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Scottish Perinatal Network Neonatal Guideline

Hypoxic Respiratory Failure in Term & Near Term Infants

Scottish Perinatal Network

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DOCUMENT CONTROL SHEET

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Revision History:

Version:	Date:	Summary of Changes:	Name:
2.0	22.04.2026	In stages 1, 2, and 3: Consider discontinuing iNO if no response; Dobutamine can be considered as an alternative to adrenaline; Avoid using dopamine; Aim for Mean Blood Pressure >45 mmHg & Pulse Pressure >20 mmHg. In stage 3: Consider targeted use of additional cardiotropes in experienced centres.	Dr Andrew McLaren and Dr Mahmoud Montasser

DISCLAIMER

Unless you have accessed guidelines from the SPN website, there is no guarantee this is the latest version. It is the responsibility of the user to confirm the version they are using is the latest published version. These guidelines have been prepared to promote and facilitate standardisation and consistency of practice using a multidisciplinary approach. Information within is current at time of publication.

The recommendations in this guideline represent the view of the National Neonatal Network Guideline Development Group, arrived at after careful consideration of the evidence available. When exercising their clinical judgement, healthcare professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of the families using their service. It is not mandatory to follow the guideline recommendations, and it remains the responsibility of the healthcare professional to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.

Introduction

This guideline has been developed for medical staff caring for term and near term (>34wk) infants throughout Scotland.

Respiratory failure is a failure of the respiratory system to oxygenate (hypoxaemia) or to clear CO_2 (hypercapnia). Invasively ventilated babies with one or more of:

- **Oxygen requirement ≥ 60%** (to achieve preductal saturation of 94% and above)
- **pCO_2 ≥ 8kPa**
- **H^+ ≥ 60 (pH <7.22)**

should be considered at risk of hypoxic respiratory failure (HRF) and persistent pulmonary hypertension of the newborn (PPHN). These babies require advanced management strategies and early discussion with a specialist centre for consideration of transfer.

The aim is to provide standardised care for these babies and provide a pathway to aid management and referral to a specialist centre if required for ongoing care. This guideline will not cover the management of babies born with congenital diaphragmatic hernia. These babies should follow the established pathways found at https://www.scans.scot.nhs.uk/guidelines-pathways-cdh/

For babies with associated hypoxic ischaemic encephalopathy, management of this should be as per the Scottish Cooling Group guideline on Therapeutic Hypothermia: Neuroprotection-Care-Pathway-for-Infants-with-HIE-3rd-Edition-Oct-2025.pdf

The monographs for medications referenced in this document can be accessed via https://www.perinatalnetwork.nhs.scot/professionals/guidance/local-regional-drug-monographs/

Alternatively, local monographs are available.

Principles of Treatment

1) Optimise lung recruitment and ventilation considerations:

- Select appropriate ETT size to minimise leak
- Optimise ventilator settings, avoid under-recruitment and over-distension.
- Consider use of High frequency oscillation if familiar with its use.
- Treat pneumothorax
- Keep airway clear of obstruction with suction where necessary
- Use surfactant if suspected surfactant deficiency/inactivation

2) Minimise pulmonary vascular resistance, optimise pulmonary blood flow:

- Minimise excessive noise and potentially disturbing bright light
- Optimise acid-base status
- Trial of pulmonary vasodilators e.g. inhaled nitric oxide.

3) Optimise cardiac function, systemic blood flow and oxygen delivery

- Treat hypovolaemia
- Consider use of inotropes to optimise ventricular function and blood pressure
- Optimise haemoglobin (target Hb > 120)
- Echocardiography if expertise available to assess function and rule out structural anomalies

4) Reduce oxygen consumption

- Use sedation and muscle relaxation
- Maintain normothermia

5) Treat possible associated conditions:

- e.g. sepsis, meconium aspiration, hypoxic ischaemic encephalopathy
- For babies with HIE, therapeutic hypothermia should be managed as per the Scottish National Cooling Group guideline. Therapeutic hypothermia is not a contraindication to ECMO.

More detailed information on the management of Hypoxic Respiratory Failure can be found in the *'Further Reading'* section of the guideline.

Referral pathway for infants needing ECMO support

<u>Pathway for referral to Royal Hospital for Children, Glasgow</u>

- For babies in a level 2 unit, initial discussions should be with their local level 3 unit.
- However, any baby where there is concern can be discussed with the on-call consultant at RHC Glasgow
- Baby fulfils criteria for ECMO (below) OR worsening respiratory failure:
- Contact RHC, Glasgow Receiving Neonatal Consultant on **0141 452 2114.**
- If transfer is thought to be required, call the **ScotSTAR Emergency Line on 03333 990 222** and request a conference call between:
    - Referring Unit
    - Receiving neonatal consultant at RHC, Glasgow
    - On-call ECMO surgeon (if thought to be required by receiving consultant)
    - ScotSTAR transport consultant
    - ScotSTAR transport team (clinician and nurse).
- In this way, advice can be given to the referring centre, a clear history and clinical status can be outlined and the decision to transfer can be carried out in a single call.

The monographs for each of the medications referenced in this pathway can be found locally or at https://www.perinatalnetwork.nhs.scot/professionals/guidance/local-regional-drug-monographs/

Stages

Stage 0 – In utero diagnosis

Plan to deliver in a Level 3 NICU or ECMO centre for likely cases of severe respiratory failure.

This would include babies with:

- Severe congenital diaphragmatic hernia. See guideline for antenatal management of congenital diaphragmatic hernia: https://www.scans.scot.nhs.uk/guidelines-pathways-cdh/
- Suspected significant pulmonary hypoplasia of other cause.
    - *Consideration should be given to antenatal transfer of any mother presenting with a history of PPROM from < 24 weeks, or PPROM with oligohydramnios from 24 – 30 weeks to a centre providing inhaled Nitric Oxide therapy.*

Stage 1

Immediate management of term or near-term babies with hypoxic respiratory failure (FiO2>60%, pCO2 > 8kPA) in first 1-2 hours of life.

Management of all term & near term infants with high FiO2 worsening on non-invasive ventilation

- Intubate & ventilate
- Start 1st line antibiotics (most commonly benzyl penicillin & gentamicin).
- Standard monitoring + Pre/post ductal saturations (difference >5% is significant)
- UVC (double-lumen)/ PICC (double-lumen)
- UAC/ peripheral arterial line
- Chest X-ray
- Commence intravenous fluids as per your local guidance. Ensure normoglycaemia.

	ENSURE:	**CONSIDER:**
Respiratory	**Ensure adequate ventilation** • Intubate and commence mechanical ventilation • Avoid atelectasis • Avoid overdistension ('flattened' diaphragm and 'narrow' heart on CXR) • Exclude pneumothorax • Aim pCO_2 of 5 - 7 kPa • Avoid acidosis – aim for H^+ <60, pH >7.2 • Aim pre-ductal SaO_2 >94%	**Pulmonary Vasodilators** • Start inhaled Nitric Oxide at 20ppm, if evidence of pulmonary hypertension (clinically or on Echo). Consider stopping if no response after discussion with receiving centre. • **Surfactant** • Surfactant 200mg/kg if evidence of surfactant deficiency/ inactivation • **Remember 'DOPE'** • Dislodgement of ETT • Obstruction • Pneumothorax • Equipment failure
Cardiovascular	**Optimise intravascular volume** • 10ml/kg bolus 0.9% NaCl if suspicion of hypovolaemia (use packed red cells if suspicion of anaemia) • Aim to keep mean BP >45mmHg • Monitor for narrow pulse pressure which is an indication of myocardial dysfunction • Monitor urine output	**Inotropes** • Commence low dose Adrenaline at 0.03 - 0.05 mcg/kg/min **OR*** • Dobutamine 5-10 mcg/kg/min** * AVOID DOPAMINE USE **Dobutamine dose above 10mcg/kg/min should be avoided due to risk of tachycardia leading to reduced cardiac output with no additional benefits but more side effects.

Vascular Access	• UAC or peripheral arterial line • UVC or PICC	
Sedation/ Analgesia	• Morphine 100mcg/kg bolus followed by infusion of 20mcg/kg/hr (titrate according to baby's response)	**Muscle Relaxation** • Vecuronium or Rocuronium **Sedation** • Midazolam 50-100mcg/kg bolus followed by infusion of 60-100 mcg/kg/hour, titrated to response
Exclude	• Congenital cardiac disease by echocardiogram (if possible)	If congenital cardiac disease cannot be excluded commence prostaglandin E1 to maintain ductal patency (5-20 nanog/kg/min)
Monitoring	• Standard bedside monitoring • Pre and post ductal saturation	
Referral	**If care is in a level 2 unit, discuss baby with local level 3 unit for advice and transfer.**	

Stage 2

At 2-4 hours with baby continuing to need high oxygen requirement (FiO_2>60%), has severe lung disease or clinical suspicion of HRF.

	ENSURE:	CONSIDER:
Respiratory	**Ensure adequate ventilation** • Avoid atelectasis • Avoid overdistension ('flattened' diaphragm and 'narrow' heart on CXR) • Exclude pneumothorax • Aim pCO_2 of 5 - 7 kPa • Avoid acidosis – Aim H^+ <60, pH >7.2 • Aim pre-ductal SaO_2 >90% **Specific pulmonary vasodilators** • Start iNO at 20ppm if evidence of PHT. If no response, discontinue and discuss further with referral centre.	**Surfactant** • Surfactant 200mg/kg if evidence of surfactant deficiency/ inactivation clinically, on CXR or lung US. **Ventilation** • Consider HFOV if familiar with its use. **Remember 'DOPE'** • Dislodgement of ETT • ETT Obstruction • Pneumothorax • Equipment failure

Cardiovascular	• Further 10ml/kg NaCl bolus if evidence of hypovolaemia • Avoid multiple fluid boluses • Keep MBP >45, ensure pulse pressure of >20. If narrow pulse pressure <20, consider inotropic support. Monitor urine output • Correct metabolic acidosis • Adrenaline 0.03-0.08mcg/kg/min • **OR** Dobutamine 5-10 mcg/kg/min • Avoid tachycardia >180/min	**Fluids** • Consider transfusion with 20ml/kg packed red blood cells to keep Hb > 120 **Inotropes** • Start IV hydrocortisone 1-2.5mg/kg QDS AVOID DOPAMINE USE
Vascular Access	• UAC or peripheral arterial line • Double lumen UVC or PICC	
Sedation/ Analgesia	• Morphine 100mcg/kg bolus followed by infusion of 20mcg/kg/hr (titrate according to baby's response) * • Vecuronium or Rocuronium	• Midazolam 50-100mcg/kg bolus followed by infusion of 60-100 mcg/kg/hr* *Beware of hypotensive effect of sedation and muscle relaxation.
Exclude	• Congenital cardiac disease by echocardiogram (if possible)	If congenital cardiac disease cannot be excluded commence prostaglandin E2 to maintain ductal patency (5-20 nanog/kg/min)
Monitoring	• Standard bedside monitoring • Pre and post ductal saturation • Advanced monitoring as in the education section	
Referral	**If this is a level 2 unit, discuss baby with local level 3 unit, ScotSTAR AND RHC, Glasgow for advice and possible transfer (as outlined below).**	

Stage 3

Continued worsening oxygen requirement or hypercarbia, has severe lung disease or clinical suspicion of PPHN

	ENSURE:	CONSIDER:
Respiratory	**Ensure adequate ventilation** • Trial of HFOV if familiar with its use. • Avoid atelectasis • Avoid overdistension ('flattened' diaphragm and 'narrow' heart on CXR) • Exclude pneumothorax • Aim pCO_2 of 5 - 7 kPa • Avoid acidosis – Aim H^+ <60, pH >7.2 • Aim to keep pre-ductal SaO_2 >85% **Specific pulmonary vasodilators** • Start iNO at 20ppm if evidence of PHT. If no response, discontinue and discuss further with referral centre.	**Remember 'DOPE'** • Dislodgement of ETT • ETT Obstruction • Pneumothorax • Equipment failure **Surfactant** • Surfactant 200mg/kg if evidence of surfactant deficiency/ inactivation clinically, on CXR or lung US. **Remember** • Consider LV dysfunction or other phenotypes of pulmonary hypertension if no response to iNO therapy.

Cardiovascular	• Keep MBP >45, ensure pulse pressure of >20. If narrow pulse pressure <20, consider inotropic support. Monitor urine output
	• Monitor urine output
	• Adrenaline 0.03-0.1mcg/kg/min
	• **OR** Dobutamine 5-10 mcg/kg/min
	• Hydrocortisone 1-2.5mg/kg QDS
	• 20ml/kg Packed RBCs (if Hb <130)
	• Correct metabolic acidosis.
		Inotropes
		• Consider targeted use of additional cardiotropes in experienced centres e.g.
		  ○ Milrinone 0.3-0.7 mcg/kg/min
		  ○ Noradrenaline 0.03-0.08 mcg/kg/min
		  ○ Vasopressin 0.0003-0.0009 mcg/kg/min
		
		Remember
		• Avoid repeatedly increasing inotropic support without further discussion as high doses can lead to reduced cardiac output via chronotropy and vasoconstriction.
		• Beware of excess tachycardia as doses of catecholamines

		increase. This can have a negative inotropic effect.
Vascular Access	• UAC or peripheral arterial line • Central line for inotropes	
Sedation/ Analgesia	**Sedation** • Morphine 100mcg/kg bolus followed by infusion of 20mcg/kg/hr (titrate according to baby's response) • Midazolam 100mcg/kg bolus followed by infusion at 60-100mcg/kg/hr **Muscle Relaxation** • Vecuronium or Rocuronium	
Exclude	• Congenital heart disease	Commence prostaglandin E2 if CHD cannot be ruled out at 5-20 nanograms/kg/min
Monitoring	• Ensure adequate monitoring • Pre and post ductal saturation	
Referral	**Is this a baby who requires ECMO?** **Contact RHC, Glasgow Receiving Consultant AND ScotSTAR (as outlined below)**	

Neonatal ECMO

Introduction

Extracorporeal Life Support (ECLS) has a long history which is interwoven with the development of cardiopulmonary bypass. In 1982 Bartlett published the initial ECMO experience with 45 neonates. ECMO had only been used when maximal conventional therapy was exhausted and the infants were considered moribund. With >50% survival in patients considered to have a 90% mortality interest in ECMO for newborn respiratory failure was high but even though these early results were promising the lack of a randomised control trial caused many medics to continue to doubt it's safety and efficacy.

Aim of Neonatal ECMO

Selecting patients for ECLS and timing of treatment are two difficult aspects. Due to the invasive nature of ECLS and its significant associated risks, ECLS has always been reserved to treat only those neonates in whom other less invasive and dangerous therapies have failed. It was originally reserved for patients whose predicted mortality was 80% (Cornish, 1995).

However, as expertise has improved and other patients have been treated, selection criteria have broadened to include patients for whom the benefits of ECLS would outweigh its risks.

Indications

Babies must have a **reversible lung condition** to be eligible for ECMO. The most common indications are:

- Meconium Aspiration Syndrome
- Congenital Diaphragmatic Hernia
- Sepsis
- Persistent Pulmonary Hypertension (other causes)
- Respiratory Distress Syndrome
- Air Leak Syndrome

AND meet the following criteria:

Criteria for consideration of ECMO:

- Weight > 2000g and >34 weeks' gestation. Smaller and more immature babies requiring maximal conventional support may be eligible as we have experience of cannulating down to 1800g.
- Not more than 7 days of high pressure ventilation
- Less than 28 days' old
- All congenital diaphragmatic hernia
- Unresponsive to maximal conventional management
- OI approaching 25 or $PaCO_2$ >90 mmHg

Contraindication to ECMO:

- Congenital/acquired CNS abnormality (including grade III-IV intraventricular haemorrhage).
- Irreversible cardiopulmonary disease
- Period of asystole (outside post-delivery period)
- Major chromosomal/ congenital abnormalities. However, some chromosomal defects are now not a contraindication (e.g. Down's Syndrome).

Further Reading

Causes of Respiratory Failure in the Term Infant

Persistent Pulmonary Hypertension of the Newborn (PPHN)

The term "PPHN" refers to a clinical syndrome characterised by hypoxic respiratory failure and associated systemic cyanosis and hypotension occurring from the time of birth. PPHN is not a single entity, but may be due to a number of possible causes. At a pathophysiological level PPHN is associated with persistence of fetal circulation at birth and ongoing elevation of pulmonary artery pressures (PAp).

Pressure in the pulmonary circulation is in simple terms the product of flow (pulmonary blood flow, PBF) and resistance (pulmonary vascular resistance, PVR). PVR is determined by the net resistance of the pulmonary arteries to the left atrium. Pulmonary hypertension (PH) refers to elevation of pulmonary artery pressure (PAP).
$PA_{Pressure} = PB_{Flow} \times PV_{Resistance}$

PPHN occurs in as many as 2-6/1000 live births and is a frequent a complicating factor of term parenchymal lung disease.[1]

PPHN is most commonly associated with increased PVR due to three potentially co-existent mechanisms, Figure 1:

- Maladaptation of the pulmonary vasculature (abnormal parenchyma with increased PVR) leading to **acute pulmonary vasoconstriction** due to acute perinatal events, such as:
- Alveolar hypoxia secondary to parenchymal lung disease, such as respiratory distress syndrome (RDS) or pneumonia
- Hypoventilation resulting from asphyxia or other neurologic conditions
- Hypothermia
- Hypoglycaemia
- Sepsis

- The second cause, **idiopathic PPHN** due to **maldevelopment of pulmonary vasculature** (normal parenchyma and increased PVR) which is associated with a normal chest radiograph and no parenchymal lung disease. Newborns with idiopathic PPHN present with pure vascular disease. This syndrome typically results from:
- Abnormally remodelled or hypoplastic pulmonary arterial bed e.g. secondary to chronic stress
- Alveolar Capillary Dysplasia with Malaligned Pulmonary Veins (ACD-MPV)
- Maternal medications including NSAIDs, SSRIs
- CDH
- Pulmonary hypoplasia of another cause.

- The third category is due to **pulmonary venous congestion (post-capillary PH)** due to:
    1. **Left ventricular dysfunction:** This may be particularly important in disease states that result in abnormal LV performance (infants with hypoxic ischemic encephalopathy [HIE], and infants born following twin to- twin transfusion [TTTS]

    2. **Increased pulmonary blood flow.** A rare cause of PPHN with or without elevation of PVR. This may be seen with large extra-cardiac shunts such as intra-cranial arterio-venous malformations (Vein of Galen Aneurysmal Malformation, VGAM

Congenital Diaphragmatic Hernia (CDH)

The assessment and management of infants with CDH is outwith the scope of this guidance and it has been agreed that infants either with an antenatal or postnatal diagnosis of CDH should be managed as per the well established pathway already in place:
https://www.scans.scot.nhs.uk/guidelines-pathways-cdh/

Meconium Aspiration Syndrome (MAS)

The passage of meconium occurs antenatally due to acute or chronic hypoxia. In utero, hypoxia can cause the fetus to gasp, which in turn can lead to aspiration of meconium. The majority of infants with meconium aspiration have symptoms of mild respiratory distress, however it can cause severe respiratory distress, hypoxaemia and associated pulmonary hypertension.

There is no evidence that routine suctioning at delivery prevents meconium aspiration as it almost always occurs antenatally.

Meconium aspiration causes lung pathology in two ways:

- emphysema with partial obstruction, caused by air entering the alveoli which is unable to leave on expiration due to blockage by meconium particles. This leads to gas trapping and areas of alveolar over distension, which in turn can cause air leak.
- atelectasis as a result of total obstruction of the airway by meconium, causing ventilation-perfusion mismatch.

The presence of meconium in the airways also causes surfactant dysfunction and chemical pneumonitis. Surfactant dysfunction causes further atelectasis and chemical pneumonitis causes cytokine release and inflammation of the lung parenchyma.

The effects of MAS can lead to gross ventilation-perfusion (V/Q) mismatch and many of these infants already have PPHN as a result of in-utero compromise. Postnatally, further hypoxaemia and hypercapnia contribute to pulmonary vasoconstriction which further increases pulmonary vascular resistance. The high pulmonary pressures cause right to left shunting through the foramen ovale and ductus arteriosus, which lowers the saturations further

Sepsis

The incidence of culture-proven sepsis is approximately 2 per 1000 live births. The mortality rate in neonatal sepsis may be as high as 50% for infants who are not treated. Infection is a major cause of fatality during the first month of life, contributing to 13-15% of all neonatal deaths. Pneumonia is more associated with early onset sepsis, whereas meningitis and bacteraemia are more commonly seen in late onset sepsis.

Respiratory Distress Syndrome (RDS)

Respiratory Distress Syndrome (RDS) occurs most commonly in premature infants and is due to deficiency in surfactant leading to alveolar collapse, atelectasis and subsequent respiratory failure due to ventilation-perfusion mismatch. Although more common in premature infants, it does occur in term infants. Term infants can have RDS when they are the infant of a diabetic mother or are delivered by elective c-section before 39 weeks. Surfactant can also be inactivated as described above, by meconium or in other circumstances such as infection, presence of blood or asphyxia. Steroids are administered to mothers antenatally, ideally 12-48 hours prior to an expected delivery at high risk of surfactant deficiency to stimulate surfactant production.

In term and near-term infants, the increased pulmonary vascular resistance which results from surfactant deficiency and dysfunction causes right to left shunting across the foramen ovale and/or ductus arteriosus, which as described above can lead to PPHN. Several diagnoses can co-exist and worsen RDS. These include:

- Pneumonia, often secondary to group B beta-haemolytic streptococci.
- Metabolic problems (e.g., hypothermia, hypoglycaemia).
- Haematological problems (e.g., anaemia)
- Retained lung fluid (so called transient tachypnoea of the newborn (TTN))
- Aspiration syndromes which may result from aspiration of amniotic fluid, blood, or meconium.
- Pulmonary air leaks (e.g., pneumothorax, interstitial emphysema, pneumomediastinum, pneumopericardium)
- Congenital anomalies (e.g., congenital diaphragmatic hernia) resulting in pulmonary hypoplasia.

Phenotypes of Acute Pulmonary Hypertension

Increased pulmonary artery pressure is variably associated with (Figure 2):

- Right to left shunting between atria and across the PDA leading to hypoxia / cyanosis
- Right ventricular (RV) dilatation and dysfunction leading to reduced pulmonary blood flow
- Left ventricular dysfunction, which may be primary or secondary to RV dysfunction, leading to systemic hypotension

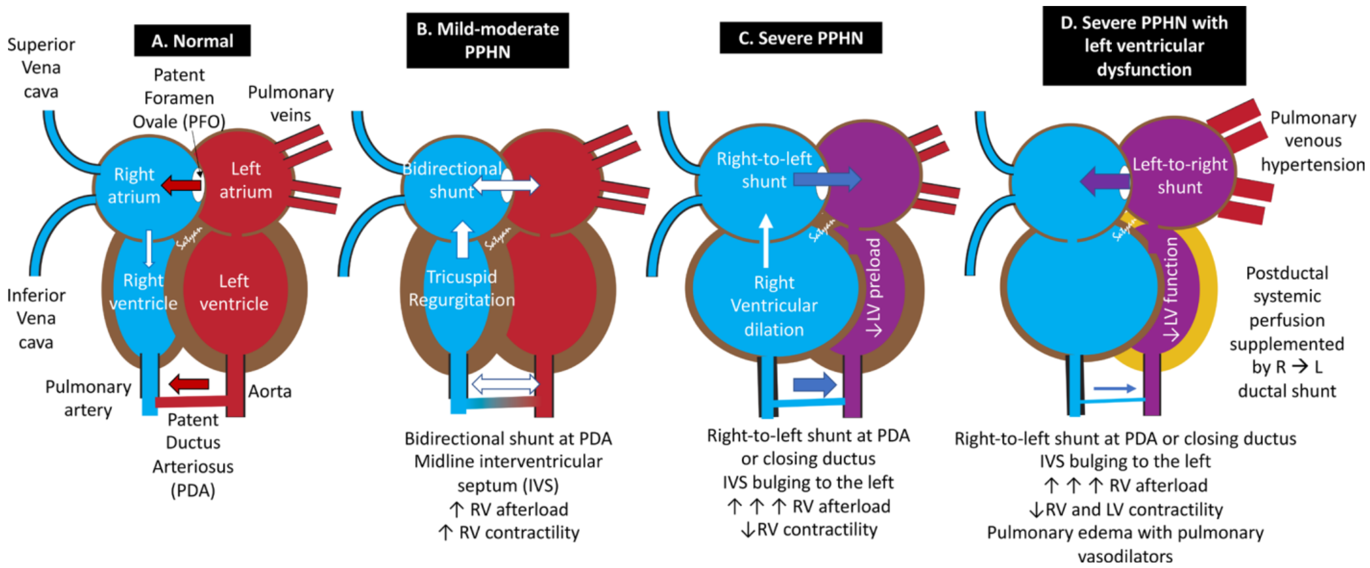

Figure 2: Pathophysiological models of PPHN

from Siefkes HM, Lakshminrusimha S. Arch Dis Child Fetal Neonatal Ed 2021

Pathophysiology of hypoxic respiratory failure

Table 1
Pulmonary hypertension phenotypes—pathophysiology and echocardiography features

PH Phenotype	Pathophysiology	Echocardiography Features
Acute PH		
Arterial (classic)	Hypoxic pulmonary vasoconstriction and V/Q mismatch	Dilated (possibly hypertrophied) RV, septal flattening in systole, predominantly R→L PDA and atrial shunts, ↑PVRi (RVET:PAAT) > 4 and/or PA Doppler notching, ↓ PV Vmax < 0.25 m/s, ↓ LVO
Flow mediated (eg, VGAM)	High volume of blood in a circuit with limited capacitance, endothelial dysfunction, and oxidative stress	Dilated RV and/or LV, discordant ventricular outputs with either ↑RVO, ↑LVO or both, septal flattening in diastole if ASD/VSD
Left heart dysfunction (postcapillary)	Poor LV compliance and high LVEDP resulting in impaired flow through pulmonary circuit	Dilated LA and/or LV, LV systolic and diastolic dysfunction [↓MVE, ↑IVRT or E:e', ↓ PV S/D ratio, PV a wave], MR and/or AI, ↓LVO
Chronic PH		
Arterial (classic) for example, associated with BPD	Pulmonary vascular remodeling, impaired angiogenesis, and alveolar hypoxia/hyperoxia	Dilated and hypertrophied RV, septal flattening in systole, predominantly R→L PDA and atrial shunts, ↑↑PVRi (RVET:PAAT) > 4 and/or PA Doppler notching, ↓ LVO
Flow mediated (eg, ASD shunt)	High volume of blood in a circuit with limited capacitance, interstitial edema, and pulmonary vascular remodeling	Dilated RV or LV, discordant ventricular outputs with either ↑RVO, ↑LVO or both, septal flattening in diastole if ASD/VSD
Systemic hypertension	High LV afterload causing ↑LVEDP, LA hypertension, and pulmonary venous congestion	Dilated LA, LV, LV diastolic dysfunction [↓MVE, ↑IVRT or E:e', ↓ PV S/D ratio, PV a wave], MR, and/or AI

Abbreviations: AI, aortic insufficiency; ASD, atrial septal defect; BPD, bronchopulmonary dysplasia; D, d wave; IVRT, isovolumetric relaxation time; LA, left atrium; LV, left ventricle; LVEDP, left ventricular end-diastolic pressure; LVO, left ventricular output; MR, mitral regurgitation; MVE, mitral valve early wave; PA, pulmonary artery; PAAT, pulmonary artery acceleration time; PDA, patent ductus arteriosus; PV, pulmonary vein; PVRi, pulmonary vascular resistance index; R-L, right-to-left; RV, right ventricle; RVET, right ventricular ejection time; RVO, right ventricular output; S, s wave; V/Q, ventilation/perfusion; VGAM, vein of Galen malformation; VSD, ventricular septal defect.

SM Boyd et al. Clin Perinatol 51 (2024) 45–76

Clinical Assessment and Monitoring

<u>Clinical assessment of Pulmonary Hypertension:</u>
In an infant with suspected PH and HRF the initial evaluation should include a thorough history, physical examination, and physiological monitoring (ECG, blood pressure, pre and post ductal oxygen saturation) and initial investigations (arterial blood gas, chest X-ray) to assess the underlying condition and severity of PH.

Differentiating cyanotic congenital heart disease (CHD) from PH is of paramount importance, but can be challenging. Until a definitive echocardiographic diagnosis can be made, PGE1 should be used to maintain ductal patency in the critically unwell newborn.

The clinical significance of PH is therefore based on combined assessment of (Table 2):

I. Oxygenation
II. Pulmonary artery pressure
III. Cardiac function (in right and left ventricles)

Direct measurement of pulmonary artery pressure (PAP) and cardiac function using "gold standard" techniques of cardiac catheterisation is not safe or practical in newborns. Instead, echocardiography is the clinical standard.

PAP can be estimated by echo using two principal techniques:

a) Peak velocity of tricuspid regurgitation jet (TR_{max}): PAP is estimated from the TR_{max} using a modified Bernouilli equation ($PAP = 4xTR_{max}{}^2$). However, TR may not always be present, even in severe PH, and the technique is prone to measurement error.
b) Direction and velocity of flow in patent ductus arteriosus (PDA): Flow through an unrestricted PDA is determined by pressure gradient differences between the pulmonary artery and aorta. Bidirectional, or right-to-left flow patterns indicate PAP equal or greater than systemic aortic pressure.

Additional echocardiographic techniques, including time to peak velocity in the pulmonary artery (PAAT) and septal position may also be used to assess PAP/PVR. Tricuspid annular plane systolic excursion (TAPSE) and Tissue Doppler Imaging (TDI) could be measured to assess systolic ventricular function.

Clinical assessment of PH in the newborn infant

Oxygenation	Pulmonary artery pressure	Cardiac function
Arterial oxygen saturations, SaO_2	Pre-post ductal oxygen saturation differences	Invasive systemic blood pressure (including pulse pressure)
Arterial PaO_2 Plasma lactate Venous oxygen saturation (SVO_2)	**Echocardiographic assessment:** • Tricuspid regurgitation velocity • PDA shunting pattern • Shunting pattern through PFO • Time to peak velocity in pulmonary artery • Septal shape	**Echocardiographic assessment:** • "Eyeballing" from 2d loops • Quantitative measures of cardiac function in right and left ventricle

Table 2: Clinical assessment of PH in newborn infant. Montasser M & Patel N. Paediatrics & Child Health, 2021.

Advanced Monitoring of Hypoxic Respiratory Failure:

It is important to continuously monitor response to treatment. There are different parameters that could be used to monitor oxygenation:

1. **Oxygen saturation histograms** can be extrapolated from bedside monitors. Target range should be equal or above 95% and avoid hypoxia (<85%) and hyperoxia (>98%) for prolonged periods.

2. **Alveolar-arterial (A-a) gradient:**
   A/a gradient = P_AO_2 - PaO_2. Normally 5 –10, if no impediment to diffusion

   Alveolar P_AO_2 can be calculated using alveolar gas equation as follows:

   Alveolar Partial pressure of O2 (P_AO_2) = [FiO_2 X (760- 47)] – ($PaCO_2$ / 1)

760 is atmospheric pressure at sea level, 47 is when assuming 100% humidity of alveoli, 1 is the respiratory quotient in neonates

3. **Oxygenation Index (OI):**
   OI = (MAP X FiO_2 x 100) / PaO_2 in mmHg. (1 Kpa = 7.5 mmHg)
   MAP= mean airway pressure

4. **Oxygen Saturation Index (OSI):**
   OSI = (MAP x FiO2 x 100) / SpO2

5. **Brain Oxygen Saturation** by NIRS (near infrared spectroscopy) monitor if available.

Degree of severity of HRF could be assessed by the following table:

Monitoring oxygenation
Always look at the trend

Parameters	Target	Moderate	Severe
Oxygen saturation histograms	100 % within the target	<5 % hypoxemia < 10 % hyperoxia	> 5 % hypoxemia >10 % hyperoxia
A-a gradient	<20	20-100	>100
Oxygenation index	<5	10-15	>15
Oxygen saturation index	<2.5	5-7.5	>7.5
Saturation : FiO2 ratio (SFR)	>350	180-350	<180
V:Q Ratio	> 0.75	0.5-0.75	<0.5
R-L shunt	< 10%	10-20	> 20%
Brain oxygen Saturation	60-80 %	<60 %	<50 %

Management

Management of Pulmonary Hypertension in HRF

Physiologic Goals & Therapeutic Recommendations:

Table 3
Physiologic goals and therapeutic recommendations by pulmonary hypertension phenotype

PH Phenotype	Physiologic Goals	Suggested Treatment Approach
Acute PH		
Arterial (classic)	Reduce PVR Augment RV performance Support SAP and maintain coronary perfusion pressure	Optimize lung recruitment and supportive care Offload RV with pulmonary vasodilators Augment RV function with inotropes if required Support SAP with vasoconstrictors which do not ↑PVR Consider maintaining ductal patency with PGE
Flow mediated	Shunt control Maintain ↑PVR	Specific shunt management Avoid selective pulmonary vasodilators Consider permissive hypercapnia (pCO_2 50–60 mmHg, pH > 7.25) Avoid hyperoxia (goal preductal SpO_2 91%–95%* and preductal pCO_2 50–80 mm Hg[138]) *higher SpO_2 may be needed if undergoing TH
Left heart dysfunction (postcapillary)	LV afterload reduction Positive inotropy Maintain ↑PVR Maintain R→L ductal shunt if ↓SBF	LV afterload reduction if SAP adequate, for example, inodilator Positive inotropy Avoid selective pulmonary vasodilators Diuretics for pulmonary edema
Chronic PH		
Arterial (classic) for example, associated with BPD	Reduce PVR	Optimize lung recruitment and supportive care Offload RV with pulmonary vasodilators Consider diuretics if RV dilation Avoid hypoxia and hyperoxia (target oxygen saturations 92%–95%[106])
Flow mediated	Shunt control Maintain ↑PVR	Specific shunt management (reduction in or closure of L-R shunt if feasible and appropriate) Avoid selective pulmonary vasodilators Diuretics for ASD/VSD Positive end expiratory pressure
Systemic hypertension	LV afterload reduction Maintain ↑PVR	Antihypertensive therapy role for ACE inhibitors/ARB Avoid pulmonary vasodilators

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; ASD, atrial septal defect; L, left; PGE, prostaglandin E, PH; pulmonary hypertension, PVR; pulmonary vascular resistance, R; right, RV; right ventricle, SAP; systolic arterial pressure, SBF; systemic blood flow, TH; therapeutic hypothermia, VSD; ventricular septal defect.

SM Boyd et al. Clin Perinatol 51 (2024) 45–76

Pulmonary vasodilator therapies:
Use of inhaled nitric oxide is associated with improved oxygenation and outcome (death/need for ECMO) in term infants with hypoxic respiratory failure (ref).

Second line pulmonary vasodilators (e.g. sildenafil) should be reserved for use in experienced centres.

<u>Pulmonary vasodilators (e.g. iNO) are contraindicated</u> in specific situations as illustrated below:

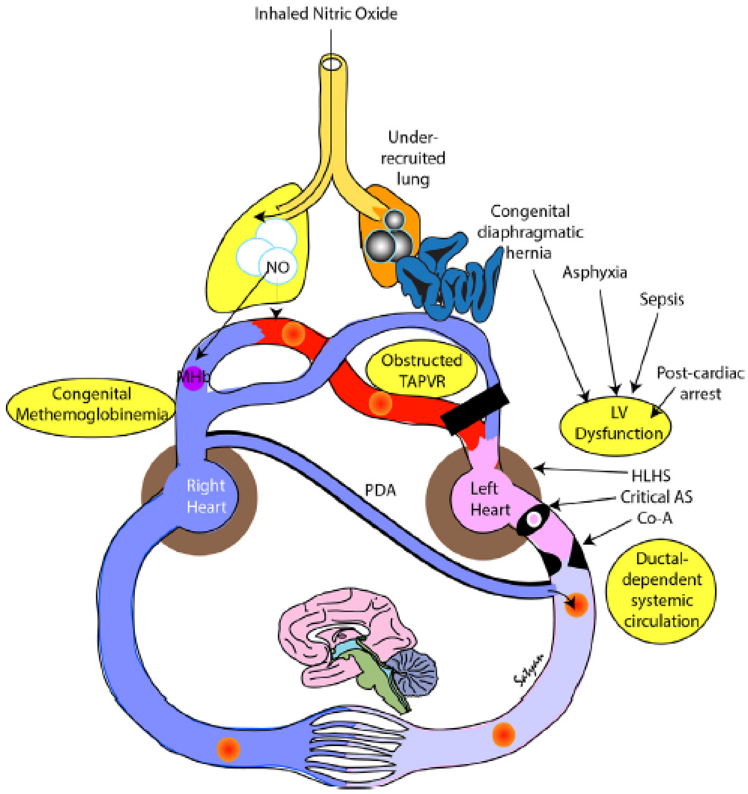

Fig. 3. Contraindications for iNO therapy in HRF. Congenital methemoglobinemia or MetHb reductase deficiency can be exacerbated by iNO therapy worsening hypoxemia. LV dysfunction and pulmonary venous hypertension are worsened by iNO due to pulmonary edema. Ductal-dependent systemic circulation as seen in hypoplastic left heart syndrome (HLHS), critical aortic stenosis (AS), or coarctation of the aorta (Co-A) maintain their systemic circulation through a right-to-left shunt across the patent ductus arteriosus (PDA). Reduced pulmonary arterial pressure by iNO abolishes this shunt and causes systemic hypoperfusion.
MW Cookson & JP. Kinsella. Clin Perinatol 51 (2024) 45–76

<u>Management of Systemic Hypotension in HRF</u>

Mechanisms of hypotension and treatment approaches are summarised in Table 2.

Table 2: Mechanisms of systemic hypotension in PPHN/HRF

Mechanism of systemic hypotension	**Clinical findings**	**Therapeutic principle**	**Therapy**
⇓ LV function (common)	⇓ pulse pressure Echo evidence	⇑ cardiac function	Adrenaline (0.03-0.05 mcg/kg/min) OR Dobutamine 5-10 mic/kg/min *Consider Milrinone in level 3 units

⇓ LV filling / Preload	⇓ PBF	⇓ pulse pressure.	⇓ PVR	Pulmonary vasodilator therapies
	Hypovolaemia		⇑	Volume / RBC transfusion
Systemic vasodilatation		⇓ diastolic pressure	Vasoconstriction	Low dose noradrenaline or vasopressin. Caution in LV dysfunction.

*Milrinone may also be considered to treat cardiac dysfunction in centres with experience. Milrinone is a systemic (and pulmonary) vasodilator so should only be used with caution if there is pre-existing hypotension.

Important considerations for Milrinone:

1. Milrinone should be used in tertiary centres preferably after formal echo assessment by cardiologist or neonatologist experienced in echocardiography and haemodynamics.
2. **Do not** give Milrinone bolus to avoid systemic hypotension.
3. Start at 0.3 mic/kg/min and gradually (every 4-6 hrs) increase to 0.5 mic/kg then finally to 0.7 mic/kg if no side effect of systemic hypotension. Milrinone should also be weaned slowly over 24-48 hrs.
4. Milrinone should be used with caution **or better avoided** in HIE infants due to significant decrease of its metabolism (renal) and it's build up and accumulation in the body leading to much more side effects. In these infants never give Milrinone bolus.
5. Dopamine and pulmonary hypertension: Due to its effect on increasing PVR, dopamine can contribute or worsen hypoxemic respiratory failure and PH. By inducing pulmonary vasoconstriction, dopamine may increase right ventricular (RV) afterload and contribute to RV dysfunction. This can increase RV end-diastolic pressure and the volume of right-to-left shunting at the atrial level. Decreased pulmonary blood flow is associated with decreased pulmonary venous return, LV preload, and lower LV output, ultimately impairing tissue blood flow and oxygen delivery. Therefore, Dopamine should be avoided in the setting of acute pulmonary hypertension and HFR.

Special Considerations in Management of Hypotension and Cardiac Function in PPHN:

1. **LV dysfunction**: LV dysfunction is common in infants with a clinical presentation of "PPHN", and may be secondary to acidosis and hypoxia during the transitional process. LV dysfunction contributes to increased PAp (and hence hypoxic shunting) and to systemic hypotension in PPHN. Inotropic therapy should be used to support cardiac function, and ECMO considered in severe cases. LV dysfunction is a

transitional phenomenon and typically improves with supportive therapy over the first days if life.

Adrenaline in lower dose (0.03-0.1 mcg/kg/min or dobutamine (5-10 mcg/kg/min) are suitable first line agents. Milrinone improves systolic (inotropic) and diastolic (lusitropic) function and may be used in experienced centres.

Pulmonary vasodilators and systemic vasoconstrictors **should be used with caution in LV dysfunction** as they may worsen LV function by increasing preload and afterload respectively.

2. **Maintaining ductal patency:** Prostaglandin infusion may be used to maintain ductal patency as a “blow-off” valve for the pressure loaded RV. This should be guided by echocardiographic evidence of 1) Supra-systemic PA pressure (i.e. PAP>Systemic BP), Dilated/dysfunctional RV, and closing PDA.

3. **Volume administration**: Fluid boluses should only be administered if there is evidence of hypovolaemia, such as low central venous pressure or diastolic pressure, documented excessive losses or concerns for increased insensible losses.

4. **Infants born to mothers with diabetes** may have hypertrophic cardiomyopathy. Catecholamine infusions may cause increased inotropy and/or chronotropy and exacerbate left ventricular outflow obstruction. Milrinone in conjunction with β-blockade, may provide improved cardiac output and oxygenation due to its inotropic effect without chronotropy, its ability to relax the heart muscle in diastole (lusitropy) and vasodilatory properties.

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Development

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Appendix

Appendix 1: Drugs used in the management of infants with hypoxic respiratory failure

Adapted from Siefkes HM, Lakshminrusimha S. Arch Dis Child Fetal Neonatal Ed 2021;0:F1–F10.

See more information and full monograph for drugs listed below at:
http://www.knowledge.scot.nhs.uk/child-services/communities-of-practice/neonatal-managed-clinical-networks/west-of-scotland/neonatal-drug-formulary-(wos).aspx

Goals of Treatment of PH:
The ultimate goal is to achieve adequate pulmonary blood flow (PBF) and systemic blood flow (SBF) by:

1. Increasing systemic vascular resistance (SVR) to an adequate level (with caution in cases with severe LV dysfunction as it might worsen the condition).
2. Decrease pulmonary vascular resistance (PVR) and pulmonary artery pressure (PAP) by using pulmonary vasodilators.
3. Optimize heart function (inotropes/lusitropes) and avoid excessive myocardial oxygen consumption (good analgesia/sedation and avoid excessive tachycardia).
4. Maintaining ductal patency in supra-systemic pulmonary hypertension with biventricular dysfunction as duct will work as a 'pop-off' valve for the right ventricle and more importantly will provide systemic blood flow by right to left shunting. In these conditions, avoid reversing the direction of shunt flow before supporting the biventricular dysfunction (e.g. with Milrinone).

Drugs	Receptors	SVR	PVR	SV	HR	Contractility	BP (MAP)	Recommended Dosage	Effects	Pearls (When to consider)
Noradrenaline	α_1 α_2 β_1	↑↑↑	↑	↑	↑	No effect	↑↑	0.02-0.5 mic/kg/min Start: 0.05 mic/kg/min	↑SVR & PVR ↑MAP ↓PAP	Start when HR>160 Adr<$\beta_{1\ activity}$<Noradr Good for septic shock
Adrenaline	α_1 α_2 β_1 β_2	↑↑↑	↑	↑	↑↑↑	↑	↑↑	0.01-0.1 mic/kg/min Start: 0.05 mic/kg/min	↑SVR, ↑MAP ↑Contractility	<0.1 (β_1 β_2) - ↑ function >0.1 (β_1 β_2 α_1 α_2) - ↑ MAP
Vasopressin	V_1 V_2	↑↑↑	↓↓	↑	No effect	No effect	↑↑	0.1-1.2 milliunit/kg/min Start: 0.1 milliunit/kg/min	↑SVR, ↑MAP ↓PVR	Increase Preload Possible 1st line ↑SVR & ↓PVR Monitor for Hypo Na Avoid w/LV Dysfunction
Hydrocortisone		↑↑↑	No effect	No effect	↑	No effect	↑↑	1mg/kg/dose q 8 hr	↑SVR, ↑MAP	Delayed response for 4-8 h Add with 2nd line agent
Milrinone	PDE III Inhibitor	↓↓	↓↓	↑↑	↑	↑	↓	0.3 - 0.7 mic/kg/min Start: 0.3mic/kg/min NO loading dose	↑Contractility ↓SVR & PVR ↓MAP	Not 1st line Use w/ severe Heat dysf & stable BP ↓PAP & will ↓SVR
Dopamine	α_1 β_1 β_2 D	↑↑	↑↑↑	↑	↑↑↑	↑	↑↑	4-10 mic/kg/min Start: 4 mic/kg/min	↑SVR & ↑PVR ↑MAP ↑Contractility	<2 : D ↑UOP 2-6: β_1 D ↑Function >6: α_1 β_1 D ↑SVR Can cause ↑PVR & ↑HR
Dobutamine	α_1 β_1 Weak β_2	No effect	No effect	↑↑	↑↑	↑	↓	4-10 mic/kg/min Start: 4 mic/kg/min	↑Contractility ↓SVR (high doses)	Cardiac dysfunction Can cause ↓ SVR

α_1 α_2	Peripheral Vasoconstriction
β_1	↑COP (Chronotropy & Inotropy)
β_2	Vasodilatation

Dop	Renal vasodilatation, Increase contractility
V_1	Systemic vasoconstriction
V_2	Pulmonary vasodilatation

Drug	Cutoff Value → consider 2nd agent
Adrenaline	0.1 microgram/kg/min
Noradrenaline	0.1 microgram/kg/min
Dopamine	7.5-10 microgram/kg/min

PPHN Goals: Adequate PBF & SBF
a) ↑SVR (avoid too high SVR)
b) ↓PVR & ↓PAP
c) Optimize Heart Fx