the combined outcome of mortality or major neuro-developmental disability by 24% at 18 months of age.[24]

Mechanism of action

TH has been shown to be protective at critical cellular and vascular sites of cerebral injury. It acts by the following mechanisms to reduce the extent of brain injury[25]:

1. Decreased cerebral metabolism and blood flow: Decrease in energy requirement and cerebral edema
2. Decreased brain lactic acid, glutamate, and nitric oxide concentrations: Less excitotoxic and oxidative injury
3. Inhibits protease activation, mitochondrial failure, free radical damage, lipid peroxidation: Less apoptosis and necrosis

Selection of neonates for TH (Table 7.4)

Contraindications

Neonates with following conditions should not be considered for TH: major congenital malformations, suspected/known chromosomal disorder, clinical and echocardiographic evidence of PPHN, active bleeding, or catecholamine resistant shock.

Cooling devices

1. Whole body cooling devices
   a) High technology devices: Examples – Tecotherm™, Blanketrol™, Meditherm™
   b) Low technology devices: Example - Miracradle™
2. Selective head cooling device: Examples - Olympic cool cap system™

High technology devices

These devices usually have a circulating water/coolant system. The water/coolant flows over and around the heating/cooling element located in the circulating reservoir. The heated or cooled water/coolant then flows out of the reservoir to the circulating pump, through connecting hoses over a water temperature sensor to the blanket. The water circulates through the blanket(s) and returns to the unit.

Low technology devices

These devices use the phase change material (PCM) technology to induce therapeutic hypothermia. PCMs are special thermal energy storage materials that store and release heat at a

Table 7.4: Selection criteria of neonates for therapeutic hypothermia

S.no	Criteria	Inborn neonates	Out-born neonates
1.	Gestation/birth weight	35 weeks/ 2kg	2 kg (if gestation not known)
2.	Age at presentation	6 hours since birth	6 hours since birth
3.	Evidence of birth asphyxia	Any one of the following: a) Apgar score at 5 minutes 5 b) Need of IPPV till 5 minutes of birth c) Cord arterial blood or blood obtained within 1h of birth pH <7.0 d) Cord arterial blood or blood obtained within 1 h of birth base deficit 16.0	Any one of the following: a) Absence of cry at 5 minutes of age b) Need of IPPV till 5 minutes of birth
4.	Staging of encephalopathy	Any one of the following: a) Clinical seizures b) Altered state of consciousness (lethargy, stupor or coma) AND any one of the following: i) Hypotonia ii) Abnormal reflexes including oculomotor or pupillary abnormalities iii) Absent or weak suck	Same as for 'inborn' neonates

Note: *Perform neurological examination hourly until 6 hours of age to ascertain if baby fulfills the eligibility criteria*

particular temperature. The thermal energy transfer occurs when the material changes phase from solid to liquid or liquid to solid.

In our unit, we use 'Blanketrol III Hyper-Hypothermia' temperature management system which is a servo-controlled whole-body hypothermia device.

How to initiate whole body hypothermia

1) Counsel the parents about indications, benefits and risks of therapy
2) Prepare the cooling system for operation
3) Set the cooling blanket temperature to 33.5^{0}C
4) Monitor and document the infant's pre-cooling vital signs
5) Place and secure central and arterial lines before starting hypothermia
6) Gently insert the rectal probe 2 cm into the infant's rectum, and secure to the infant's leg with tape
7) Place the infant on the warmer in the supine position with the entire head and body resting on the cooling blanket
8) The infant must lie directly on the cooling blanket, wearing a diaper only

Monitoring after initiating TH

The frequency of monitoring and investigations after initiating TH are depicted in Table 7.5:

Table 7.5: Monitoring (frequency)

Parameter	Day 1	Day 2	Day 3
Vitals monitoring including invasive blood pressure monitoring	Q 1 hour	Q 1 hour	Q 1 hour
Neurological monitoring	Q 12 hours	Q 12 hours	Q 12 hours
Urine output	Q 6 hours	Q 6 hours	Q 6 hours
ECG	Continuously	Continuously	Continuously
aEEG	Continuously	Continuously	Continuously
Skin integrity	Q 6 hours	Q 6 hours	Q 6 hours
Investigations			
Glucose	Q 6 hours	Q 6 hours	Q 6 hours
Blood gas	Q 6 hours or as indicated by condition of baby	Q 12 hours or as indicated	Q 12 hours or as indicated
Renal function test	Once	Once	Once
Electrolytes	Once	Once	Once
Complete hemogram	Only if required	Only if required	Only if required
Neurosonogram	If abnormal	If abnormal	If abnormal

Rewarming

1) Increase the infant's core temperature by 0.5 ^{0}C every hour until 36.5^{0}C has been reached
2) When the infant's core temperature is 36.5^{0}C, remove the patient from the cooling blanket/device
3) Re-activate the radiant warmer, monitor and document the infant's temperature with the skin probe
4) Problems while rewarming: seizures and hypotension

Supportive therapy during TH

Sedative/analgesics	Morphine (preferred) or fentanyl may be given by infusion during therapeutic hypothermia
Enteral feeds	Start MEN, if hemodynamically stable
Antibiotics	Prophylactic antibiotics should not be given
Anticonvulsants	Anticonvulsants should be given in the presence of seizures; electric seizures in absence of clinical correlates should be treated
Platelet concentrate	If platelet count is less than 100,000 / cmm
Fresh frozen plasma	Only if there is active bleeding

Adverse effects of TH[24]

The common adverse effects include sinus bradycardia (heart rate < 80/min) and thrombocytopenia (platelet count < 150 ×109/L).

2. Prophylactic phenobarbitone

A dose of 40 mg/kg of phenobarbitone administered prophylactically was associated with a better neurodevelopmental outcome at 3 years of age.[26] However, the Cochrane review that included 5 RCTs reported no difference in the risk of death or neurodisability.[26]

Prophylactic phenobarbitone in HIE: What is the evidence?

The systematic review 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).[26]

3. Drugs under investigation

A large number of drugs are under investigation for neuroprotection in HIE. They need to be used in the early period of hypoxic ischemic injury along with therapeutic hypothermia. They act by causing blockade of free radical generation (allopurinol, oxypurinol, melatonin), scavenging of oxidants (superoxide dismutase, glutathione, N-acetyl cysteine), calcium channel blockade (flunarizine, nimodipine), blockage of NMDA receptors (magnesium, Xenon, dextromethorphan) and blockage of inflammatory mediators (phospholipase A_2,

indomethacin, erythropoietin).[27] A recent multicenter 'Total body hypothermia plus Xenon' (TOBY-XE) trial reported no effect of this intervention on reduceing lactate to N-acetyl aspartate ratio, a surrogate marker of poor neurodevelopmental outcome.[28]

Follow-up

It is essential to follow all the neonates with the moderate and severe asphyxia, especially those with stage II and III HIE. They should have a complete neurological assessment and early intervention, if needed, during the follow-up. A formal psychometric assessment at 18 months should be performed in them.

Long-term outcome

Among the neonates who survive severe HIE, the sequelae include mental retardation, epilepsy, and cerebral palsy. CP 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.

Predictors of mortality and neurological morbidity after perinatal hypoxic ischemic insult:

1. Extended very low APGAR scores (at 20 minutes or more)
2. Time to establish spontaneous respiration (for 30 or more minutes)
3. Neonatal neurological examination (severe HIE)
4. Brain imaging (USG, MRI)
5. Other investigations (EEG, aEEG, evoked potentials like BERA)

The incidence of long-term complications depends on the severity of HIE. Upto 80% of neonates with stage III HIE die whereas rest 20% have neurological sequelae. Up to 80% of neonates who survive severe HIE develop serious complications, 10-20% develop moderately serious disabilities, and up to 10% are normal. The incidence of death is up to 5% after moderate birth asphyxia. Among the neonates who

survive moderately severe HIE, 30-50% may suffer from serious long-term complications, and 10-20% with minor neurological morbidities. Neonates with mild HIE tend to be free from death or any neurological sequelae.[29,30]

A recent study on long-term outcomes of whole body hypothermia for HIE revealed the rate of combined end point of death or an IQ of less than 70 at 6 to 7 years of age to be lower among neonates undergoing whole body hypothermia (47%) than those undergoing usual care (62%).[25]

References

1. Liu L, Johnson HL, Cousens S, Perin J, Scott S, Lawn JE, Rudan I, Campbell H, Cibulskis R, Li M, Mathers C, Black RE. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. Lancet 2012;379:2151-61.
2. Lawn JE, Blencowe H, Oza S, You D, Lee AC, Waiswa P, Lalli M, Bhutta Z, Barros AJ, Christian P, Mathers C, Cousens SN; Lancet Every Newborn Study Group. Every Newborn: progress, priorities, and potential beyond survival. Lancet 2014;384:189-205.
3. Lawn JE, Blencowe H, Pattinson R, Cousens S, Kumar R, Ibiebele I, Gardosi J, Day LT, Stanton C; Lancet's Stillbirths Series steering committee. Stillbirths: Where? When? Why? How to make the data count? Lancet 2011;377:1448-63.
4. Report of the National Neonatal Perinatal Database (National Neonatology Forum, India) 2003 .
5. Sankar MJ, Natarajan CK, Das RR, Agarwal R, Chandrasekaran A, Paul VK. When do newborns die? A systematic review of timing of overall and cause-specific neonatal deaths in developing countries. J Perinatol 2016;36 Suppl 1:S1-S11.
6. World Health Organization. Perinatal mortality: a listing of available information. FRH/MSM.96.7.Geneva:WHO,1996.
7. Committee on fetus and newborn, American Academy of Pediatrics and Committee on obstetric practice, American College of Obstetrics and Gynecology. Use and abuse of the APGAR score. Pediatr 1996;98:141-2.
8. Perlman JM, Tack ED, Martin T, Shackelford G, Amon E. Acute systemic organ injury in term infants after asphyxia. Am J Dis Child 1989;143:617-20.
9. Sarnat HB, Sarnat MS: Neonatal encephalopathy following fetal

distress: A clinical and electroencephalographic study. Arch Neurol 1976;33:695-706.
10. Levene MI. The asphyxiated newborn infant. In: Levene MI, Lilford RJ. Fetal and neonatal neurology and neurosurgery. Edinburgh: Churchill Livingstone 1995: 405-426.
11. Thompson CM, et al: The value of a scoring system for hypoxic encephalopathy in predicting neurodevelopmental outcome. Acta Paediatr 1997; 86:757.
12. Wyckoff MH, Aziz K, Escobedo MB, et al. Part 13: Neonatal Resuscitation: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 2015;132:S543–60.
13. Malin GL, Morris RK, Khan KS. Strength of association between umbilical cord pH and perinatal and long term outcomes: systematic review and meta-analysis. BMJ 2010; 340: c1471.
14. Laptook A, Tyson J, Shankaran S, McDonald S, Ehrenkranz R, Fanaroff A, Donovan E, Goldberg R, O'Shea TM, Higgins RD, Poole WK; National Institute of Child Health and Human Development Neonatal Research Network. Elevated temperature after hypoxic-ischemic encephalopathy: risk factor for adverse outcomes. Pediatrics 2008;122:491-9.
15. Zubrow A B, Hulman S, Kushner H, Falkner B. Determinants of blood pressure in infants admitted to neonatal intensive care units: a prospective multicentre study. J Perinatol 1995;15:472-9.
16. Ranjit M S. Cardiac abnormalities in birth asphyxia. Indian J Paediatr 2000;67:529-32.
17. Menache CC, Bourgeois BF, Volpe JJ. Prognostic value of neonatal discontinuous EEG. Pediatr Neurol 2002;27:93-101.
18. Osredkar D, Toet MC, van Rooij LG, van Huffelen AC, Groenendaal F, de Vries LS. Sleep wave cycling on amplitude integrated electroencephalography in term newborns with hypoxic ischaemic encephalopathy. Pediatrics 2005;115:327-32.
19. Lianne J, Woodward, Anderson PJ, Austin NC, Howard K, Inder TE. Neonatal MRI to predict neurodevelopmental outcomes in preterm infants. N Engl J Med 2006;355:685-94.
20. van Laerhoven H, de Haan TR, Offringa M, Post B, van der Lee JH.Prognostic tests in term neonates with hypoxic-ischemic encephalopathy: a systematic review. Pediatrics 2013;131:88-98.
21. Edwards AD, Brocklehurst P, Gunn AJ, Halliday H, Juszczak E, Levene M, Strohm B, Thoresen M, Whitelaw A, Azzopardi D. Neurological outcomes at 18 months of age after moderate hypothermia for perinatal hypoxic ischaemic encephalopathy: synthesis and meta-analysis of trial data. BMJ 2010;340:c363.

22. Thayyil S, Chandrasekaran M, Taylor A, Bainbridge A, Cady EB, Chong WK, Murad S, Omar RZ, Robertson NJ. Cerebral magnetic resonance biomarkers in neonatal encephalopathy: a meta-analysis. Pediatrics 2010;125:e382-95.
23. Bhardwaj SK, Bhat BV. Therapeutic hypothermia using gel packs for term neonates with hypoxic ischemic encephalopathy in resource-limited settings: a randomized controlled trial. J Trop Pediatr 2012;58:382-8.
24. Jacobs SE, Berg M, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG. Cochrane Database Syst Rev 2013;1:CD003311.
25. Shankaran S. Hypoxic-ischemic Encephalopathy and Novel Strategies for Neuroprotection. Clin Perinatol 2012;39:919–29.
26. Evans DJ, Levene MI, Tsakmakis M. Anticonvulsants for preventing mortality and morbidity in full term newborns with perinatal asphyxia. Cochrane Database Syst Rev 2007 Jul 18;(3):CD001240.
27. McAdams RM, Juul SE. Neonatal Encephalopathy: Update on Therapeutic Hypothermia and Other Novel Therapeutics. Clin Perinatol 2016;43:485-500.
28. Azzopardi D, Robertson NJ, Bainbridge A, et al. Moderate hypothermia within 6 h of birth plus inhaled xenon versus moderate hypothermia alone after birth asphyxia (TOBY-Xe): a proof-of-concept, open-label, randomised controlled trial. Lancet Neurol 2015; 15:145-53.
29. Rutherford MA, et al. Abnormal magnetic resonance signal in the internal capsule predicts poor neurodevelopmental outcome in infants with hypoxic ischemic encephalopathy. Pediatrics 1998; 102: 323.
30. Robertson C, Finer N. Term infants with hypoxic ischaemic encephalopathy: outcome at 3.5 years. Dev Med Child Neurol 1985; 27:473-84.