Asphyxia

Introduction

This guideline covers perinatal asphyxia. (See seizures and encephalopathy protocols for diagnosis and management of these related conditions).

The definition of asphyxia is controversial. The NH&MRC report of the Health Care Committee Expert Panel on Perinatal Morbidity defined 'perinatal asphyxia' as "a condition in the neonate where there is the following combination:

- An event or condition during the perinatal period that is likely to severely reduce oxygen delivery and lead to acidosis; and
- A failure of function of at least two organs (may include lung, heart, liver, brain, kidneys and hematological) consistent with the effects of acute asphyxia."

Incidence and risk factors

Incidence: The incidence of neonatal encephalopathy probably lies between 0.3 and 1.8%. In 1995 in Australia the incidence of antepartum fetal death was 3.5/1000 live births, the incidence of intrapartum fetal death was 1.0/1000, and the incidence of neonatal death was 3.2/1000. Apgar scores of 1-3 at 1 minute were recorded in 2.8% and at 5 minutes in 0.3% of live births in Australia (Victoria not included) in 1995.

Risk factors: The incidence of antenatal and intrapartum asphyxia is higher in complicated pregnancies, particularly those associated with diminished placental reserve including:

1. Hypertensive disease of pregnancy or pre-eclampsia,
2. Intrauterine growth restriction,
3. Placental abruption,
4. Fetal anaemia (e.g., rhesus incompatibility),
5. Postmaturity,
6. Unphysiological labour (e.g., induction), and
7. Malpresentation including vasa praevia.

Detection of infants at risk of perinatal asphyxia:

Only about half of the infants needing resuscitation are predicted by antenatal history or signs during labour. The following predictors have been assessed for their ability to predict low Apgar scores:
1. Fetal movement counting (typical sensitivity 12 to 50%, specificity 91 to 97%),
2. Non-stress testing (typical sensitivity 14 to 59%, specificity 79 to 97%),
3. Fetal biophysical profile (typical positive likelihood ratio 2.5 to 27.4, negative likelihood ratio 0.2 to 0.9),
4. Abnormal fetal heart rate (FHR) recording (typical sensitivity 70%, specificity 80%),
5. Fetal scalp pH (decreases sensitivity to 31% and increases specificity to 93% of FHR monitoring).

In addition, the following clinical factors may be associated with a low Apgar score:

6. Reduction of liquor volume, and
7. Meconium staining of the liquor.

**Consequences**

Perinatal asphyxia may result in fetal demise, neonatal death, or a period of recovery during which there is organ dysfunction with possible long-term effects, particularly in neurological function\(^1\). Clinical manifestations of perinatal asphyxia include\(^6\):

1. **Depression of the neonate at birth with a low Apgar score and acidosis,**
2. **Hypoxic ischaemic encephalopathy** (HIE),
3. **Multiorgan system dysfunction** (% of infants with HIE):
   - Renal compromise with oliguria and elevated creatinine (40%),
   - Hypoxic cardiomyopathy (ECHO or ECG abnormality) (25%),
   - Pulmonary complications including respiratory distress and persistent pulmonary hypertension of the neonate (25%),
   - Disseminated intravascular coagulation,
   - Hepatic failure, and
   - Necrotising enterocolitis.
4. **Fluid, electrolyte and metabolic abnormalities** including:
   - Fluid overload, hyperkalaemia, hypoglycaemia, and acidosis.

One third or more of infants with HIE will have 2 or more organ systems involved, which may include lung, heart, liver, brain, kidneys and hematological\(^6\).

**Prediction of outcome:**

No single clinical factor predicts outcome (death or neurodevelopmental abnormality) of perinatal asphyxia or HIE with absolute certainty. The following prognostic factors may be used as guides in management and counseling:

1. **During Resuscitation:**
   a. **Apgar scores:**
      i. Although the 1 and 5 minute Apgar scores are poor predictors of neonatal acidosis an Apgar score of \(\leq 3\) increases the risk of a low cord pH 4.8 times\(^6\).
      ii. The decision to cease cardiopulmonary resuscitation should be based on cause of arrest, response to resuscitation, and remediable factors. Death or severe neurological abnormality is predicted by a failure to obtain a
heart rate by 10 minutes (Apgar score 0 at 10’) despite adequate resuscitation and failure to respond to adrenaline.iii.

iii. Jain’ followed 613 infants with an Apgar score of 0 at 1 minute (apparent still birth). Resuscitation was attempted on 124, 93 being successfully resuscitated and 31 not responding. Twenty-two died neonatally and 36 survivors were discharged home. Of 23 followed up, 14 were normal, 6 were abnormal and 3 were suspect.

iv. Nelson and Ellenberg 8 examined Apgar scores in 49 000 infants. Of infants with an Apgar score 0 - 3 at 20 minutes, 59% of survivors died before 1 year, and 57% of the survivors had cerebral palsy.

b. Cord blood gas: documents acidosis, hypoxia and hypercarbia at birth. In the series of 30 000 infants, Goldaber 10 found the incidence of neonatal death and neonatal seizures did not increase until an umbilical artery (Ua) pH < 7.05 was reached. The absolute incidence of otherwise unexplained neonatal seizures was 1.1% for UapH < 7.05 and 9.2% for UapH < 7.00. The mortality increased to 1.1% for UapH < 7.05 and 8% at a UapH < 7.00.

c. Time to spontaneous respiration: the overall risk of death or handicap was 72% in the pooled series of infants with > 30 minutes to sustained spontaneous respiration.

2. Clinical assessment of encephalopathy:

The clinical practice in John Spence Nursery is to document the clinical stage of HIE accurately and to document progression or recovery from HIE. EEGs are performed on infants with Grade 2 or 3 HIE, on whom seizures are suspected without clinical certainty, and on infants who are unable to be examined (eg muscle relaxed).

a. Degree of encephalopathy: the overall risk of death or severe handicap in a pooled series of infants was 6.

   i. Grade 1 HIE: 1.6%
   ii. Grade 2 HIE: 24%
   iii. Grade 3 HIE: 78%

   iv. More prolonged encephalopathy (eg. > 6 days stage 211) is also highly predictive of severe neurological abnormality.

b. EEG abnormality: the rates of death or severe handicap for grade of EEG abnormality from pooled studies were 6:

   i. Severe abnormality (burst suppression, low voltage or isoelectric) = 95%,
   ii. Moderate abnormality (slow wave activity) = 64%, and
   iii. Mild or no abnormality = 3.3%

3. Imaging and evoked potentials:

Early imaging is relatively insensitive at finding abnormalities. Ultrasound, CT and MRI are available at RPAH. CT and MRI diagnose late structural problems. They are NOT used routinely.

a. Ultrasound abnormality: May detect haemorrhage. Infants with small or poorly visualised ventricles, and hypoechogenicities are at increased risk of abnormal neurodevelopment. The ultrasound tends to underestimate cortical damage. Lesions may take 2-3 days to develop.

b. Computerised tomography: Hypodensities may take 10-14 days to develop. Abnormalities include haemorrhages and hypodensities. The risk of death or severe neurological disability was 82% in infants with severe hypodensities or haemorrhage in 4 pooled studies.

c. Nuclear magnetic resonance: NMRI (proton NMR) and NMRS (31P NMRS) provide information on brain structure and function that is highly predictive of outcome. They are not routinely available in Australia.
d. **Somatosensory evoked potentials**: There is a close correlation between outcome and SEP. Infants with normal outcome have a normal SEP by 4 days of age, whereas those with abnormal or absent responses beyond 4 days have abnormalities at follow up\(^8\).

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**Diagnosis**

On basic principles the assessment should include a history of maternal and intrapartum risk factors for problems that may affect the infant including pre-existing medical conditions in the mother, problems of pregnancy, abnormalities identified antenatally in the fetus, the presence of meconium stained liquor, CTG abnormalities, scalp pH, maternal indicators of infection, presentation and method of delivery.

**Document:**

1. **Apgar score**: (see resuscitation - Apgar score) at 1 and 5 minutes and every 5 minutes until Apgar > 7.
2. Umbilical arterial and venous blood gases (from placenta if no cord blood - arteries cross over veins on placental surface),
3. Time to sustained spontaneous respiration,
4. Neurological status (grading of HIE),
5. Multiorgan system function including:
   - Respiratory status,
   - Cardiac status (hypotension, cardiac ECHO),
   - Renal impairment - urine output, creatinine and electrolytes (watch for fluid overload and hyperkalaemia),
   - Liver dysfunction - LFT's,
   - DIC - coagulation profile (APTT, PI - if abnormal: fibrinogen degradation products and fibrinogen level),
   - Gastrointestinal - feed intolerance and NEC.

**Neurological examination:**

Perinatal asphyxia may result in **hypoxic ischaemic encephalopathy**. This is graded according to the classification of Sarnat and Sarnat\(^{11}\):

**Grade 1:** mild encephalopathy with infant hyperalert, irritable, and over-sensitive to stimulation. There is evidence of sympathetic over-stimulation with tachycardia, dilated pupils and jitteriness. The EEG is normal.

**Grade 2:** moderate encephalopathy with the infant displaying lethargy, hypotonia and proximal weakness. There is parasympathetic overstimulation with low resting heart rate, small pupils, and copious secretions. The EEG is abnormal and 70% of infants will have seizures.

**Grade 3:** severe encephalopathy with a stuporous, flaccid infant, and absent reflexes. The infant may have seizures and has an abnormal EEG with decreased background activity and/or voltage suppression.
Interventions

Limiting the exposure of neonates to perinatal asphyxia requires the use of appropriate obstetric monitoring of pregnancy and labour for risk factors of perinatal asphyxia. As yet, there is no data that intervention following signs of fetal distress alters outcome in terms of long-term morbidity. Appropriate and adequate resuscitation of the newborn is logical (see resuscitation).

Principles: clinical management is directed at appropriate and rapid resuscitation, and preventing hypoxia, hypercarbia and acidosis. Early arterial blood gas and blood sugar level should be performed and acidosis and hypoglycaemia treated. The infant's cardiorespiratory status should be monitored and signs of multiorgan system dysfunction sought and treated where appropriate.

1. **Correction of hypoglycaemia**: obtain an early BSL and correct hypoglycaemia - see hypoglycaemia
2. **Correction of acidosis**: obtain early ABG and correct respiratory acidosis (hypercarbia and acidosis) with appropriate ventilatory support. Correct persistent severe metabolic acidosis with bicarbonate over 30-60 minutes. Do not give bicarbonate to an infant not adequately ventilated (either spontaneously or mechanically) as it causes hypercarbia and a paradoxical acidosis - see acidosis
3. **Treatment of seizures**: Treat seizures initially with phenobarbitone. Failure to control with phenobarbitone - add phenytoin. Persistent seizures - add clonazepam (infant will require ventilation - see seizures).
4. **Temperature**: maintain core temperature 36 - 37°C, skin temperature 36 - 36.3°C. **Avoid hyperthermia**.
5. **Respiratory status**: monitor for hypoxia, acidosis and hypercarbia. Respiratory distress may have multiple aetiology including acidosis, meconium aspiration, sepsis or persistent pulmonary hypertension. Aim for normocarbia (pCO₂ 35-45). **Avoid hypoxia and hypercarbia**.
6. **Cardiac status**: blood pressure is a poor predictor of low cardiac output. Cardiac ECHO may identify hypovolaemia or poor myocardial contractility and low flow states - see hypotension. Use inotropes (dobutamine or dopamine) early if hypotension present or low flow states documented on ECHO.
7. **Fluid therapy and renal impairment**: Infants with anuria / oliguria should receive 40-60 mls / kg /day until adequate urine output documented. Regular assessment of fluid balance, electrolytes and creatinine should be performed - (watch for fluid overload and hyperkalaemia).
8. **DIC**: if evidence of bleeding or petecchiae: perform platelet level and a coagulation profile (APTT, PI - if abnormal: fibrinogen degradation products and fibrinogen level). Give vitamin K and replace clotting factors (eg with FFP).
9. **Gastrointestinal -feeding**: the decision to feed will depend on a clinical assessment of the severity of asphyxia and associated system dysfunction (respiratory distress, encephalopathy, hypotension and renal impairment). Feed intolerance is common and NEC may complicate perinatal asphyxia. **Breast milk is preferred**.

Interventions to decrease severity of hypoxic ischaemic encephalopathy:

**Probably effective:**

- **Hypothermia**: There have now been 4 published randomised controlled trial of hypothermia as neuroprotection after HIE. The two largest of these studies are the CoolCap study of selective head cooling and the NICHD trial of systemic hypothermia.
The CoolCap trial followed 218 infants to 18 months, and reported no significant difference in the primary outcome of death or severe disability in the infants treated with selective head cooling with mild systemic hypothermia after neonatal encephalopathy hypothermia (unadjusted: 55% vs 66%, p=0.10, OR 0.61 [95% CI 0.34-1.09]), or on any secondary outcome measures. Predefined subgroup analyses based on pre-randomization background aEEG amplitude abnormalities demonstrated no effect of delayed cerebral hypothermia on outcome in infants with severe aEEG abnormalities, but significant benefit in infants with intermediate (moderate) aEEG abnormalities (n=172: 48% vs 58%, P=0.021, OR 0.47 [95% CI 0.26-0.87]; adjusted P=0.009, OR 0.42 [95% CI 0.22-0.88]). The NICHD trial followed 205 infants to 18-22 months, and reported a reduction in the primary outcome of death or moderate/severe disability in infants treated with whole-body hypothermia (44% vs 62%, RR 0.72 [95% CI 0.54-0.95]; p=0.01).

Need further evaluation:

- **Allopurinol**: a single randomised controlled trial of allopurinol in preterm infants failed to show any benefit in reducing the incidence of periventricular leucomalacia. There is evidence from animal models that allopurinol may be additive to cerebral cooling as a neuroprotectant. Further study is required before this therapy is recommended in neonates with HIE.
- **Steroids**: animal data show increased mortality and no benefit in extent of neurological injury. Steroids are of no benefits in adult studies for head trauma, stroke or HIE. No randomised trial has been performed in neonates. Case series and a cohort demonstrated a temporary fall in intracranial pressure and no improved outcome in neonates with HIE. Further study is required before this therapy is recommended in neonates with HIE.
- **Mannitol**: insufficient evidence exists to recommend the use of mannitol.
- **Magnesium sulphate**: one dose comparison trial has been performed in newborn infants showing that MgSO$_4$ (400 mg/kg) has an unacceptable risk of hypotension; 250 mg/kg MgSO$_4$ was not associated with hypotension although respiratory depression can occur. Trials comparing MgSO$_4$ to placebo are required before it can be recommended.

Proven to be ineffective:

- **Barbiturates**: there is no data to support the use of prophylactic barbiturates for HIE (one RCT).
- **Naloxone**: there is no data to support the use of prophylactic Naloxone for HIE (one RCT).
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1. an event or condition during the perinatal period that is likely to severely reduce oxygen delivery and lead to acidosis; and
2. A failure of function of at least two organs consistent with the effects of acute asphyxia."

Grade of HIE (Sarnat and Sarnat) provides the best prediction of outcome

Hypothermia to between 33°C and 34°C initiated as soon as possible after delivery reduces mortality and disability in babies with HIE.

Naloxone and barbiturates are ineffective in treating HIE

Allopurinol, MgSO₄, Mannitol and steroids require further study in treating HIE

References


