CARE OF NEWBORN
WITH ACUTE PULMONARY HYPERTENSION

Background

- In PPHN there is an imbalance between vasoconstrictor and vasodilator mechanisms resulting in elevated pulmonary vascular resistance (PVR) to the point that systemic venous blood is diverted to some degree through intra- and extra-cardiac (e.g. ductus arteriosus and foramen ovale) channels into the systemic circulation bypassing the lungs and leading to systemic arterial hypoxemia.
- Often aggravated by associated left ventricular dysfunction, which leads to pulmonary venous congestion and oedema.
- More common in babies > 34 weeks gestation but is also seen in preterm infants mainly in the context of severe RDS or sepsis. Higher incidence in pregnancies with no antenatal care and with tobacco and illicit drug use.

Conditions associated with PPHN

Associated with lung disease

- Meconium aspiration syndrome (50%)
- Pneumonia /sepsis (20%)
- Respiratory distress syndrome (5%)
- Congenital diaphragmatic hernia (CDH) with severe lung hypoplasia (see CDH Guideline)

Not associated with lung disease – idiopathic

- Primary (20%)
- Others (5%) – asphyxia, maternal diabetes, polycythaemia, etc

Diagnosis

- Underlying predisposing factors e.g. meconium aspiration syndrome (MAS), CDH
- Severe hypoxaemia (< 6 kPa) despite FiO_2 1.0 and disproportional to associated lung disease
- Pre- and post-ductal saturation difference of ≥5-%, pO_2 difference >3 kPa (may not be present if the majority of shunting is at atrial level)
- Structurally normal heart (no duct dependent lesions requiring a right to left shunt) on echocardiography with evidence of pulmonary hypertension.

Echocardiograpy (for technical guidance please refer to ECHO Guideline)

- The diagnosis of PPHN should ideally be confirmed by echocardiography before starting specific treatment and otherwise as soon as possible.
- Confirmation of the diagnosis is based on assessment of the following echocardiographic qualitative and quantitative markers suggestive of pathological pulmonary arterial pressure (PAP):
    - Qualitative:
        - 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 Veins Drainage (TAPVD) until proven otherwise). Bowing of the inter-atrial septum to the left is commonly seen.
        - Ductal Flow: Bidirectional shunt through the duct is common and normal in the first 12 hours of life. Pure R-L shunting occurs when Pulmonary Arterial Pressure (PAP) is higher than the aortic pressure throughout the cardiac cycle. If the PAP is equal to the systemic pressure, L-R shunting occurs in diastole and right to left in systole.
        - Shape of ventricular septum: With increasing pulmonary pressure the ventricular septum bows into the left ventricle. A curved septum bowing

slightly into the right ventricle suggests normal pulmonary pressure, a flat septum suggests equal pressures between pulmonary and systemic circulation (moderate PPHN) and a bowing into the left ventricle suggests a pulmonary pressure higher than the systemic pressure (severe PPHN).

- Quantitative:
  - Tricuspid Regurgitation (TR): The peak velocity of the TR jet on Doppler assessment is a direct indicator of right ventricular pressure and thus PAP. A velocity of > 2.8 m/s suggests PPHN.
  - Ratio of pulmonary artery acceleration time (PAAT) and the Right ventricular ejection time (RVET): With PPHN there is a fall in the PAAT/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. PAAT / RVET ratio < 0.23 suggests significantly raised PAP and a value 0.23 - 0.3 suggests moderately raised PAP.
- Assessment of left and right ventricular function:
  - Ventricular function can be compromised and lead to underestimation of pulmonary pressure and consequently PPHN.
  - Assessment of cardiac function is important in assisting the choice of inotropic support, inhaled nitric oxide, and other interventions affecting cardiac output and pulmonary perfusion.
  - Fractional shortening < 25% indicates Left Ventricular (LV) dysfunction.
  - Tricuspid Annular Plane Systolic Excursion (TAPSE) <5mm indicates Right Ventricular (RV) dysfunction. Not uncommonly, there is enlargement of the RV and Right Atrium (RA), as well as the main pulmonary artery.
  - As cardiac output is dependent on venous return to the RA and LA, cardiac output (both right and left) is frequently reduced with PPHN. Severe PPHN may be associated with a low Left Ventricular Cardiac Output or Right Ventricular Cardiac Output (LVCO or RCVO) below 100 ml/kg/min (normal 150 - 300 ml/kg/min).
- Cautionary note:
  - Exclude right outflow tract obstruction, if the RA and RV appear dilated or pulmonary vein obstruction and TAPVD, if the LA and LV appear underfilled.

General Management

Investigations

- **Chest X-ray, ECHO, FBC, U&E, CRP, Ca++, Mg^{++}, clotting, blood glucose, blood** culture and viral panel (if suspected viral sepsis)

General treatment

- Babies with PPHN are critically ill and complex to manage. Involve the neonatal consultant in the management early.
- Eliminate reversible factors that worsen pulmonary vasoconstriction – irritability, hypothermia, acidosis, hypoxia, etc.:
  1. 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.
  2. Sedate adequately with infusions of morphine / midazolam (only babies > 34 weeks). Consider paralysis with a continuous infusion of vecuronium.
  3. Maintain normal temperature, blood glucose, calcium and haematocrit (0.4-0.55).
  4. Optimise ventilation aiming for good oxygenation (see specific treatment below) until the primary condition improves or spontaneous postnatal pulmonary vascular adaptation occurs.

5. Obtain arterial access and central venous access (usually UAC and UVC with tip just at the diaphragm) swiftly by the most skilled person available.
6. Monitor blood pressure continuously, ideally invasively and avoid systemic arterial hypotension.
7. Promote pulmonary vasodilatation by specific use of oxygen and consider inhaled NO and other intravenous drugs (see cardiovascular treatment below).
8. Improve cardiac contractility and systemic blood pressure by judicious use of volume and inotropes thus reducing the right-to-left shunting (see cardiovascular treatment below).
9. Initiate septic screen and start on first line antibiotics.

Respiratory Support

- Aim for oxygen saturations pre-ductal of >90% in preterm and >94% in term babies and pO_2 > 8 kPa and post ductal saturations above 85%.
- 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.
- Aim for a pO_2 > 8 kPa as oxygen is the strongest pulmonary vasodilator (compared to CO_2 and pH).
- Aim for a pH within the normal range (7.35 - 7.45) and pCO_2 between 4.5 – 6.0 kPa (avoid hypocarbia < 4.5 kPa as it affects cerebral perfusion) and correct any concomitant metabolic acidosis. As pH has a more direct effect on the pulmonary vasodilation than pCO2 acidosis should be avoided at all cost.
- 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 whilst avoiding hyperinflation as it not only compress the alveolar vascular supply but also causes systemic hypotension thus aggravating the right-to-left shunt.
- Use surfactant in standard dose for RDS (max. total dose 2 x 200 mg/kg) and meconium aspiration syndrome. Repeat as often as needed in meconium aspiration syndrome, if there was a good response to the first dose and there is an oxygen and ventilatory requirement rebound
- If PIP exceeds 30 cmH_2O, consider HFOV (see HFOV guideline). 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.

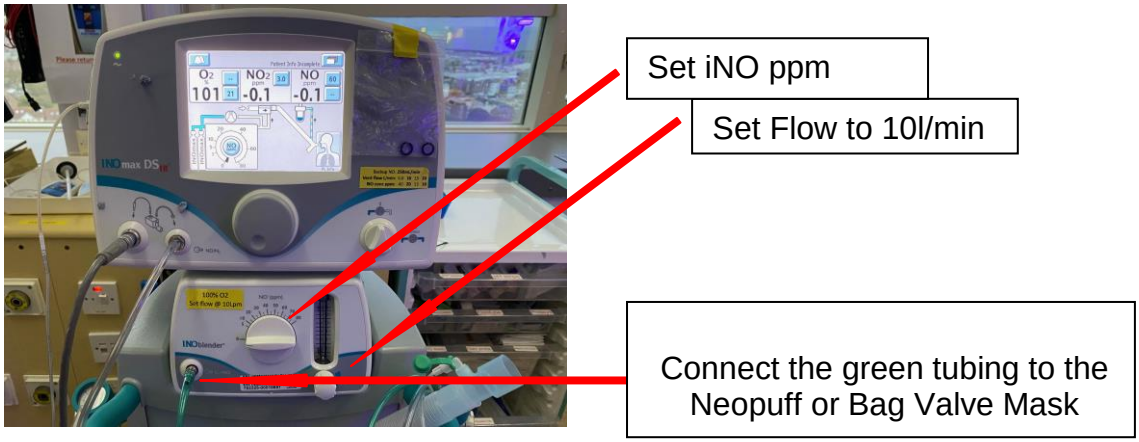
Inhaled nitric oxide (INO)

- INO is a selective pulmonary vasodilator and has several advantages as its effect is confined to the pulmonary vascular bed due to its rapid inactivation by haemoglobin in the pulmonary circulation. Its vasodilator effect is not altered by extra-pulmonary shunts and it can improve ventilation-perfusion mismatch as pulmonary vasodilatation occurs in the ventilated sections of the lung.
- Consider treatment with INO if OI > 15 with echocardiographic evidence of PPHN or if OI > 20 without echocardiographic evidence of PPHN irrespective of gestational age. Earlier initiation of INO with an OI of > 20 does not reduce the need for ECMO but may have a tendency to reduce the risk of progression to severe hypoxemic respiratory failure. An OI of 30 is a relative indication for ECMO as it is associated with a 50% risk of requiring ECMO or mortality. An OI of > 40 is generally accepted as an absolute indication for ECMO. Contact ECMO centre for advice if OI > 30 for more than 4-6 h.
- The routine use of INO in preterm newborns < 34 weeks gestation is not recommended for both early and late treatment. However, INO is preferred over other pulmonary vasodilators in view of its narrow side-effect profile.
- Before starting INO, please check and correct as possible:

- No CHD with duct dependant lesions with right > left shunt such as Hyperplastic Left Heart Syndrome (HLHS), interrupted Aortic Arch, Pulmonary Veins Stenosis, TAPVD, etc.
- Cranial USS should be performed prior to starting therapy and at least 24 - 48 hours after starting therapy

- **Start INO** at 20 ppm, expect response in 2/3 of babies within 30 to 60 minutes.
- Repeat ABG after 30 minutes of starting INO. A positive response to INO is defined as a rise in pO_2 > 3 kPa. Other clinical clues are a reduction in the pre-post ductal saturation difference and a reduction in FiO_2 > 0.1.
- **Start weaning INO** after an initial stabilisation period of at least 1 hour if the FiO_2 can be reduced to < 0.6. Reduce the INO dose to the minimum effective dose by 2ppm every 1 – 2 hours until the pre-ductal oxygen saturation drops > 5% or the pO_2 drops below 8 kPa. At this point the increase the INO dose back to the previous effective dose. This dose should be maintained and formal weaning process undertaken when OI reaches 10.
  Continue monitoring saturations, arterial blood gas and oxygen requirement to demonstrate persistent response.
- **Continue weaning INO** once the OI is around 10. Wean INO at a rate of 5 ppm every 2 - 4 hours. Once INO dose is 5 ppm, wean at a rate of 1 ppm every 4 hours. 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.
- **Stop INO** in responders and non-responders at a dose of 1 ppm to avoid rebound hypoxaemia. Before stopping INO increase the FiO_2 by 0.2 - 0.4. The nitric oxide circuit should remain connected to the ventilator for 24 hours after stopping INO.
- **Non-responders to INO** should be weaned off as soon as possible so as to avoid dependence. INO switches off endogenous NO production and causes 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.
- **Monitor NO_2 levels** using in-line NO_2 monitoring because NO_2 is toxic to the lung. Aim for levels < 2 ppm. Levels above 1 ppm should be taken as warning and a delivery system failure investigated. At levels > 2 ppm INO dosage should be reduced.
- **Monitor methaemoglobin** binding of NO to haemoglobin as 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 methaemoglobin are unlikely and usually < 2% with INO doses < 20 ppm. Thus a level of 2% should be taken as warning and INO dosage reduced if the methaemoglobin levels are > 4%.

- **A hand ventilating system**
  Keep in mind that the gas that we are ventilating with is 100% O2.



Cardiovascular support

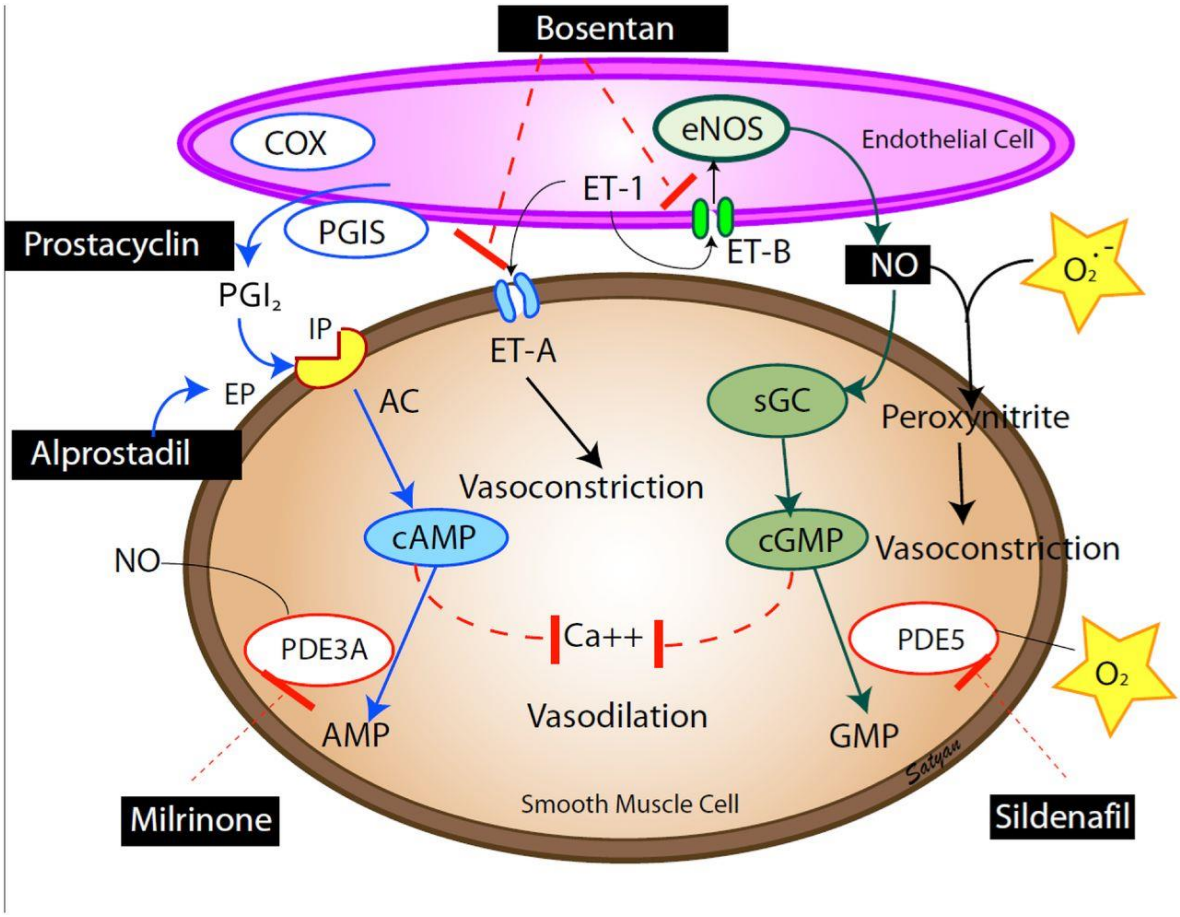
- Aim to maintain systemic systolic blood pressure close to/above normal systemic systolic pressure for gestational age (50th centile):
  - usually > 70 mmHg in babies ≥ 36 weeks gestation
  - usually > 65 mmHg in babies ≥ 28 weeks gestation
  - usually > 55 mmHg in babies < 28 weeks gestation
- Consider a fluid bolus, noradrenaline and hydrocortisone in patients responding to INO with systemic systolic blood pressure below the 50th but above the 3rd centile.
- Assess cardiac function as soon as possible and review drug choice based on ECHO.
- Review cardiac function with ECHO as soon as possible:
  - Presence of TR will help estimate the pulmonary arterial pressure and form a guide for the desired systemic systolic pressure.
  - Consider adding Milrinone in presence of RV dysfunction with an unrestrictive, large PDA. However, if the PDA is restrictive and small, give Prostin instead.
  - Consider stopping Nordrenaline in presence of LV dysfunction and start Milrinone plus Adrenaline.
  - Consider additional fluid boli, if the IVC appears collapsed (however, a dilated IVC does not prove adequate preload).
  - In INO non-responders consider inhaled Prostacyclin (Iloprost) and/or Milrinone and Vasopressin. Consider referral for ECMO. Under no circumstances a referral for ECMO should be delayed while waiting for a therapeutic response of these agents.

ECMO Referral

- Referrals are made via the dedicated ECMO contact line 020 7813 8523 or CATS. This should be done on a consultant to consultant referral basis to discuss important decisions regarding stabilisation and finding a bed in an ECMO centre.
- Location for ECMO depends on bed availability and availability of suitable transport team established after discussion with the ECMO consultant on call.
- In addition to an OI > 30 the following criteria are considered for referral to ECMO:
  - No lethal congenital anomalies
  - Disease is thought to be reversible
  - Gestation > 34 weeks and weight >1.9 kg
  - Less than10 days of high pressure ventilation
  - Respiratory or cardio-respiratory failure, including severe barotraumas (PIE, recurrent chest drain)

- No major intracranial haemorrhage
- Babies on INO waiting for ECMO retrieval within the next few hours should continue on the INO system until they arrive at the ECMO centre and are cannulated as there have been reports of severe hypoxaemia in transit and death when INO was stopped prior to transfer in view of INO ineffectiveness.

Overview of pulmonary vasodilators and their mechanisms of action



Endothelium-derived mediators: the vasodilators prostacyclin (PGI_2) and nitric oxide (NO) and the vasoconstrictor endothelin (ET-1). Cyclooxygenase (COX) and prostacyclin synthase (PGIS) are involved in the production of prostacyclin. Prostacyclin acts on its receptor (IP) in the smooth muscle cell and stimulates adenylate cyclase (AC) to produce cyclic adenosine monophosphate (cAMP). cAMP is broken down by phosphodiesterase 3A (PDE3A). Milrinone inhibits PDE3A and increases cAMP levels in arterial smooth muscle cells and cardiac myocytes. Endothelin acts on ET-A receptors causing vasoconstriction. A second endothelin receptor (ET-B) on the endothelial cell stimulates NO release and vasodilation. Endothelial nitric oxide synthase (eNOS) produces NO, which stimulates soluble guanylate cyclase (sGC) enzyme to produce cyclic guanosine monophosphate (cGMP). cGMP is broken down by PDE5 enzyme. Sildenafil inhibits PDE5 and increases cGMP levels in pulmonary arterial smooth muscle cells. cAMP and cGMP reduce cytosolic ionic calcium concentrations and induce smooth muscle cell relaxation and pulmonary vasodilation. NO is a free radical and can avidly combine with superoxide anions to form the toxic vasoconstrictor peroxynitrite. Medications used in PPHN are shown in black boxes.