Yorkshire and Humber Neonatal ODN Clinical Guideline

Title: Persistent Pulmonary Hypertension of the Newborn (PPHN)

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Date ratified: Dec 2020

Review date: Dec 2024

This clinical guideline has been developed to ensure appropriate evidence based standards of care throughout the Yorkshire and Humber Neonatal ODN. The appropriate use and interpretation of this guideline in providing clinical care remains the responsibility of the individual clinician. If there is any doubt discuss with a senior colleague.

Aims of the guideline

To provide a coordinated approach to initial stabilisation of term or near term infants with PPHN in non-tertiary settings

To provide ongoing best practice guidance for management by Embrace and within tertiary centres

Key points

Early recognition is essential

Cases should be discussed with NICU for advice via Embrace at earliest possible opportunity

In severe cases ECMO may be required – this should be considered during discussions regarding transfer to ensure moved to appropriate centre

Introduction

Persistent pulmonary hypertension of the newborn (PPHN) occurs secondary to failure of the normal circulatory transition at birth. It is a syndrome characterized by elevated pulmonary vascular resistance (PVR) causing labile hypoxemia due to decreased pulmonary blood flow and right-to-left shunting of blood.

Management aims to improve pulmonary blood flow, and thus oxygenation, whilst treating any identified underlying cause. For purposes of clarity we describe an initial ABC approach. However, in reality the aim is to address all aspects together, in order to achieve appropriate balance between the pulmonary and systemic circulations.

Careful history and examination are an important in recognising and assessing the condition, and can guide ongoing management. This is important in all settings.

System	Comments	Relevant Investigations
Airway	Low threshold to intubate (Consider if requiring > 45-50% O2 to maintain saturations on non-invasive support).	
Breathing	Optimise oxygenation and ventilation Monitor pre and post ductal saturations Aim for pre-ductal saturations 95 -98%, (note lower saturations can potentiate hypoxia and further exacerbate PPHN) and pre-post gap of <5% Adjust ventilator settings to optimise alveolar recruitment (ideally using VG, +/- increase in PEEP) – aim for 8-9 posterior ribs on CXR Surfactant 200mg/kg where indicated (e.g. RDS or MAS – if uncertain discuss) Maintain normal CO2 (4.5 -5.5) and pH (7.35 -7.45)	Pre and post ductal saturations CXR (to exclude other pathologies and identify potential causes such as MAS). Regular (ideally arterial) blood gases. Oxygenation Index*
Circulation	Insert UAC and UVC Aim MBP > 45-50mmHg Fluid bolus if clinically indicated (e.g. Sepsis or history to suggest hypovolaemia, also consider if raised haematocrit). Do not give >20ml/kg without further discussion with tertiary centre. Consider “useful” fluids such as blood or clotting products to keep Hb >140 g/L and normalise clotting, or sodium bicarbonate if acidotic. Medication to support blood pressure – see Box 1. “Prostin”- to d/w tertiary team if no improvement with initial measures and unable to obtain echo.***	Echo** FBC, clotting, U+E, LFT, Ca, Mg, lactate, blood culture.

Disability	Minimal handling whilst still responding to care needs. Sedation and paralysis may be needed to gain control of oxygenation and ventilation (note may negatively affect blood pressure). Document neurological status carefully prior to use.	CrUSS if referral for ECMO is being considered
Environment	Aim for normothermia.****	
Infection	Antibiotics according to local policy.	
Other	Keep ionised Ca >1.0 and Mg in normal range	

Table 1: Initial stabilisation measures in referring hospital

*** Oxygenation Index (OI) = FiO2 x100 x Mean Airway Pressure (cmH2O) / (PaO2 (kPa) x 7.5)**

Note FiO2 is the inspired fraction (e.g. 21% = 0.21, 100% = 1.0), kPa x 7.5 converts to the equivalent PaO2 in mmHg. If using an online calculator ensure correct units are used. Note a UAC will give post-ductal paO2.

**Although echo is the ideal for diagnosis it is not always readily available. If clinical signs are of PPHN echo confirmation should not delay treatment.

***"Prostin" should be started following discussion with tertiary or cardiac team if there is doubt regarding diagnosis. It is unlikely to harm, and can potentially be of benefit in PPHN through off-loading of the right heart.

****Hypothermia can exacerbate PPHN. In life threatening PPHN with concurrent HIE discuss target temperature with tertiary centre

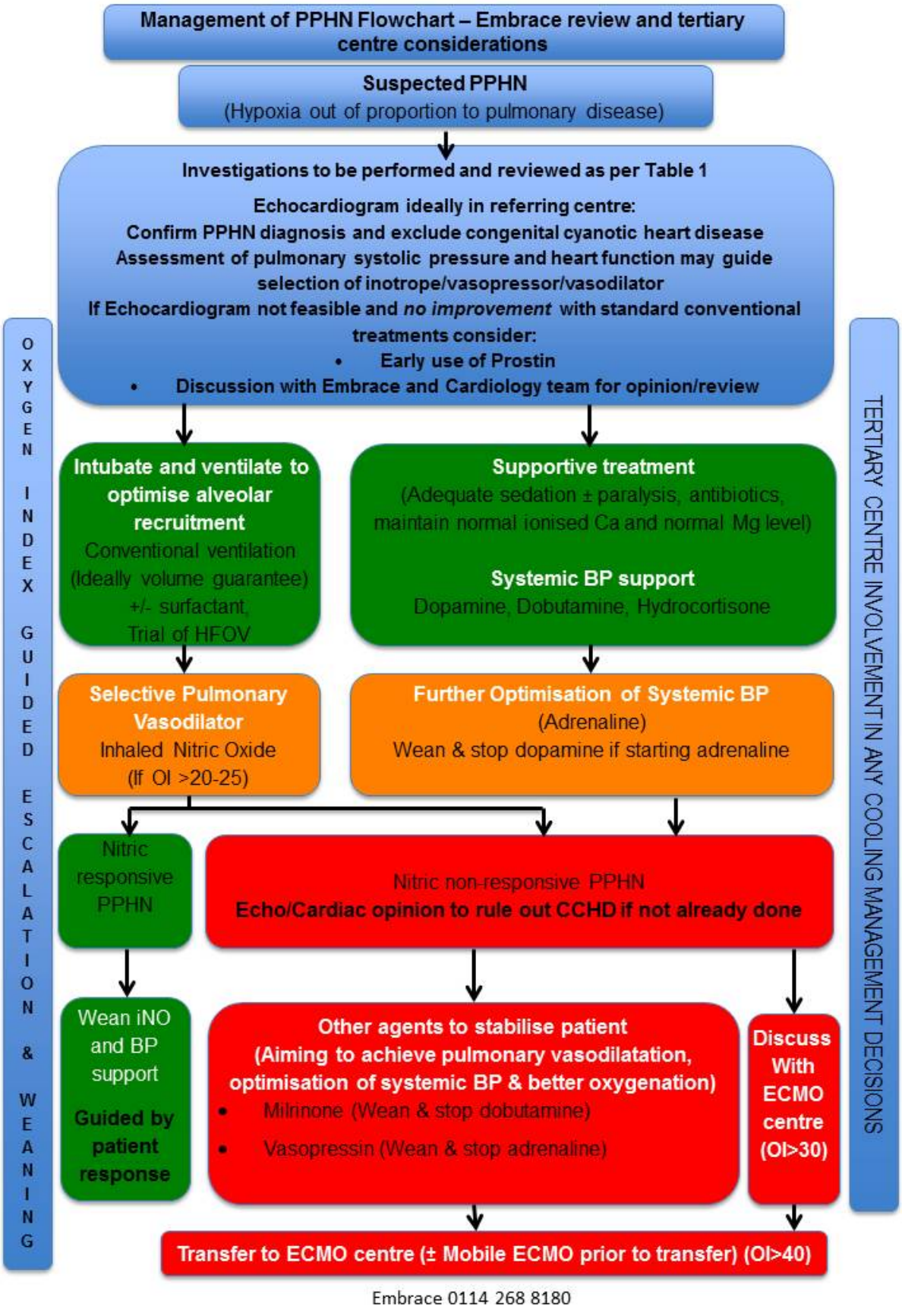

Figure 1: Flow-chart to guide management by Embrace and tertiary centre

2. **Additional considerations on Embrace arrival**

Ensure all measures suggested in Table 1 appropriately addressed.

Use ongoing management flow-chart (Figure 1) to aid management decision making and discussion with tertiary centre.

Nitric oxide if OI > 15-20 (or if unable to calculate OI, if requiring >60% oxygen to maintain saturations). Start at 20ppm and assess response.

If no response to iNO consider echo/cardiac opinion to rule out congenital cardiac disease if not already done.

Consider other agents to stabilise patient as per ongoing management flow-chart.

Discuss with ECMO centre if OI >30 and/or not responding to treatment (note exclusions: known non-reversible underlying condition, <34/40, <2kg, significant intracranial injury).

All discussions should be conference calls via Embrace, also including the tertiary NICU.

Additional agents

See flow chart and Box 1. Note although a numerical BP target has been suggested this should be used in conjunction with observed response in oxygenation, a narrowing in pre and post ductal saturations differential, and other signs of end organ perfusion such as lactate and urine output.

Box 1: Additional agents including circulatory support

1. **Start dopamine at 10 microgram/kg/min**

If inadequate response:

2. **Add dobutamine at 10 microgram/kg/min**

If inadequate response following titration of both to 20mcg/kg/min*:

3. **Add hydrocortisone 2.5 mg/kg IV QDS**

*note dopamine may cause pulmonary vasoconstriction at higher doses - reduce to 15mcg/kg/min as soon as possible if good response, or if no response or associated deterioration

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If further optimisation of oxygenation is required consider the following (in discussion with tertiary NICU +/- ECMO centre) depending on the clinical situation:

A. **Adrenaline 0.1 – 1.0 micrograms/kg/min (and wean and stop dopamine)**

May be first line in sepsis or where systemic blood pressure is primary problem

*note adrenaline may cause pulmonary vasoconstriction and increased myocardial demand at higher doses – decision to use and increase in dosages to be discussed with tertiary team

B. **Milrinone 500-750 nanogram/kg/min or *30-45 microgram/kg/hr** (and wean and stop dobutamine)**

May be first line in those non-responsive to nitric oxide as an alternative pulmonary vasodilator. Note can adversely affect BP – consider 10ml/kg 0.9% NaCl prior to commencing and using adrenaline in conjunction

C. **Vasopressin 0.02 -0.1 units/kg/hr (and wean and stop dopamine and/or adrenaline)**

Usually started following discussion with ECMO team.

*nb milrinone may be prescribed either as nanogram/kg/min or microgram/kg/hr - please check local policy or prescribe as per tertiary advice.

3. Tertiary centre management

Re-assess and ensure all aspects of Table 1 and Flow-chart 1 adequately addressed.

Start nitric oxide (if not already commenced by Embrace).

Consider trial of HFOV (if not already done).

Ensure echo performed (where possible) and consider change in circulatory support depending on findings.

Is there an identified cause? Has this been adequately treated?

Is the baby responding to current treatment?

Is discussion with ECMO team required if not improving and OI remains >25?

Section 4: Overview

The problem

Persistent pulmonary hypertension of the newborn (PPHN) occurs secondary to failure of the normal circulatory transition at birth. It is a syndrome characterized by elevated pulmonary vascular resistance (PVR) that causes labile hypoxemia due to decreased pulmonary blood flow and right-to-left shunting of blood.

It is primarily considered a disorder of late preterm and term infants, although can occur at any gestation. It is thought to occur in around 2/1000 live births. Mortality ranges from 4-33%.

Aetiology/pathophysiology

PPHN may be idiopathic (around 10% of cases) or secondary to other conditions (see Figure 2). Identification of an underlying cause is important as different conditions will require different treatments, alongside other supportive measures.

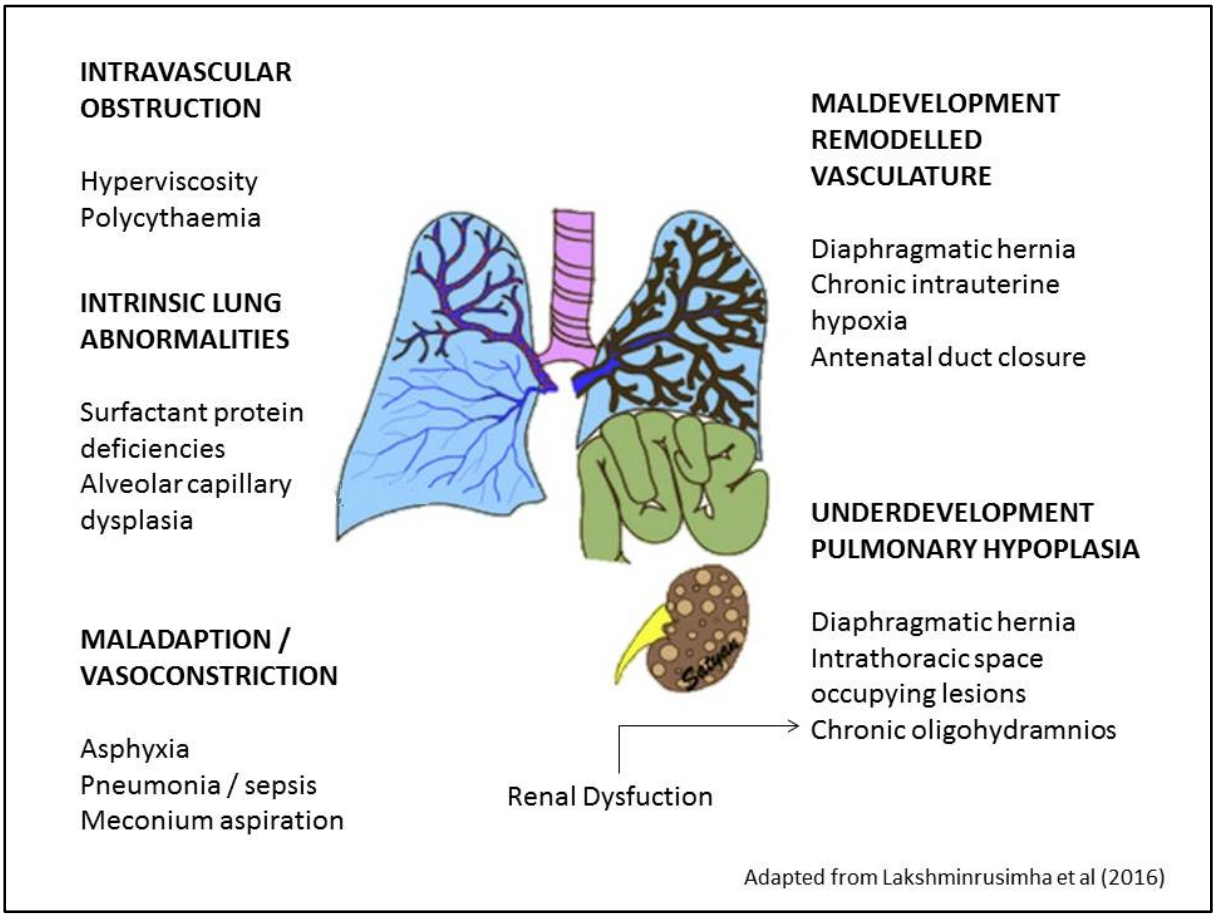

Figure 2: Possible aetiologies of PPHN

Diagnosis

Consider in any term or near term infant with hypoxaemia, presenting most often at, or a few hours after birth. The degree of respiratory distress may not be in proportion to the difficulty in achieving oxygenation. A difference in pre and post-ductal saturations of >5% is the classic finding (with post-ductal lower than pre-ductal), but may not be present if shunting is at the intra-atrial level.

Careful history and examination may help identify an underlying cause if this is not immediately obvious.

Differential diagnosis

Congenital heart disease is an important differential which requires exclusion. Where echo is not available signs suggestive of congenital heart disease over PPHN include cardiomegaly, weak pulses, active precordium, murmur and a lack of response to oxygen therapy. However, differentiating PPHN from ductus-dependant pulmonary cardiac lesions can be very difficult. If uncertainty exists, a “Prostin” infusion is generally the safest option during transport to a tertiary care centre.

Investigation

Oxygen saturations – a difference in pre (right hand) and post-ductal (feet) saturations of >5-10% is suggestive of PPHN. An improvement in this differential suggests a reduction in right to left shunting and improvement in pulmonary blood flow.

Cardiac echo – ideal for diagnosis, but not always readily available. Echo allows identification of features of PPHN (i.e. raised pulmonary pressures and tricuspid regurgitation), as well as exclusion of congenital heart disease (although total anomalous pulmonary venous drainage can be difficult to exclude).

CXR + AXR – to exclude other pathology (such as pneumothorax) and guide respiratory management (aiming for inflation with 8-9 posterior ribs visible). Also allows confirmation of tube and lines positions.

Bloods – FBC, clotting, U+E, LFT, CRP, Ca, Mg, lactate and blood culture.

Note the hyperoxia test is no longer thought to be useful, and may cause harm through over-oxygenation and release of reactive oxygen species which can promote pulmonary vasoconstriction). A complete lack of response to oxygen therapy may however suggest a cardiac rather than respiratory cause.

CrUSS – is required to exclude abnormality in cases where ECMO is being considered.

Management

Management largely aims to improve oxygenation through improving pulmonary blood flow.

Treatment of any underlying cause should occur in parallel to supportive measures. The aim is to improve pulmonary blood flow and achieve balance between the pulmonary and systemic circulation. The main aspects of treatment are outlined in Table 1 with other relevant measures in sections 2 and 3 of this guideline.

HFOV can be useful in PPHN but is not generally available outside of tertiary centres. It should be considered in tertiary settings if there is a sustained increase in OI despite optimisation of conventional ventilation, or there are difficulties in achieving a normal pCO_2.

Surfactant is only likely to be useful if there is evidence of deficiency (ie suggestive history and CXR findings) or in severe MAS. Repeat doses are only recommended in these situations and should be discussed with the tertiary centre.

ECMO is sometimes required and should be considered in a baby with an OI >30, or with an increasing OI despite adequate management. The need for ECMO should be considered before any transfer to ensure movement to the most appropriate centre for ongoing care.

Oxygen saturations

Achieving adequate oxygenation forms the mainstay of PPHN therapy. Hypoxia causes pulmonary vasoconstriction and increases pulmonary vascular resistance, thus contributing to the pathophysiology of PPHN (hence low saturations should not be tolerated). However, there is emerging evidence to suggest exposure to hyperoxia may also be detrimental through free-radical injury. Reactive oxygen species can directly deactivate iNO. Animal studies have suggested increased pulmonary artery contractility and reduced responsiveness to iNO with even brief exposure to 100% O2. There is currently no conclusive evidence to guide oxygenation targeting in PPHN. Attention to paO2 and OI are equally important in titrating oxygen delivery.

Circulatory support

There is little available evidence to suggest which inotropes are “best” in infants with PPHN. Medications are used to increase systemic blood pressure to encourage pulmonary blood flow, and improve the balance between the pulmonary and systemic circulations. Rather than chasing a specific numerical BP target, a response should be seen as an improvement in oxygenation, suggestive of an improvement in pulmonary blood flow.

Dopamine and dobutamine have traditionally been used as first line agents. Babies will often respond to these agents and most practitioners have at least some experience of their use. We have therefore chosen these as first line in this guideline, particularly if being used in a non-tertiary setting.

Caution should be taken if using high doses of dopamine (>15mcg/kg/min) or adrenaline (>0.5mcg/kg/min) as this can cause pulmonary vasoconstriction, reducing pulmonary blood flow, and therefore having a deleterious effect on oxygenation.

Dopamine, Dobutamine and Adrenaline in higher doses can cause severe tachycardia, increasing myocardial O_2 demand and reduced coronary flow. Dopamine and Adrenaline in higher doses also increase pulmonary vascular resistance (PVR) and therefore can cause RV dysfunction.

Vasopressin leads to selective vasodilatation in pulmonary, cerebral, renal and coronary vasculature beds under hypoxic conditions by its action on V1 receptors whose stimulation induces release of endothelial-derives NO in animal experiments. Reports from case series has suggested benefit in infants with PPHN refractory to other treatments. It is most often used following discussion with the ECMO team. Doses above 0.04units/kg/hr should be used with caution due to the risk of side effects.

Pulmonary vasodilators

iNO is the only pulmonary vasodilator for which there is evidence to support use in term or near-term infants (excluding those with congenital diaphragmatic hernia). iNO achieves potent and selective pulmonary vasodilation through the production of cGMP, without decreasing systemic vascular tone. A Cochrane review suggests a reduced need for ECMO, but not mortality. Potential adverse effects related to toxicity from nitrogen dioxide (NO2),

methaemoglobinaemia, hypoxia and pulmonary oedema are negated through monitoring of MetHb, NO2, and clinical response. Forty percent of infants do not respond or sustain a response to iNO.

Milrinone is a PDE-3 inhibitor and causes vasodilation (both systemic and pulmonary) through reduced degradation of cAMP. Its use makes clinical sense due to its actions both as an inotrope and a vasodilator. Its use has been established in congenital heart disease surgery (PRIMACORP study). As yet there are no randomised controlled trials to support routine use of milrinone in PPHN but information from small cohort studies is encouraging. Its use can be considered in individual cases (particularly those who do not respond to iNO). This should be discussed with the tertiary centre if being considered prior to transfer. Note because of its dilator effects systemic blood pressure may fall.

Sildenafil is a PDE-5 inhibitor causing vasodilation (both systemic and pulmonary) through reduced degradation of cGMP. Although reduced mortality is reported in resource poor settings, these findings are not generalizable to the UK (where iNO is more readily available) and due to its slow onset of action, as well as ongoing safety and efficacy concerns its use is not recommended for acute PPHN.

There is insufficient evidence to support use of prostacyclins (such as epoprostenol), bosentan, adenosine, tolazoline or magnesium sulphate. Although supraphysiological magnesium levels are not recommended it is wise to aim to keep magnesium at normal physiological concentrations (0.7-1.0mmol/L).

Section 5: References

Lakshminrusimha, S, Matthew, B, and Leach, C. 2016. Pharmacological Strategies in Neonatal Pulmonary Hypertension other than Nitric Oxide. *Seminars in Perinatology,* pp. 40(3):160-173.

Vali,Payam; Lakshminrusimha, Satyan. The fetus can teach us: Oxygen and the pulmonary vasculture. *Children* Aug 2017 Vol 4
Nair, J. Update of PPHN: Mechanisms and Treatment. *Semin Perinatol.* 2014 Mar; 38(2): 78–91.

Barrington, K, Finer, N, Pennaforte, T, et al. 2017. Nitric oxide for respiratory failure in infants born at or near term. Cochrane Database of Systematic Reviews, p. Issue 1. Art No.: CD000399. DOE:10.1002/14651858.CD000399.pub3.

Hoffman, T, Wernovsky, G, Atz, A, et al. 2003. Prophylactic intravenous use of milrinone after cardiac operation in pediatrics (PRIMACORP) study. Prophylactic intravenous use of milrinone after cardiac operation in pediatrics. Circulation, pp. 107:996-1002.

Bassler, D, Kreutzer, K, McNamara, P, et al. 2010. Milrinone for persistent pulmonary hypertension of the newborn. Cochrane Database of Systematic Reviews, p. DOI: 10.1002/14651858.CD007802.pub2.

McNamara, P, Shivananda, S, Sahni, M, et al. 2013. Pharmacology of milrinone in neonates with persistent pulmonary hypertension of the newborn and suboptimal response to inhaled nitric oxide. Pediatric critical care medicine, pp. 14(1):74-84. doi: 10.1097/PCC.0c013e31824ea2cd.

Kelly, L, Ohlsson, A, and Shah, P. 2017. Sildenafil for pulmonary hypertension in neonates.. Cochrane Database of Systematic Reviews, p. Issue 8. Art. No.: CD005494. DOI: 10.1002/14651858.CD005494.pub4.

Adel Mohamed, Nehad Nasef, Vibhuti Shah, Patrick J. McNamara. Vasopressin as a Rescue Therapy for Refractory Pulmonary Hypertension in Neonates. Retrospective Case Series: Pediatr Crit Care Med. 2014;15(2):148-154

NICHe Group DRAFT guideline on Management of Persistent Pulmonary Hypertension of Newborn (PPHN) in near term and term infants.