RESPIRATORY PROBLEMS

Respiratory Distress Syndrome

Introduction: It is not possible to design a management plan that will satisfy all possible contingencies in a child with a respiratory distress syndrome. Hopefully these guidelines will provide a useful framework for planning the management of such infants but they should be regarded as guidelines rather than as golden rules.

Definition: In order to make the diagnosis of RDS two out of the following three signs must be present for more than one hour in the first four hours of life.

a) Tachypnoea - respiratory rate greater than 60/minute.

b) Recession - this may be subcostal or intercostal.

c) Expiratory grunting. This is a partial valsalva manoeuvre to increase peak expiratory pressure and decrease alveolar collapse.

The symptoms should persist for greater than 24 hours if the diagnosis of RDS is to be made. Note that cyanosis is not a necessary feature to make the diagnosis.

Differential Diagnosis: Remember that several other conditions can produce some or all of the features of respiratory distress in the first few hours of life. Careful examination, CXR and simple investigations will normally allow one to differentiate between them.

a) Hyaline membrane disease (Surfactant deficiency).

b) Transient tachypnoea of the newborn (delayed re-absorption of lung liquid).

c) Aspiration - meconium and rarely blood.

d) Cardiac - anatomical or persistent foetal circulation.

e) Infection - e.g. pneumonia, septicaemia, particularly group B beta haemolytic streptococcal infection.

f) Pneumothorax/pneumomediastinum.

g) Congenital abnormalities - e.g. tracheo-oesophageal fistula, diaphragmatic hernia, choanal atresia, hypoplastic lungs, etc.

Management of RDS: The management of RDS can be divided into prenatal and postnatal measures. The prenatal measures include the use of steroids the measurement of LS ratios and intrapartum monitoring of the foetus to avoid asphyxia. The benefits of operative delivery of preterm infants are unclear except with breech deliveries where vaginal delivery is associated with a marked increase in intracranial haemorrhage.

The postnatal measures are aimed at maintaining the infant's vital functions until spontaneous recovery occurs.

1. Minimal handling.

2. Maintenance of body temperature.

3. Fluid, electrolyte and caloric maintenance.

4. Maintenance of packed cell volume greater than 40%.

5. Correction or avoidance of acidosis (pH less than 7.25).

6. Monitoring of oxygen.

7. Ventilatory assistance.

   (i) Head box
   (ii) CPAP
   (iii) IPPV
   (iv) HFOV

8. Surfactant

1. Minimal handling
   Even slight handling can produce dramatic changes in arterial oxygen levels as shown by continuous oxygen electrodes. However avoidance of excessive handling does not mean that the infant should not have a complete rapid examination on admission. Absence of this examination may lead to failure to diagnose one of the conditions which can mimic hyaline membrane disease.

2. Maintenance of body temperature
   Aim to keep the environmental temperature in the neutral thermal range. If the temperature is above or below neutral range, oxygen consumption rises steeply. Surfactant synthesis ceases if body temperature falls below 35 degrees.

3. **<u>Fluids, electrolytes and nutrition</u>** See clinical guidelines.

4. Blood pressure and haemoglobin
   All sick infants with respiratory distress syndrome should have their blood pressure measured early in the course of their disease. Evidence exists that mortality rises rapidly if the systolic pressure is less than 40 mmHg. Hypotension may indicate either hypovolaemia but is also seen with severe acidosis and in the presence of severe infection or a pneumothorax. Treatment is aimed at treating the cause if possible. If the cause is hypovolaemia, then consider giving blood if the packed cell volume is low or falling, or plasma if the packed cell volume is high. We should aim to maintain the Hb greater than 12 in infants with severe respiratory distress. The haemoglobin needs to be measured on the first blood taken and should be checked daily in infants receiving IPPV. It is reasonable to cross match any infant receiving IPPV as almost all these infants will require transfusion, all request pedipacks on the initialform. Infants requiring less ventilatory support but with significant RDS should have maternal and infant blood sent for grouping and saving.

5. Correction of acidosis

Is the acidosis metabolic? (low HCO_3) or respiratory? (increased Pco_2). Obviously the management of these two causes differs. The importance of acidosis is that Surfactant synthesis is depressed if the pH falls below 7.25: <u>therefore pH of less than 7.25 demands investigation and treatment</u>.

If the acidosis is metabolic then one should consider volume expansion and/or inotropes. Sodium bicarbonate (4.2%) should probably only be given if the pH is less than 7.15 on more than one occasion. Sodium bicarbonate is very hypertonic and rapid administration can be associated with rapid fluid shifts and intraventricular haemorrhage. Therefore it is best to administer it extremely slowly unless the infant is extremely acidotic. (e.g. a rate of 1 to 2 ml. hourly in the burette).

6. Oxygen monitoring

RDS cannot be treated adequately without the ability to monitor inspired oxygen fraction (FiO_2) and arterial Po_2 (PaO_2). Hypoxaemia (PaO_2 less than 5 Kpa) will result in acidosis and decrease in Surfactant production. Hyperoxia (Po_2 greater than 10-11 KPA) is associated with Retinopathy of Prematurity in infants less than 32 weeks gestation and weighing less than 1500 grams.

Several methods are available for assessing hypoxia:

(i) 'Eyeball'

This is extremely deceptive and do not delude yourself into thinking you can judge Po_2 accurately. Particularly in the first few hours of life it is very simple to over-estimate the Po_2 level.

(ii) Capillary blood gases

If arterial gases cannot be obtained a capillary blood sample from a warm heel gives reasonable pH and Pco_2. The Po_2 is not accurate and therefore this technique should be avoided if possible for O_2 levels.

(iii) <u>Arterial catheters</u> - (see guidelines on ventilation)

We currently use umbilical, radial and posterior tibial arterial lines. Umbilical lines are easier to insert and tend to last longer but have the disadvantage of possibly being associated with necrotising entrocolitis. However in small (less than1500 gm) preterm infants with definite features of RDS an arterial catheter should be inserted in the first two or three hours of life, especially if an FiO_2 of greater than 30% is required. Great care must be taken with the securing of all arterial lines as severe haemorrhage is a major complication.

(iv) Percutaneous puncture

Puncture of the radial, and posterior, tibial arteries can be used. However the crying associated with this procedure can give deceptively low Po_2's. (Po_2 may drop by 50% during the procedure and may take 20 minutes to recover to the previous level). The femoral artery is taboo because of the risk of septic arthritis and large haematoma formation.

(v) Continuous skin electrodes

These have the advantage of being non-invasive and give continuous readings. However we still need to know pH and Pco_2 and therefore in children with RDS skin electrodes should be regarded as an adjunct rather than a replacement for arterial blood gases.

(vi) Saturation monitors

Oxygen therapy/monitoring

General considerations:

Supplemental oxygen must always be monitored.
There are risks of too little or too much oxygen. 1. Preterm infants are at risk of retinopathy of prematurity with levels that are too high. CLD may be caused by free radical damage. Too much oxygen may also prolong oxygen treatment in CLD. 2. Term infants are at risk of pulmonary hypertension if hypoxemic. 3. Preterm infants with chronic neonatal lung disease are at risk of pulmonary vascular hypertension if too hypoxic.

General consideration of pulse oximetry:

Any baby who is given oxygen therapy should have continuous pulse oximetry and monitoring. For the CLD infant going home on O_2, define the optimal O_2 flow (including overnight SaO_2 profile) then stop continuous monitoring, do spot checks only, and do not change O_2 flow within a week of discharge.
The accuracy of the pulse oximetry is about ± 2%. Remember the oxygen dissociation curve in interpreting the results. Before believing any pulse oximetry reading, one should always double-check for artefacts and errors in reading or fixing of the device. If there is still uncertainty, an arterial blood gas may be warranted.
Be sure to decrease FiO2 after desaturations and avoid overshooting oxygen levels too high. Remember that babies with apnoea may rather benefit from stimulation or bagging rather than increasing the oxygen alone.

Recommendations for saturation limit settings according to infant category (reviewed May 2012):

	Infants	Alarm Limits
Initial saturation limits	Very low birth weight infants (< 34 weeks at birth)	84-94%
	Low birth weight infants (>34 weeks at birth)	89-96%
	Term/post term infants (at birth)	94% (lower limit)
Changes at 28 days and/or >36 weeks	Very low birth weight infants (> 28 days old)	89-96%
	Infant with Chronic Lung Disease **AND** 36 weeks corrected	94% (lower limit)
	Infants with congenital malformations of the heart	As prescribed by doctor

A different range from the above for an individual baby should be prescribed and signed by a doctor.

Ref: 1. Newborn Services Medical Guidelines, Auckland District Health Board, published August 2002 **2.** Lloyd J, Askie L, Smith J, Tarnow-Mordi W. Supplemental oxygen for the treatment of prethreshold retinopathy of prematurity (Cochrane Review) **3.** British Association of Perinatal Medicine, report of 2nd working group, Guidelines for good practice in the management of Neonatal Respiratory Distress Syndrome, November 1998.

(PD Dr Heike Rabe, August 2003, review date August 2005)

8. Surfactant

Which babies receive surfactant?

Intubated preterm babies - regardless of gestation or weight with a clinical diagnosis of IRDS requiring ventilation and increased inspired O_2 concentration.

Surfactant is given via the ET tube (and not by any other route). It is not currently thought justified to intubate solely for the purpose of administering surfactant and the decision to intubate a baby should be based on traditional criteria for managing developing RDS. However, the proven benefits of early surfactant administration dictate that if an infant <30 weeks gestation requires intubation for labour ward resuscitation the ETT should usually remain in situ and surfactant given. If there is doubt about ETT position, transfer ventilated to the neonatal unit and confirm position by CXR prior to administration.

Summary:

1) Surfactant is given to intubated babies.

2) The aim should be to administer surfactant early, within 2 hrs of birth in intubated pre-term babies (or intubation if this is delayed).

a) Admit and stabilise baby

Ensure adequate ventilation - Chest movements
Surface O_2 monitor (Transcutaneous but saturation monitoring helpful at this stage as well) Arterial blood gas (as soon as baby is settled in). Consider sedation (rarely paralysis).

IVI 10% dextrose

Blood cultures

Antibiotics

Ensure adequate circulation. Treat further as indicated. IV 4.5% HAS, 10 mls/kg over 30 mins, +- Dopamine 5 mcg/kg/min initially.

Nurse baby on back with head central and ETT vertical.

b) Obtain CXR

This is to:

1) Check ETT position - a wrongly positioned tube may lead to uneven distribution of surfactant.

2) To exclude other diagnoses - pneumothorax, diaphragmatic hernia, pneumonia, TTN.

3) To support but not necessarily confirm the clinical diagnosis of IRDS.

Do not delay requesting X ray. Remember the aim is to give surfactant within 2 hrs.

c) <u>Obtain arterial access for gas and BP monitoring</u>

This may be peripheral or umbilical but should not hold up the process of surfactant administration significantly. Some form of arterial blood gas monitoring is necessary during surfactant administration but if access proves difficult could be provided by 'stab' gases.

Remember the aim is to administer surfactant within 2 hrs of intubation.

d) <u>Ensure adequate monitoring</u>

You will need:

a recently calibrated transcutaneous Po_2 (and ideally Pco_2) monitor,

a saturation monitor,

ECG and BP monitoring.

e) Administer Surfactant

Reasons for possible delay in administration:

Uncertainty of diagnosis - contact consultant

Baby very unstable

In general surfactant administration should be a priority task, with the aim of giving the first dose within 2 hrs of intubation, therefore if you have other tasks/deliveries to attend or if you are inexperienced in surfactant administration or ventilator management help should be summoned.

f) Adjust ventilation as indicated

Base initial changes on chest movement and monitors but repeat blood gas about 1/2 hrs after administration, earlier if concerned.

Stay with baby until acute effects stabilised.

Remind nurse to try to avoid suctioning for as long as possible after surfactant administration, ideally several hours.

g) Administer subsequent doses as indicated, 6-12 hrly if FiO_2 >30%

h) Monitor baby for signs of PDA

Monitor baby for symptomatic left to right shunt through PDA. Surfactant administration may be associated with pulmonary haemorrhage probably due to the more rapid fall in pulmonary artery pressure.

Consideration should be given to active treatment of the PDA.

ADMINISTRATION OF SURFACTANT – CUROSURF

Indications:

Prophylactic use in preterm infants
Rescue treatment of babies with RDS

Dosage:

Prophylaxis: single dose of 100-200mg/kg (1.25-2.5ml/kg), given as soon as possible after birth (CXR not required). A further dose of 100mg/kg may be given as early as 6 hours after the first and another 100mg/kg dose 12 hours later for persistent RDS.

Rescue: single dose of 100-200mg/kg (1.25-2.5ml/kg), given as soon as possible after diagnosing RDS. Up to two further doses of 100mg/kg at 12 hourly intervals may be given.

Administration:

Single dose vials of 1.5ml or 3ml contain either 120mg or 240mg of phospholipid fraction. Curosurf is stored 'ready for use' refrigerated at 2-4^{o} C. While preparing baby for administration take the surfactant from the fridge and allow it to warm to room temperature. Place vial in incubator or hold in hand to warm. About 30 minutes should be allowed for this. Do not warm artificially as this will inactivate the surfactant. Once room temperature is reached the efficacy of the surfactant is gradually lost and therefore delay before administration should be avoided.

Use an aseptic technique to administer surfactant.

Invert vial gently a few times to mix and draw up surfactant dose into syringe. A little air left in the syringe will ensure all the Curosurf is expelled from the catheter on administration.

Trim 5 FG end-hole catheter to just reach the end of the ET tube from the point of entry into the circuit, i.e. the tube length + ETT connector but also to include the ventilator T-piece if using the suction port. Attach tube to syringe containing surfactant.

Position baby supine with ETT central. It may help to support ETT with strapping and/or the baby's head with towel rolls. Check the ETT position is correct. If, prior to surfactant administration, the infant is on 'trigger' ventilation it will be necessary to switch to IPPV as the administration will interfere with triggering.

Continuous monitoring of $tcPaO_2$ or oxygen saturation should be in place.

Give the full dose as a rapid ETT bolus using one of the following techniques:

Either: As deftly as possible, disconnect infant from ventilator, insert catheter, syringe surfactant into trachea. Withdraw catheter. Reattach to ventilator and adjust ventilation as needed.

The data sheets advise attaching the bag and mask and inflating the lungs with 5 controlled breaths before reconnecting to the ventilator. It is not clear whether this has any particular benefit.

Or: alternatively and to be preferred the catheter can be inserted through the suction port of the ETT connector, allowing surfactant administration without disconnection from the ventilator. Bagging should not be necessary.

Care following administration:

Confirm chest movement. The initial effect of the surfactant bolus may cause a temporary mechanical obstruction to ventilation. It is usually transient and suctioning of tube is not usually necessary and is to be discouraged.

Be prepared to make rapid adjustments to ventilatory settings as compliance may improve rapidly increasing the risk of hyperoxia, overdistension and air leak.

Adjust FiO_2 on basis of monitoring. Once the oxygen requirement is dropping significantly and chest movement is restored reduce peak pressure and/or I time observing for chest movement. Check a blood gas when initial adjustments complete.

Side effects:

The rapid action of natural surfactant can lead to a sudden increase in pulmonary blood flow. However, there is no evidence of direct links between Curosurf administration and an increased incidence of pulmonary haemorrhage.
Trials suggest that there is a reduced incidence of air leak in preterms with RDS when treated with Curosurf.

References:

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Speer CP, Robertson B, Curstedt T et al. Single versus multiple doses of Curosurf. Pediatrics 1992; 89: 13-20

ADMINISTRATION OF SURFACTANT - TROUBLE SHOOTING

1. Surfactant bubbling up ETT or out of baby's mouth	Administration of surfactant too fast - stop for a period and restart at lower rate. Tube blocked or malpositioned - if chest not moving increase peak pressure and/or insp. time. If ETT close to carina try lifting out a little.Consider possibility of accidental extubation
2. Deterioration in blood gases during administration	Usually due to mechanical blockage of airway. Will usually respond to slowing down of rate of administration and/or increase in peak pressure. Rarely needs suctioning and this should be avoided if possible.
3. Acute deterioration possibly with bradycardia	Possibly as in 2 (is the chest moving?) but ?Surfactant too cold.
4. Late deterioration in blood gases	Could obviously have a number of causes, underventilation being the most likely, but if you have used one of the 'animal' surfactants with rapid effect overventilation should be considered - may be indicated by low Pco_2, low BP, further deterioration on increasing the ventilation.

5. No or poor response to administration	Usual after Exosurf which often shows little acute response and acts over some hours. May indicate other pathology either instead of or as well as surfactant deficiency e.g. sepsis, pulmonary hypertension,pulmonary hypoplasia, extreme pulmonary immaturity. Discuss treatment options with Consultant.
6. Blood from ETT	May be due to infection or trauma but concern is that this is true pulmonary haemorrhage secondary to large left to right shunt through PDA. See guidelines for pulmonary haemorrhage, assess ductal status and consider strategies to close duct.

(May 2002 - FW, updated May 2004, review May 2006)

Meconium Aspiration syndrome (MAS)

Definition:

Meconium aspiration syndrome is defined as respiratory distress in an infant born through meconium stained liquor whose symptoms cannot be otherwise explained.

Incidence:

Approximately 13% of all live births are complicated by meconium stained liquor. The incidence of meconium passage increases with gestational age and reaches 30% at 40 weeks gestation and 50% at 42 weeks. It is rare for the fetus to pass meconium in utero before 34 weeks gestation and should raise the suspicion of GI obstruction (bilious vomiting masquerading as meconium) or perinatal infection such as Listeria (Fetal diarrhoea). Fortunately, only 5% of babies born through meconium stained liquor i.e 0.65% of live births develop meconium aspiration syndrome.

Mechanism of meconium aspiration:

Passage of meconium in utero is not independently associated with fetal hypoxia. However, passage of meconium and concomitant fetal hypoxia increases the chances of meconium aspiration syndrome. Continued fetal hypoxia leads to in utero ‘gasping’ of the fetus following primary apnoea leading to inhalation of meconium stained fluid into the airways. Thus the timing of meconium aspiration often is intrapartum rather than after birth.

Resuscitation:

The 2005 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science and Treatment Recommendation (CoSTR) has been adopted by the European Resuscitation Council.

It clearly states that attempts to aspirate meconium from the nose and mouth of the unborn baby, while the head is still at the perineum, is no longer recommended as it does not prevent meconium aspiration syndrome. After birth the following algorithm can be used -----

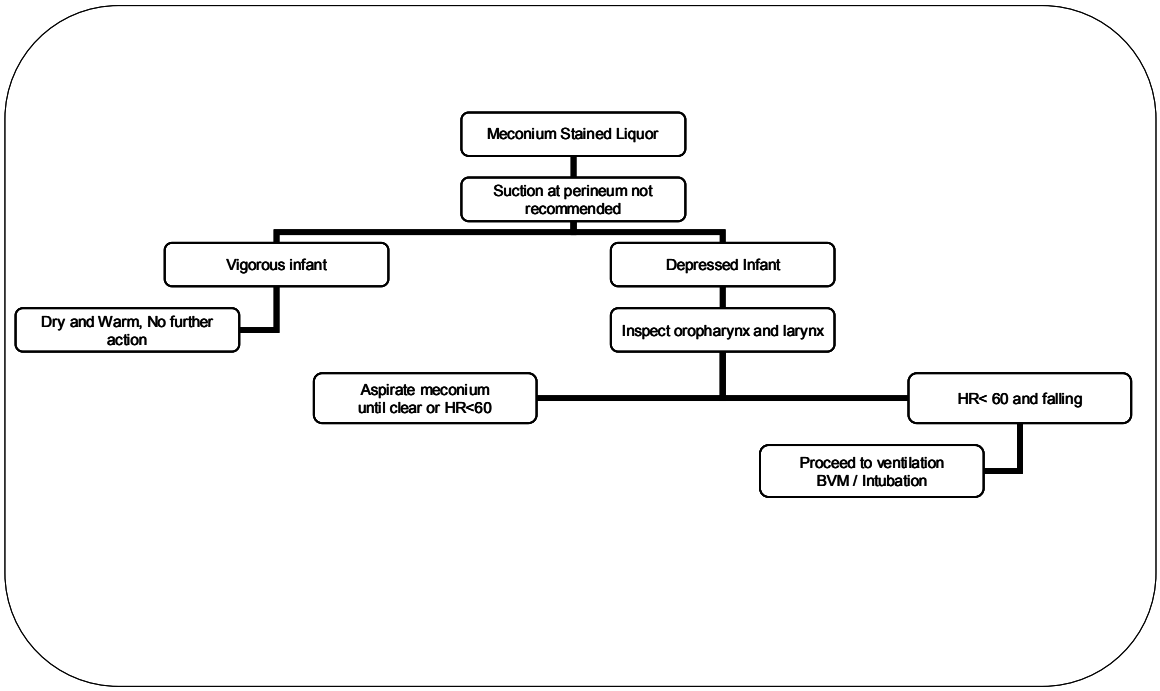

Figure A: Algorithm of resuscitation for babies born through Meconium stained liquor

Vigorous infant:	Depressed infant:
HR>100/min Active movements Flexed tone Pink centrally	Hypotonic HR<100/min Poorly responsive Pale / Cyanosed

Suction should be done under direct vision with a large bore catheter (Black) or preferably a Yanker sucker. Negative suction pressure should be set between 80 and 100 cm of water.

The balance is between clearing the airway of thick meconium to prevent mechanical obstruction and entry of meconium into lower airways during subsequent ventilation and oxygenating a baby who may already be dangerously hypoxic. Heart rate is a very good guide to assess severity and duration of asphyxial insult.

Babies born with meconium stained liquor who require resuscitation at birth and show any signs of respiratory distress (Grunting, RR >60/min) should be admitted to the NNU.

All other babies born with meconium-stained liquor should be admitted to transitional care and observed on the postnatal ward very closely using the “meconium obs” chart (hourly respiratory rate, heart rate, colour and temp for 4 hours and then 2

hourly for 8 hours).Babies should be observed during feeds and managed according to the breastfeeding guidelines during this period.

All babies on meconium observation should be reviewed at 12 hrs by a trained midwife. If the following criteria are fulfilled, the observations on the baby may be discontinued:

- Respiratory rate 45 or below
- Mucous membranes of tongue (central colour) pink
- Baby is warm and well perfused
- Heart rate 110-140 awake – may be less than 110 if deeply asleep
- Normal tone and activity
- Baby has had a normal feed

If any of these criteria are not fulfilled, the midwife should ask for a paediatric review. Note that, in a baby who is breastfed, they may not have had a proper feed within the first twelve hours but if they have not the baby should be carefully assessed to make sure there is nothing that may be interfering with feeding. If the baby's observations are abnormal, the baby should be admitted to NNU for a chest x ray and blood gas and consideration of blood cultures and intravenous antibiotics.

Mechanism of lung injury and symptoms:

Meconium is toxic to lungs and the mechanism of hypoxia and lung injury is thought to be multifactorial –

- Mechanical obstruction of airways
- Chemical pneumonitis
- Inactivation of surfactant
- Vasoconstriction of pulmonary vessels
- Activation of complement

The lung pathology has varying combination of alveolar inflammation, atlectasis, airway obstruction and air trapping which makes the treatment of this condition very difficult. The meconium and subsequent inflammation of distal airways can cause a ball valve obstruction resulting in air trapping and ventilation perfusion mismatch. There is a high risk of pneumothorax estimated to be 15-33%.

Severe MAS is associated with features of PPHN. In fact sometimes PPHN can be the predominant clinical problem rather than the meconium aspiration. This is due to pulmonary vasoconstriction caused by vasoactive mediators released secondary to in-utero stress and direct effect of bile acids present in the meconium. Displacement of surfactant from the alveolar surface and its direct inactivation by meconium results in atlectasis, reduced lung compliance and poor oxygenation.

Management Principles:

Once on NICU, conventional therapy of MAS is aimed to improve oxygenation while minimising barotrauma that may lead to air-leak syndromes. Proper oxygenation

need to be achieved rapidly in order to avoid the cascade of hypoxaemia and pulmonary hypertension

Initial management:

1. Babies admitted to NNU should be assessed rapidly with regards to work of breathing, oxygen saturations (Right hand and lower limb), oxygen requirement systemic perfusion and blood pressure and blood gases.

2. Babies with mild respiratory distress and FiO2 less than 0.4 could be tried on ambient oxygen / CPAP for short period. However, due to the high risk of pneumothorax, a low threshold for elective intubation and ventilation should be adopted particularly in vigorous and large babies who do not tolerate CPAP.

3. Intubation should be elective with adequate fentanyl premedication and paralysis

4. All babies should have a blood culture and started on IV fluids and first line antibiotics. Early chest X-ray to assess optimum lung inflation is recommended

5. Babies who will need ventilation should have an arterial line and a central venous line (UVC with tip just above the diaphragm)

Ventilation strategy:

No particular ventilation strategy has been shown to be superior to any other methods in clinical trials. However, it seems logical to ventilate these babies with –

1. Slower rates and higher expiratory times (I:E ratio 1:2, 1:3) if possible to avoid hyperinflation.
2. PEEP should be optimised to allow adequate functional residual capacity but to avoid hyperinflation. Chest X-ray early on may be helpful
3. Depending on the degree of atlectasis, a high PIP may be required to ensure adequate tidal volume
4. Adequate sedation and synchronised ventilation are important because of the high risk of pneumothorax. Paralysis is frequently required.

Natural surfactant replacement therapy has been shown to improve oxygenation and reduce the need for ECMO in randomised controlled trials. In the recent Cochrane meta-analysis, natural surfactant (100-150mg/kg/per dose up to a maximum of 4 doses) resulted in a reduction in pneumothorax and need for ECMO (typical risk difference -0.17, numbers needed to treat (NNT) =6). Trials of dilute surfactant lavage have been undertaken with increased oxygenation and reduced duration of mechanical ventilation. However this procedure is complicated by hypotension and transient hypoxaemia and further trials are required before this therapy could be recommended as routine. However it could be considered as “rescue therapy” if there is no response to optimal medical management and while waiting for ECMO.

Although there are no trials to prove that HFOV is superior to conventional ventilation, clinicians have found it useful to use HFOV if PIP approaches 24 cm of water, with difficulty in oxygenation. HFOV has been shown in experimental animal trials to reduce movement of meconium into lower airways and increase meconium

clearance. In the context of established PPHN, the combination of HFOV and INO has been shown to be better than conventional ventilation and INO in randomised controlled trials of term babies with significant parenchymal lung disease and PPHN

Aggressive chest physiotherapy has shown some benefits in animal models of meconium aspiration syndrome but human data is sparse. Local resources of specialist physiotherapy and facilities to institute upgraded intensive care rapidly such as ECMO should be taken into account before recommending such therapy.

MAS and PPHN:

As severe MAS is associated with features of PPHN, further assessment to assess pulmonary artery pressure, myocardial contractility and degree of right to left shunting should be undertaken. For assessment and detailed management see PPHN guideline.

These babies are often the sickest and most complex babies on the unit and can deteriorate rapidly. Discuss with the consultant early

The general principles of management of PPHN are (For details refer to PPHN guideline)

1. Liberal oxygen to keep postductal saturation >95%
2. Deep sedation and paralysis. Vecuronium infusion ensures controlled paralysis
3. Blood gases should be maintained aiming for pH around 7.4 and pCO_2 in normal range of 4.5 -5.5 kpa
4. Systemic blood pressure should be maintained at or above the pulmonary pressures to reduce the R-L shunting. Generally systemic blood pressure should be maintained above 45-50 mm Hg but echocardiography could be useful to provide guidance. This may need early use of inotropes usually a combination of dopamine (increases peripheral vascular resistance) and dobutamine (increases effective cardiac output)

5. Calculate oxygenation index [HOW to calculate OI: **Mean airway pressure (cmH_2O) x FiO_2 (%) / PaO2 (mmHg)** [*To convert kPa to mmHg multiply by 7.5]*. Start Nitric Oxide when OI approaches 25 (See NO guidelines). Ensure systemic blood pressure within target range before starting NO

6. Discuss with an ECMO centre early (see ECMO guidelines - the logistics of identifying a cot, and transfer may take a long time) It is possible to discuss a *potential* baby for ECMO with an ECMO centre without making an actual referral

Other systems:

1. Watch out for features of CNS irritability. Baseline cranial USS should be undertaken as soon as possible. CFM monitoring may be useful if baby paralysed and there are concerns for ongoing seizures or peinatal asphyxia

2. Maintain PCV at 55-60. Check U&E, LFT, coagulation profile

3. Monitor urine output. Aim for urine output >1ml/kg/hr

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Guidelines on Persistent Pulmonary Hypertension of the Newborn (PPHN) – May 2006

Introduction:

Persistent pulmonary hypertension of the newborn (PPHN) is the result of elevated pulmonary vascular resistance (PVR) to the point that systemic venous blood is diverted to some degree through fetal channels (i.e. the ductus arteriosus and foramen ovale) into the systemic circulation bypassing the lungs, resulting in systemic arterial hypoxemia.

The incidence of PPHN is estimated to be 0.2% of term infants. It is more common in babies greater than 34 weeks gestation but is also seen in preterm infants mainly in the context of severe RDS or sepsis. Higher incidence is reported in pregnancies with no antenatal care and with the use of tobacco and other illicit drugs

Pathophysiology:

A proper understanding of the balance between pulmonary and systemic vascular pressures is essential for effective management of infants with PPHN. During fetal life placenta is the primary source of oxygenation and is a low resistance / low pressure vascular bed. In contrast the pulmonary vessels in the fetal lung are vasoconstricted in response to low arterial oxygen tension and allow only 5-10% of cardiac output to go through and thus not involved in gas exchange. During the first few minutes of postnatal life the pulmonary arterial pressure drops by 50% and the pulmonary blood flow increases by ten-fold to match lung perfusion with the onset of ventilation. Failure of this pulmonary vasodilatation leads to inability to establish oxygenation during postnatal life.

The regulation of pulmonary vascular tone is determined by the balance between constrictor and dilator mechanism.

The key vasoconstrictors are endothelins, thromboxane and mediators of cytochrome p450 pathway. Endothelin 1 is produced by endothelial cells in response to hypoxia, cytokines, cell wall stress, growth factors and free oxygen radicals. Endothelin 1 is converted to endothelin A (ETA) and endothelin B (ETB), both of which are potent vasoconstrictors.

The key mediators of vasodilatation are nitric oxide (NO) and prostaglandins released by vascular endothelium. Both vasodilators act by production of cGMP and cAMP respectively from GTP and ATP in smooth muscle cells of pulmonary blood vessels. These second messengers regulate K^{+} and Ca^{++} efflux from cytosol resulting in relaxation and consequent vasodilatation.

In PPHN there is an imbalance of vasoconstrictors and vasodilators. Endothelin levels are raised in infants with PPHN and decreased production of NO and Prostacyclin. The mechanism and possible strategies to reverse this process are summarised in Figure 1.

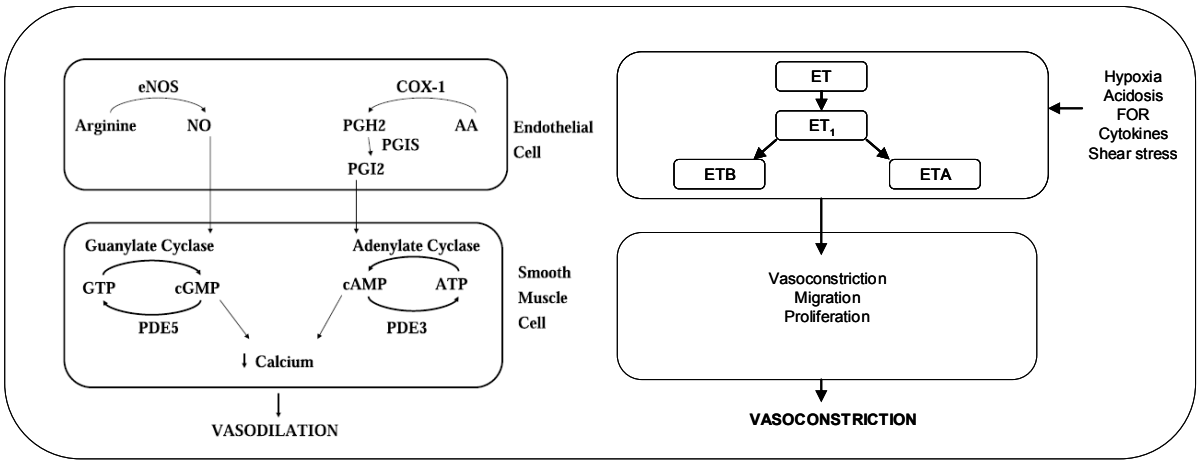


Figure1: Pathogenesis of pulmonary hypertension
NO – Nitric oxide, cAMP – cyclic adenosine monophosphate, cGMP-cyclic guanosine monophosphate, ET –endothelin
PDE5- Phosphodiesterase enzyme 5, FOR – Free oxygen radicals, AA – arachidonic acid, PGI_2 - Prostacyclin

Haemodynamic consequence of PPHN:

The elevated pulmonary artery pressure decreases pulmonary blood flow and leads to right-to-left shunting across the patent ductus arteriosus or the patent foramen ovale leading to systemic hypoxia. The condition is often aggravated by associated left ventricular dysfunction, which leads to pulmonary venous congestion and oedema.

Conditions associated with PPHN:

1. Associated with parenchymal lung disease
    a) Meconium aspiration syndrome (50%)
    b) Pneumonia /sepsis (20%)
    c) Respiratory distress syndrome (5%)

1. Not associated with parenchymal lung disease/systemic disorder – Idipathic (Primary) (20%)

2. Others – (5%) – asphyxia, maternal diabetes, polycythaemia etc

Congenital diaphragmatic hernia (CDH) is also often associated with PPHN. However infants with CDH have severe underlying pulmonary hypoplasia and the course and management is different from other causes of PPHN

Diagnosis:

- Severe hypoxaemia (<6 kpa) despite 100% oxygen & disproportional to associated lung disease
- Pre and post ductal saturation difference of 3%, PO2 difference >3 kpa (may not be present if the majority of shunting is at the atrial level)
- Structurally normal heart on echocardiography with evidence of right to left shunting across the patent ductus arteriosus or foramen ovale
- Underlying predisposing factors e.g. meconium aspiration syndrome, CDH

Principles of management:

1. Eliminate reversible factors that worsens pulmonary vasoconstriction – hypothermia, acidosis, hypoxia etc
2. Improve cardiac contractility and systemic blood pressure by judicious use of volume and inotropes thus reducing the right-to-left shunting
3. Promote pulmonary vasodilatation by specific use of drugs such as NO, prostacyclin, phosphodiesterase inhibitors
4. Maintain oxygenation by the above measures until the primary condition improves or spontaneous postnatal pulmonary vascular adaptation occurs

Investigations to establish underlying cause:

Chest X-ray

Blood culture, FBC, U&E, CRP, Ca++, Mg^{++}, Clotting, blood glucose

Further assessment and management:

Babies with PPHN are critically ill and complex to manage. Involve the neonatal consultant in the management early

General measures:

a) Maintain normal temperature, blood glucose, calcium and PCV (0.4-0.55)

b) Initiate septic screen and start on first line antibiotics

c) Obtain arterial access and central venous access (usually UAC and UVC with tip just at the diaphragm). The lines should be inserted swiftly by the most experienced and skilled person available. Monitor invasive blood pressure continuously.

d) Minimal handling -- the pulmonary vascular resistance in these infants is so labile that small changes in oxygenation or pH caused by handling and stress can result in rapid changes in PVR and instability which may take many hours to rectify

e) Sedate adequately with infusions of morphine / midazolam infusions. Monitor blood pressure carefully and avoid systemic hypotension

f) Paralysis is often required and is best achieved with a continuous infusion of vecuronium

g) Aim for oxygen saturations above 95% and Po2 > 10 Kpa and pre-post ductal saturation difference of <3%

h) Perform baseline cranial USS to rule out intracranial haemorrhage and large intraparenchymal lesions. Presence of more than Grade 2 intraventricular haemorrhage is a contraindication for using nitric oxide

Ventilation:

a) Optimum lung inflation is fundamental in the treatment of respiratory failure. Alveolar recruitment enhances the distribution of inhaled nitric oxide (INO) to the pulmonary circulation

b) Aim for a pH within the normal range (7.35-7.45) and can usually be achieved by maintaining pco_2 between 4.5-5.5 Kpa and correcting any concomitant metabolic acidosis. Ph has a more direct effect on the pulmonary vasculature than Pco2 and acidosis should be avoided at all costs. Aim for a PO_2 > 10kpa if possible. Hypocarbia (Pco2 < 4.5 kpa) should be avoided as it promotes cerebral vasoconstriction with its consequences

c) It may be necessary to use high inspiratory pressures to maintain blood gas parameters and an adequate oxygenation. Adjust PIP and PEEP to achieve lung inflation equivalent to 8-9th posterior ribs on the chest X-ray.

d) It is important however, to avoid hyperinflation as it not only compress the alveolar vascular supply but also causes systemic hypotension thus aggravating the right-to-left shunt

e) For meconium aspiration syndrome and RDS use surfactant. Repeat in 4-6 hours if good response to the first dose and oxygen and ventilatory requirement rebounds. Surfactant therapy has been shown to decrease ECMO use / mortality in term infants with hypoxic respiratory failure, particularly when given at an OI<22

f) If PIP exceeds 25 cm, consider HFOV (For details see HFOV guidelines). The combination of HFOV and INO has been shown to be better than conventional ventilation and INO in randomised controlled trials of term babies with significant parenchymal lung disease and PPHN

g) The overall use of surfactant and HFOV in PPHN has increased in recent years (reaching 80% in some RCTs of early INO therapy) and may have contributed to the lower incidence of ECMO and death in this condition

h) Calculate Oxygenation index (OI) and start nitric oxide when OI reaches 25

Preparation for setting up nitric oxide can take a long time and thus this process should be initiated when OI approaches 20

Oxygenation index (OI) = MAP $\times$ 100$\times$ FiO_2 / PaO_2 (mmHg)

MAP = Mean airway pressure
PaO_2 = Partial pressure of oxygen in arterial gas
1kpa = 7.6 mm Hg

<u>Cardiovascular support:</u>

a) Echocardiographic assessment – The role of echocardiogram in management of PPHN is several fold ---

a) Exclusion of congenital heart disease – This is particularly important before commencing nitric oxide to rule out lesions that are dependant on a right to left shunt across the ductus arteriosus for survival

b) Confirmation of the diagnosis and estimation of pulmonary arterial pressure (PAP)
Estimation of PAP is an important aspect of the diagnosis and management of PPHN. There are a number of echocardiographic indicators which directly or indirectly measure PAP

- Tricuspid regurgitation: It is the most accurate way of measuring PAP. The peak velocity of the TR jet on Doppler assessment is a direct indicator of right ventricular pressure and thus PAP. This is usually measured in the apical 4 chamber or the parasternal long axis view of the tricuspid valve

  Using the Bernoulli's equation ($p=4v^2$ where v is the peak velocity of the TR jet) the pressure in the RV can be estimated as

  RV pressure = RA pressure + $4v^2$

- Ductal Flow: The direction and velocity of the ductal flow can give useful information on the PAP. Pure R-L shunting occurs when PAP is higher than the aortic pressure through out the cardiac cycle. If the PAP is equal to the systemic pressure, L-R shunting occurs in diastole and right to left in systole. Bidirectional shunt through the duct is common and normal in the first 12 hours of life.

- Atrial Shunting: Some degree of right-to-left atrial shunting through the patent foramen ovale is common, although it is rare for this to be purely right-to-left (pure right-to-left flow is Total Anomalous Pulmonary Venous Drainage [TAPVD] till proven otherwise!). Bowing of the interatrial septum to the left is commonly seen.

- Other indicators: The ratio of time to peak velocity (TPV) of the pulmonary blood flow and the Right ventricular ejection time (RVET) can indirectly indicate PAP. This is measured by Doppler with the gate in the middle of the pulmonary artery just beyond the pulmonary valve. With PPHN there is a fall in the TPV/RVET ratio due to sudden acceleration of blood flow to the pulmonary artery followed by early deceleration of the pulmonary blood flow due to increased resistance. A TPV / RVET ratio <0.21 suggests significantly raised PAP and a value 0.21-0.3 suggests moderately raised PAP.

- In PPHN, the period of isovolumetric contraction (between closure of the tricuspid valve and the opening of the pulmonary valve - RPEP, Right Ventricular Pre-Ejection Period) is prolonged as the RV generates enough pressure to open the pulmonary valve, resulting in an elevated RPEP/RVET ratio. There can be poor repeatability of these measures but they do have a role when you cannot measure the velocity of the TR jet.

a) Assessment of left ventricular function – Elevated PAP is generally associated with decreased pulmonary blood flow and increased pulmonary vascular resistance. Not uncommonly, there is enlargement of the RV and RA, as well as the main pulmonary artery. There may be flattening or even bowing of the interventricular septum to the left if RV pressures exceed LV

pressures. As cardiac output is dependent on venous return to the RA and LA, cardiac output (both RVO and LVO) is frequently reduced with PPHN. Severe PPHN may be associated with LVO below 100ml/kg/min (normal 150-300ml/kg/min) Quantitative assessment of cardiac function may assist with decisions and assessments of the roles of inotropes, inhaled nitric oxide, and other interventions affecting cardiac output. If the LA and LV appear under-filled, it is critical to exclude TAPVD.

In an emergency situation INO must be started prior to an Echo, but this should be performed as soon as possible

b) Systemic blood pressure:

a) Try to maintain systemic blood pressure close to and above the pulmonary arterial pressure (usually >50 mm Hg in term babies). Presence of TR will help estimate the pulmonary arterial pressure and form a guide for the desired systemic pressure(target 5 mm Hg above pulmonary pressure)

b) This is achieved by giving volume and inotrope infusion. Give 10mls/ Kg of saline if the IVC appears collapsed (particularly important if oscillated)

c) Start on 5-10mcg/kg/min of dopamine via central line to raise systemic blood pressure. If there is evidence of left ventricular dysfunction add in dobutamine at 5-10 mcg/kg/min. In severe ventricular dysfunction use of adrenaline may be necessary

<u>Pulmonary vasodilatation:</u>

Strategies for pulmonary vasodilatation will work best once

- Optimum lung inflation achieved – Surfactant, HFOV, 100% oxygen etc
- Systemic blood pressure is within normal range and Left ventricular function is optimised as much as possible
- Correction of aggravating factors – hypothermia, acidosis, anaemia / polycythaemia hypoglycaemia etc

<u>Nitric Oxide</u>

The use of INO has revolutionised the management of PPHN.

INO is a selective pulmonary vasodilator and has several advantages as compared to other available agents
Its effect is confined to the pulmonary vascular bed due to its rapid inactivation by haemoglobin in the pulmonary circulation. Thus INO has very short half life of minutes
Its vasodilator effect is not altered by extrapulmonary shunts
It has the ability to improve ventilation-perfusion mismatch as pulmonary vasodilatation occurs in the ventilated sections of the lung
INO causes vasodilatation even in the presence of endothelial cell injury and dysfunction

When to start INO

Studies which showed a benefit of INO in term babies with PPHN in reducing ECMO/ death were able to recruit babies at an OI>25. A more recent study demonstrated that beginning INO earlier, for an OI > 15 did not change the primary outcome of incidence of ECMO/ death.

It is known that in rapidly deteriorating hypoxic infant, the OI at which treatment is initiated is significantly higher than targetted (most babies in earlier RCTs of INO reached an OI of >35 at recruitment). Therefore INO set up should be initiated as the OI approaches 20

Check list before starting INO (Term babies):

No evidence of uncorrectable bleeding disorder Platelet count should be >50, APTT <72 and INR <2 (INO increases bleeding time but this reversed within 1 hour of stopping therapy)
No lethal chromosomal abnormality

Starting dose:

The AAP recommended starting dose for INO in term babies with respiratory failure is 20 ppm. The maximum fall in directly measured pulmonary arterial pressure is also demonstrated at 20 ppm although improvement in oxygenation occurred at low doses of 5 and 10 ppm.

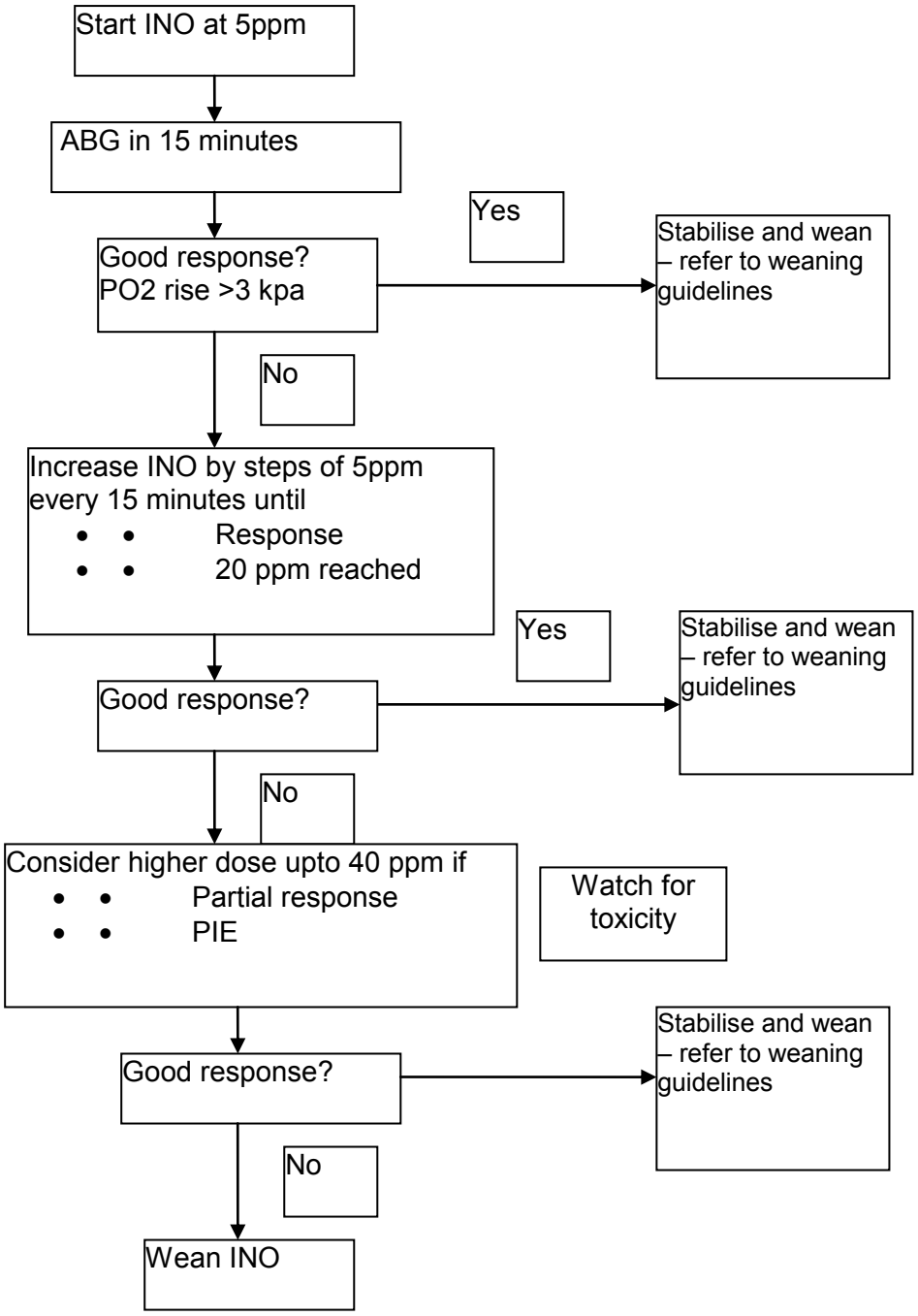
However, two recent randomised controlled trials showed that low doses of 5-6 ppm was equally effective in improving oxygenation as 20ppm. Starting at lower doses also ensures quicker weaning time and less chance of adverse effects.

There is also evidence that starting INO at a very low dose of 2 ppm may alter subsequent response. Therefore the data suggests that the optimum initial dose to start INO therapy may be close to 5ppm

Judging response to INO – success criteria

Repeat ABG after 15 minutes of starting INO. A response is defined as a rise in PO2 of greater than 3 kpa after starting INO. Other clinical clues are a reduction in FiO2 >0.1 and a reduction in the pre-post ductal saturation difference.

Optimising dosage of INO:



Other approaches in term babies such as starting on 20ppm of INO and weaning down to the minimum tolerated dose is also an accepted way of optimising dosage

Monitoring:

Babies on nitric oxide need careful monitoring.

NO_2 levels: All nitric oxide delivery system have in line NO_2 monitoring. NO_2 is toxic to the lung and its level should be maintained less than 2 ppm. Levels above 1 ppm should be taken as warning and delivery system failure investigated. At levels >2 ppm INO dosage should be reduced

Methaemoglobin:

The binding of NO to haemoglobin results in the production of methaemoglobin. This is not in itself toxic, but methemoglobin is not able to carry oxygen. Therefore high levels of methaemoglobin will reduce the oxygen carrying capacity of the blood.

Methaemoglobin levels should be checked 1 hour after starting INO and then every 6-12 hours. Toxic levels of methemoglobin are unlikely with INO dose <20 ppm

With INO doses less than 20 ppm, methaemoglobin levels are usually less than 2%. Thus a dose of 2% should be taken as warning and INO dosage reduced if the methaemoglobin levels are >4%.

Platelet count and coagulation profile should be monitored and corrected as necessary

Cranial USS should be performed prior to starting therapy and at least 24-48 hours after starting therapy

Stabilisation period:

Responders:
After an initial stabilisation period of 1 hour or so attempts should be made to reduce the INO dose to the minimum effective dose. The INO dose could be reduced by 10% every 2-3 minutes until a drop in oxygen saturation of 2-3% is noted. At this point the INO dose should be increased to the previous dose and an arterial blood gas performed to demonstrate persistent response.

This dose should be maintained and formal weaning process undertaken when OI reaches 10.

Weaning:

Non-responders:

Those babies who do not respond to INO, treatment should be weaned off as soon as possible so as to avoid dependence. INO switches off endogenous NO production and cause hypoxia on withdrawal even in those babies who do not respond to INO

INO dose should be reduced by 20% of the maximum dose every 15 – 30 minutes (INO has a very short half life)

Responders:

Weaning should be in steps of 20% of the effective dose initially. At each step success of weaning should be recorded by arterial blood gases and saturation monitoring.

If at any step there is deterioration, INO dose should be increased to the previous successful step and weaning reconsidered after 8-12 hours. A smaller step in weaning can be considered at this stage.

Final Stages of Weaning:

The final step in both responders and non-responders should be an INO dose of 1 ppm. There is evidence that rebound hypoxaemia can be significantly reduced if the INO dose is reduced to 1 ppm before stopping.

Before finally stopping INO the Fio2 should be increased by 0.2-0.4

The nitric oxide circuit should be connected to the ventilator for 24 hours after stopping INO

Hand Ventilation on INO:

A hand ventilating system delivering INO when disconnected from the ventilator should be available. This is in built in the INOVENT system delivering a fixed dosage of 10 ppm. With our current system of INO delivery (Printer Nox) if you need to hand ventilate ensure same proportion of INO and O_2 delivery.

From conventional ventilation: set O_2 flow on the bag to 8L/min. Do not alter INO flow rate
From HFO (Sensormedics): Set O_2 flow to 7 litres/ min. Reduce INO flow rate to 1/3 rd.

Transport issues:
Those babies who are started on INO and do not respond and are waiting for ECMO retrieval within the next few hours should continue on the INO until they arrive at the ECMO centre and are cannulated. There are reports of severe hypoxaemia in transit and death in some babies when INO was stopped prior to transfer in view of ineffectiveness

INO and Preterm babies:

There have been few randomised trials involving prematurely born babies but none had demonstrated benefits. A Cochrane meta-analysis in 2001 concluded that there was no significant benefit in terms of death or chronic lung disease in preterms with the use of INO. However more recently, there have been conflicting reports on the outcome of preterm babies with hypoxaemic respiratory failure. Mestan et al in a single centre randomised controlled trial reported improved survival, reduced rate of BPD and improved neurodevelopmental outcome. On the other hand Van Meurs et al in a multicentre study reported no difference in outcome of death and/or BPD with INO therapy when compared to placebo. More interestingly babies under 1000gms had worse mortality and incidence of intraventricular haemorrhage and parenchymal lesions. The infants in the latter trial were smaller and sicker (OI: 20 vs 7). Post hoc analysis of the subgroup with birth weights greater than 1000 g actually revealed a significantly reduced rate of the combined outcome of death or BPD (P=0.03) with INO therapy.

Therefore it is safe to conclude that there is insufficient evidence to recommend routine use of INO in hypoxaemic respiratory failure of preterm babies. Until more evidence emerges, INO should only be used in preterms with hypoxaemic respiratory failure in exceptional circumstances, restricting to those >1000gms after full explanation of the potential risks and benefits to the parents.

ECMO

Extracorporeal membrane oxygenation should be considered in very sick babies with hypoxic respiratory failure who do not respond to nitric oxide therapy and OI > 25.

There are strict entry criteria for babies eligible for ECMO

ECMO is considered for children where the following criteria are met:
Respiratory or cardio-respiratory failure (secondary to meconium aspiration, pulmonary hypertension, pneumonia, sepsis, RDS, ARDS, diaphragmatic hernia or cardiac disease)
Failure to respond to maximum treatment
Less than10 days of high pressure ventilation
Weight >1.9 Kg
Gestation >34 weeks
No major intracranial haemorrhage (>Grade 1)
Severe barotraumas (PIE, recurrent chest drain)
No lethal congenital anomalies
Disease is thought to be reversible
OI >25

Important decisions need to be taken in these babies regarding stabilisation, finding a suitable cot in an ECMO centre and transportation. This should be done on a consultant to consultant referral basis

There are 4 centres in the U.K. that undertake ECMO – GOSH, Leicester, Newcastle and Glasgow. The nearest centre for us is GOSH, and in the context of this transport service, the service from Great Ormond Street Hospital would be the one to refer to.

The most appropriate hospital for a child needing ECMO depends on bed availability and availability of suitable transport team. This can only be finalised after discussion with the ECMO consultant on call, who if necessary liaise with other ECMO centres and discuss patients on a case-by-case basis. . Referrals are via the dedicated ECMO contact line 020 7813 8523 or via CATS. Following discussion with the ECMO team, it can be decided whether the NTS team or the CATS team would be most appropriate to expedite the transfer.

The main considerations should be optimisation of treatment and timely movement of the baby before secondary hypoxic deterioration and damage occurs

Other Pharmacologic Therapy:

These agents should only be considered in cases where there is poor response to INO in exceptional circumstances in a confirmed life threatening clinical scenario of PPHN and unacceptable delay in the institution of ECMO. Under no circumstances a referral for ECMO should be delayed while waiting for a therapeutic response of these agents.

A brief discussion of these drugs are given in Appendix 1

Appendix 1.

Non-specific vasodilators

As a group, the use of these agents has been limited by the availability of INO and their side effects of systemic hypotension and myocardial dysfunction resulting in worsening of the
R-L Shunt

Prostacyclin (PGI_2):
Prostacyclin is a potent vasodilator and its effect on vascular tone is complimentary to that of INO as they increase the levels of cAMP and cGMP respectively. Its use has largely replaced the use of tolazoline and is probably the treatment of choice if INO is not available or until it is available. Prostacyclin's major side effect is systemic hypotension, which precludes its use in those infants who are already hypotensive. A proportion of infants will not respond to prostacyclin. Other side effects include inhibition of platelet aggregation and bleeding, bradycardia and hyperglycaemia. It is administered by intravenous infusion at 5-40 ng/kg/min.

There are reports of decreased systemic side effects of aerosolised PGI_2 but RCTs are required to establish efficacy and safety

Magnesium sulphate:
Intravenous Magnesium Sulphate in a dose of 200mg/kg given as a bolus followed by infusion of 20-150 mg/Kg/hour has been shown to improve oxygenation and decrease oxygenation index in three uncontrolled trials in babies with PPHN who were not receiving other vasodilators. Magnesium levels need to be monitored closely (8-12 hourly) and levels maintained between 3.5-5.5 mmol/l. There are currently no randomised controlled trials of this agent in PPHN. The potential for causing systemic hypotension and depression of CNS along with availability of INO limits its use in developed countries

Selective pulmonary vasodilators:

Phosphodiesterase Inhibitors:

Phosphodiesterases (PDE) are enzymes that catalyse the hydrolytic cleavage of the cyclic nucleotide second messengers such as cAMP and cGMP. Inhibition of these enzymes result in increased intracellular levels of cAMP and cGMP and hence vasodilatation. There are several different isoforms of PDE distributed within specific tissues and PDE5 is predominantly present in the lung. PDE5 inhibitors such as sildenafil and zaprinast thus should act as selective pulmonary vasodialtors.

Sildenafil:
Sildenafil has shown a lot of promise in animal models of acute and neonatal pulmonary hypertension and shown to be a selective pulmonary vasodilator with no effect on systemic arterial pressure, potentiating the effect of INO when given orally, as an intravenous infusion or in an aerosolised form.

Clinical experience with Sildenafil is limited to a few case series and an open labelled trial involving a total of 73 patients (Adults, children and neonates) with PHT from various causes. Sildenafil was reported to be as effective as INO in improving pulmonary vasodilatation and the combination of the two being more effective than

either drug used alone. However there are no large randomised controlled trials to support its efficacy and safety in this age group.

The dose range was 0.5 mg/kg as a test dose via NG tube followed by incremental increase upto 2 mg/Kg 6 hourly

However, there are potential concerns that sidenafil may worsen VQ mismatch, myocardial dysfunction and cause irreversible retinal damage and larger safety studies need to be performed before its routine use can be recommended. It is eliminated primarily by the hepatic route and thus safety of its use in the presence of liver dysfunction and its interaction with other antimicrobials and antifungals need to be established.

In the current situation the use of Sildenafil should be considered in exceptional circumstances in a confirmed life threatening clinical scenario of PPHN (after discussion with a cardiologist) when there is poor response to INO and unacceptable delay in the institution of ECMO. The pros and cons of such treatment should be clearly explained to the parents.

Other agents:

Adenosine:
Purine nucleoside adenosine is potent selective pulmonary vasodilator due to its rapid uptake and inactivation by the pulmonary vascular endothelium. Adenosine given IV at 25-50 mcg/kg/min was shown to improve oxygenation in babies with PPHN in a randomised placebo-controlled pilot study. There were no arrhythmias or systemic hypotension reported although the improvement was not sustained

Recently Ng et al demonstrated improved oxygenation and decreased pulmonary artery pressure with adenosine infusion (50mcg/kg/min) in 6 out of 9 infants with PPHN already receiving INO therapy

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(Updated June 2006 – Dr Sujoy Banerjee)