National Neonatal Network

Scotland

Clinical Guidelines

Hypoxic Respiratory Failure in Term & Near Term Infants

Disclaimer

This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient's case notes at the time the relevant decision is taken.

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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: https://www.clinicalguidelines.scot.nhs.uk/media/2889/neuroprotection-care-pathway-for-infants-with-hie.pdf

The monographs for medications referenced in this document can be accessed via http://www.knowledge.scot.nhs.uk/child-services/communities-of-practice/neonatal-managed-clinical-networks/west-of-scotland/neonatal-drug-formulary-(wos).aspx

Alternatively, local monographs are available.

Contents

SUGGESTED STEP-WISE MANAGEMENT OF TERM & NEAR TERM INFANTS WITH HYPOXIC RESPIRATORY FAILURE

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

Pathway for referral to Royal Hospital for Children, Glasgow

- 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 990 240** 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 http://www.knowledge.scot.nhs.uk/child-services/communities-of-practice/neonatal-managed-clinical-networks/west-of-scotland/neonatal-drug-formulary-(wos).aspx

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 (FiO_2>60%, pCO_2 > 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 **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 >40mmHg • Monitor urine output	**Inotropes** • Commence Adrenaline at 0.03 - 0.05 mcg/kg/min **OR*** • Dopamine 5-10 mcg/kg/min** *Use adrenaline and dopamine together with caution to avoid excessive tachycardia **Dopamine dose above 10mcg/kg/min should be used with caution due to risk of tachycardia leading to reduced cardiac output
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	**Surfactant** • Surfactant 200mg/kg if evidence of surfactant deficiency/ inactivation **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 mean BP >40mmHg • Monitor urine output • Correct metabolic acidosis • Adrenaline 0.03-0.1mcg/kg/min • **OR** Dopamine 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
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	**Remember 'DOPE'** • Dislodgement of ETT • ETT Obstruction • Pneumothorax • Equipment failure **Surfactant** • Surfactant 200mg/kg if evidence of surfactant deficiency/ inactivation. **Remember** • Consider LV dysfunction if no response to iNO therapy.
Cardiovascular	• Keep mean BP >40mmHg • Monitor urine output • Adrenaline 0.03-0.1mcg/kg/min • **OR** Dopamine 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 e.g. Dobutamine or Milrinone in experienced centres **Remember** • Avoid repeatedly increasing inotropic support without further discussion as high doses can lead to reduced cardiac output via chronotropy and vasoconstriction. • Combination of Dopamine + Dobutamine should be used with extreme caution as both will cause excessive tachycardia.
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.

Pathophysiological consequences of pulmonary hypertension in HRF

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

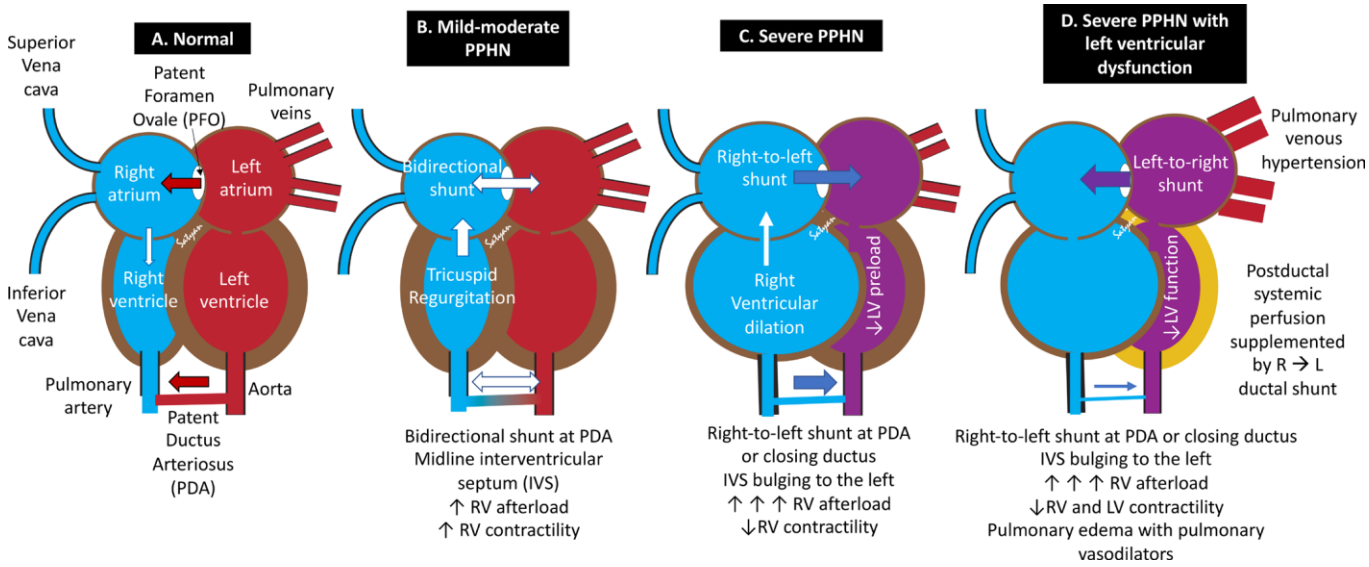

Figure 2: Pathophysiological models of PPHN
from Siefkes HM, Lakshminrusimha S. Arch Dis Child Fetal Neonatal Ed 2021

Clinical assessment of Pulmonary Hypertension:

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	**Echocardiographic assessment:**	**Echocardiographic assessment:**
Plasma lactate	• Tricuspid regurgitation velocity	• "Eyeballing" from 2d loops
Venous oxygen saturation (SVO_2)	• PDA shunting pattern	• Quantitative measures of cardiac function in right and left ventricle
	• Shunting pattern through PFO	
	• Time to peak velocity in pulmonary artery	
	• Septal shape	

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 of Pulmonary Hypertension in HRF

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). However, response to iNO is variable which may be partly related to the presence of LV dysfunction (which can be exacerbated by pulmonary vasodilatation).

We recommend a systematic approach based on each infant's underlying condition and pathophysiology, Figure 3.

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

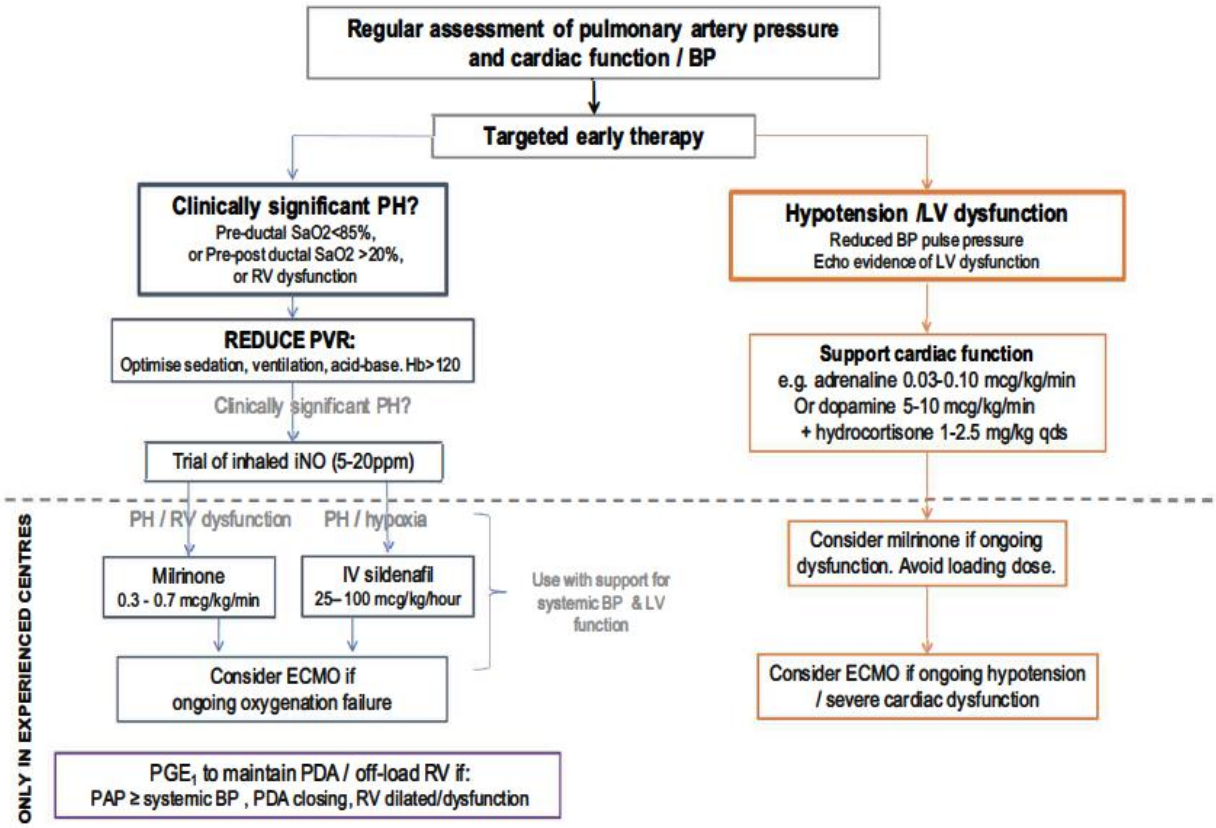

Figure 3: Systematic approach to management of the circulation in HRF / PH
Adapted from Montasser M & Patel N. Paediatrics & Child Health, 2021.

Management of Systemic Hypotension in HRF

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 (0.03-0.1 mcg/kg/min) or Dopamine (5 -10 mcg/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.

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.

Dopamine and dobutamine in higher doses (>10mcg/kg/min) must be avoided due to their positive chronotropic actions (increased heart-rate) which may exacerbate cardiac dysfunction. Systemic vasoconstrictors should be used cautiously in LV dysfunction, to avoid increased LV afterload and worsening dysfunction.

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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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