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NARRATIVE REVIEW

Persistent pulmonary hypertension of the newborn, Part 2: optimising supportive and pharmacologic therapies. A review

Hipertensão pulmonar persistente do recém-nascido, parte 2: otimização das terapêuticas de suporte e farmacológicas. Uma revisão

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Abstract

Persistent pulmonary hypertension of the newborn (PPHN) is a serious and potentially life-threatening condition characterised by a persistently elevated pulmonary vascular resistance and right-to-left shunting of blood, leading to severe hypoxaemia. It occurs due to an abnormal transition from foetal to extrauterine circulation. Effective management relies on a comprehensive approach that includes both supportive care and targeted pharmacologic interventions. This review focuses on optimising current treatment strategies, emphasising the role of supportive measures such as adequate oxygenation, ventilation strategies, sedation and haemodynamic stabilisation. In addition, it explores the use of selective pulmonary vasodilators, with particular attention to inhaled nitric oxide as the first-line agent, as well as the roles of sildenafil, prostacyclin analogues and other emerging therapies. For severe and refractory cases, extracorporeal membrane oxygenation offers lifesaving cardiopulmonary support while allowing time for pulmonary vascular adaptation and recovery. Early recognition and individualised treatment are essential to improving outcomes in neonates with PPHN.

Keywords: ECMO. Newborn. Supportive care. Persistent pulmonary hypertension. Pulmonary vasodilators.

Resumo

A hipertensão pulmonar persistente do recém-nascido (HPPRN) é uma condição grave e potencialmente fatal, caracterizada por uma resistência vascular pulmonar persistentemente aumentada e *shunt* sanguíneo da direita para a esquerda, conduzindo a uma hipoxemia severa. Ocorre devido a uma transição anormal da circulação fetal para a extrauterina. O tratamento eficaz baseia-se numa abordagem abrangente que inclui tanto cuidados de suporte como intervenções farmacológicas específicas. Esta revisão centra-se na otimização das estratégias terapêuticas atuais, com ênfase no papel das medidas de suporte, como uma oxigenação adequada, estratégias ventilatórias, sedação e estabilização hemodinâmica. Adicionalmente, explora o uso de vasodilatadores pulmonares seletivos, com particular destaque para o óxido nítrico inalado como agente de primeira linha, bem como os papéis do sildenafil, dos análogos da prostaciclina e de outras terapias emergentes. Nos casos graves e refratários, a oxigenação por membrana extracorporal oferece um suporte cardiopulmonar vital, permitindo tempo para a adaptação e recuperação da vasculatura pulmonar. O reconhecimento precoce e o tratamento individualizado são essenciais para melhorar os resultados em recém-nascidos com HPPRN.

Palavras-chave: ECMO. Recém-nascido. Cuidados de suporte. Hipertensão pulmonar persistente. Vasodilatadores pulmonares.

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Keypoints

What is known?
- PPHN is a life-threatening condition resulting from a failed circulatory transition after birth.
- Inhaled nitric oxide (iNO) is the standard first-line therapy for PPHN.
- Supportive care, including ventilation and haemodynamic management, is essential to optimise oxygenation.

What is added?
- The article emphasises practical bedside decision-making guided by the underlying pathophysiology of PPHN.
- A comprehensive supportive treatment approach is proposed, incorporating new insights into individualised therapy.
- It summarises updated information on pulmonary and vasoactive drugs and their clinical applications in the treatment of PPHN.

Introduction

Persistent pulmonary hypertension of the newborn (PPHN) remains a significant cause of morbidity and mortality in neonates, particularly among term and late preterm infants.[1] As discussed in Part 1 of this review, PPHN is characterised by the failure of normal circulatory transition after birth, resulting in sustained elevated pulmonary vascular resistance (PVR) and right-to-left shunting of blood.[1] Understanding the underlying pathophysiology, clinical presentation, aetiological factors and diagnostic approach is essential for timely recognition and appropriate management.[2,3]

In this second part, the author focus on the therapeutic strategies for PPHN. Effective treatment requires a comprehensive and individualised approach aimed at optimising oxygenation, reducing PVR and supporting cardiopulmonary function while addressing the underlying cause. In this second part, both conventional and advanced therapies, including the use of inhaled nitric oxide (iNO), ventilatory support modalities, pharmacological agents and emerging treatments, will be discussed.[4] Additionally, this section will explore the challenges related to treatment selection, therapeutic response monitoring and long-term outcomes. Among survivors, long-term morbidities are common and may include neurodevelopmental delays, cognitive impairments and hearing abnormalities.[5-10]

Management of PPHN

The management of newborns with PPHN is based on a thorough clinical assessment aimed at identifying any underlying pathology, whenever possible, through the perinatal history, clinical presentation and diagnostic investigations.[1,2,4,11] Recognising the primary cause is essential for guiding targeted therapy. In parallel, general supportive measures play a fundamental role.[1,2,4,11] The primary objectives are to optimise oxygenation, reduce oxygen consumption, minimise physiological stress and stabilise cardiorespiratory function.[1] These non-specific interventions represent the initial cornerstone of therapy and are essential complements to targeted pulmonary vasodilator treatments. Supportive strategies should be carefully individualised based on the infant's clinical status and therapeutic response.[1] Importantly, they establish the physiological conditions necessary for pulmonary vasodilators to exert their maximal effectiveness. In many cases, timely, precise and well-coordinated supportive care can lead to significant clinical improvement even before the initiation of advanced pharmacological interventions. Table 1 provides an overview of key supportive interventions in PPHN management.[1,2,4,11] Once supportive care is established, specific pulmonary vasodilator therapy is introduced to reduce PVR and improve oxygenation. A combined approach that integrates both aetiology-directed treatment and pulmonary vasodilation offers the best chance of improving outcomes in neonates with PPHN.[1,2,4,11]

Pharmacologic pulmonary vasodilation

PPHN is characterised by sustained elevated PVR, right-to-left shunting and hypoxaemia. Affected neonates often present with systemic hypotension. Timely and targeted pharmacologic intervention is critical to reduce PVR and improve oxygenation.[12] Two main classes of drugs are frequently employed: pulmonary vasodilators and vasoactive amines, as shown in table 2.

Pulmonary vasodilators

The cornerstone of treatment for PPHN is iNO, a selective pulmonary vasodilator that improves ventilation–perfusion matching without causing systemic hypotension.[13] iNO is indicated in term and near-term infants with PPHN or hypoxemic respiratory failure who have an OI that exceeds 20-25.[14] iNO can be beneficial for preterm infants with severe hypoxaemia that is due primarily to PPHN physiology rather than parenchymal lung disease, particularly if associated with prolonged rupture of membranes and oligohydramnios.[14]

Table 1. General supportive strategies for the management of persistent pulmonary hypertension of the newborn[1,2,4,11,12]

Aspect	Main description	Clinical goal	Interventions/examples
Identifying and treating underlying conditions	Early diagnosis and treatment of causes.	Reduce pulmonary vascular resistance (PVR).	CDH (surgery), RDS (surfactant), sepsis and pneumonia (antibiotics), MAS (supportive), tension pneumothorax (drainage).
Environmental and comfort measures	Reduction of external stressors through environmental control and comfort measures are paramount.	Lower sympathetic tone and vasoconstriction.	Quiet, stable low-stress environment, dim lighting, minimal handling. Thermal regulation since hypothermia increases metabolic demand and oxygen consumption, while hyperthermia may induce vasodilation and haemodynamic instability.
Urinary catheterisation	Monitor urine output and fluid status.	Assess renal perfusion and fluid balance. Helps detect early signs of fluid overload or dehydration.	Aseptic catheter insertion. In critically ill neonates receiving sedation and analgesia, or vasoactive medications, spontaneous voiding may be absent, making catheterisation essential for reliable assessment.
Vascular access	To ensure delivery of fluids, parenteral nutrition, medications and blood products, as well as blood sampling for frequent laboratory monitoring, and to monitor blood pressure.	The choice and timing of vascular access should balance the urgency of treatment, and the neonate's overall condition.	Peripheral IV, umbilical lines, PICC. An umbilical arterial or radial catheter may be placed for continuous blood pressure monitoring. Meticulous care of vascular lines is paramount to prevent complications such as infection and thrombosis.
Analgesia and sedation	Control pain and agitation. Pain, discomfort and agitation can lead to increased sympathetic nervous system activity, resulting in elevated PVR and worsening hypoxaemia.	Prevent stress-induced increased PVR.	Morphine, fentanyl, midazolam (with caution). The choice and dosage of sedative and analgesic medications should be individualised, aiming for the lowest effective dose to maintain comfort while avoiding respiratory or haemodynamic compromise. Continuous assessment using validated pain and sedation scales is recommended to ensure appropriate titration and avoid over-sedation. Short-term muscle relaxation may be beneficial in labile infants, to achieve respiratory synchrony with mechanical ventilation. Muscle relaxants may have unwanted side effects such as hypoxaemia, hypotension and bradycardia. Prolonged muscle relaxant infusions may also exacerbate oedema and are associated with prolonged muscle blockade and post-extubation muscle weakness.
Correction of metabolic disturbances	Treat acidosis, hypoglycaemia and electrolyte imbalances. Hypocalcaemia can exacerbate pulmonary vasoconstriction and impair myocardial function.	Improve heart and lung function.	Bicarbonate (carefully), glucose, calcium and magnesium. Metabolic acidosis, in particular, increases PVR and should be promptly identified and treated. Bicarbonate may be considered, although this must be balanced against the risk of intracellular acidosis and carbon dioxide retention. Magnesium may assist in pulmonary vasodilation; therefore, levels should be kept in the upper normal ranges.
Oxygen therapy	Use of supplemental oxygen. Oxygen has potent pulmonary vasodilatory effects.	Reduce PVR and improve oxygen delivery. Avoid both hyperoxia and hypoxia.	Initial management often involves administration of 100% oxygen during acute hypoxemic episodes. Titrate FiO_2 to pre-ductal SpO_2 92-97%; monitor OI.
Mechanical ventilation	Ensure adequate gas exchange.	Prevent lung injury and maintain oxygenation. Aim for pH near 7.4, $PaCO_2$ of 35-45 mmHg, SpO_2 of 92-97% and PaO_2 of 60-90 mmHg in blood gas test.	Non-invasive ventilation, such as nasal continuous positive airway pressure (nCPAP), may be appropriate in mild cases. Conventional ventilation and HFOV are mostly used. The choice of ventilation type and mode should be individualised, balancing oxygenation goals with the risk of lung injury and haemodynamic effects. Keep the lungs well expanded, showing nine posterior ribs on the chest x-ray.

Continues

Table 1. General supportive strategies for the management of persistent pulmonary hypertension of the newborn (*continued*)

Aspect	Main description	Clinical goal	Interventions/examples
Lung volume optimisation	Adequate lung inflation prevents alveolar collapse and maintains functional residual capacity, facilitating effective oxygenation and ventilation. PEEP is a critical component.	Enhance oxygenation and reduce PVR.	Lung-volume optimisation aims to achieve stable functional residual capacity using gentle, lung-protective ventilation. Conventional modes (SIPPV with VG) are initiated first, with adequate PEEP and controlled tidal volumes to prevent atelectasis and overdistension. When oxygenation remains unstable, typically with FiO_2 > 0.60, rising MAP requirements, suboptimal recruitment or limited response to iNO, VAFO should be introduced. VAFO allows precise control of lung volume through incremental increases in MAP, improving recruitment, gas exchange and ventilation–perfusion matching while minimising ventilator-induced lung injury.
Acid–base balance	Monitor and correct imbalances. Acidosis (respiratory or metabolic) can significantly increase PVR, exacerbate hypoxaemia and promote myocardial dysfunction.	Prevent acidosis-related PVR increase.	Adjust ventilation. Cautious bicarbonate administration; avoiding overcorrection is essential to prevent complications such as intracellular acidosis and carbon dioxide retention.
Haemoglobin levels	Maintain adequate oxygen-carrying capacity.	Improve systemic oxygen delivery.	Transfusion thresholds should be carefully considered. Target haemoglobin levels are generally individualised based on the infant's clinical condition, oxygenation status and overall haemodynamic stability. In most cases, keep haemoglobin > 14 g/dL. Polycythaemia and hyperviscosity will increase PVR. Partial exchange transfusion aiming for a haematocrit level of 50% to 55% might be considered in an infant with PPHN whose central haematocrit is > 65%.
Gastric tube and enteral feeding	Decompress stomach and initiate feeding. A gastric tube decompresses the stomach, reduces the risk of aspiration, improves diaphragmatic movement and enhances respiratory mechanics.	Prevent aspiration and support gut health.	Orogastric tube; trophic feeds once stable. Enteral feeding is usually initiated cautiously once the infant demonstrates haemodynamic stability and adequate respiratory function. Feeding plans should be individualised, considering the infant's clinical condition, risk of aspiration and gastrointestinal function.
Nutritional support	Meet metabolic needs.	Support growth and avoid fluid overload.	In the acute phase, many infants with PPHN require parenteral nutrition due to respiratory instability. As clinical status improves and haemodynamic stability is achieved, gradual introduction of minimal enteral nutrition is encouraged.
Stress ulcer prevention	Prevent mucosal injury.	Reduce GI bleeding risk.	H2 blockers/proton pump inhibitors in high-risk cases; early enteral feeds.
Antibiotic therapy	Treat possible infections early.	Reduce inflammation and disease progression.	Start empirically if sepsis suspected; stop if cultures negative.
Volume and diuresis management	Ensure euvolemia and appropriate urine output.	Optimise preload and prevent overload	Diuretics; fluid balance monitoring. Both hypovolaemia and hypervolaemia can have detrimental effects; hypovolaemia may lead to decreased preload and impaired cardiac function, while fluid overload can exacerbate pulmonary oedema, worsening oxygenation and pulmonary hypertension.
Volume expanders and albumin	Restore intravascular volume.	Improve cardiac output in select cases.	Crystalloids, cautious albumin use. Albumin is reserved for hypoalbuminaemic infants or those with capillary leak syndrome.
Monitoring	Continuous observation and assessment.	Guide therapy and detect deterioration early.	SpO_2 (pre/post-ductal), OI, blood pressure, serial echocardiography, heart rate, blood gases, laboratory tests and diuresis. Central venous pressure monitoring may be employed in cases requiring inotropic support to assess fluid status and cardiac function.

CDH: congenital diaphragmatic hernia; GI: gastrointestinal; IV: intravenous; RDS: respiratory distress syndrome; MAP: mean airway pressure; MAS: meconium aspiration syndrome; OI: oxygenation index ($OI = FiO_2 \times MAP \times 100/PaO_2$, where FiO_2 is the fraction of inspired oxygen, MAP is the Mean Airway Pressure and PaO_2 is the arterial partial pressure of oxygen); PaO_2: arterial partial pressure of oxygen; $PaCO_2$: arterial partial pressure of carbon dioxide; PEEP: positive end-expiratory pressure; PICC: peripherally inserted central catheters; PVR: pulmonary vascular resistance; SIPPV: synchronised intermittent positive pressure ventilation; SpO_2: peripheral oxygen saturation; VAFO: high frequency oscillatory ventilation; VG: volume guarantee.

Table 2. Pulmonary vasodilators and vasoactive agents in persistent pulmonary hypertension of the newborn[1,2,4,9,11-18,29-40,45-62]

Drug	Class	Dose/regimen	Primary effect	Risks/adverse effects
Inhaled nitric oxide (iNO)	Pulmonary vasodilator	5-20 ppm (start at 20 ppm; titrate based on response).	Selective pulmonary vasodilation.	Rebound PH, NO_2 toxicity, methemoglobinemia.
Sildenafil (oral/IV)	PDE5 inhibitor	IV: Loading: 0.4 mg/kg administered over three hours followed by: Maintenance: 1.6 mg/kg/day (0.067 mg/kg/hour) as a continuous infusion for up to seven days. PO: Start at 0.5 to 1 mg/kg/dose given six to eight hourly and titrate up to 2 mg/kg/dose according to response. NOTE: Higher doses of up to 3 mg/kg/dose every six hours have been reported in selected settings; however, safety data is limited, and this regimen should not be presented as standard neonatal practice.	Pulmonary vasodilation; improves oxygenation.	Systemic hypotension, retinopathy, priapism (rare). Note: To avoid the possible occurrence of sudden clinical deterioration during the withdrawal of sildenafil, a gradual dose reduction should be considered when stopping sildenafil.
Bosentan (oral)	Endothelin receptor antagonist	Oral: 0.5-2 mg/kg/dose, twice daily. Commence at 0.5 mg/kg/dose 12 hourly. Increase incrementally in consultation with cardiologist to a maximum of 2 mg/kg/dose 12 hourly.	Broad pulmonary vasodilation.	Hepatotoxicity, anaemia, oedema, drug interactions.
Iloprost (inhaled)	Prostacyclin analogue	1-2 mcg/dose every 2-4 hours via nebulisation; 4-8 inhalations/day.	Pulmonary vasodilation.	Cough, bronchospasm, hypotension.
Epoprostenol (IV)	Synthetic prostacyclin	Start with 1-2 ng/kg/min; Titrate 1-2 ng/kg/min up to 10 ng/kg/min continuous IV.	Potent vasodilator, antithrombotic effects.	Severe hypotension, bleeding, haemodynamic instability.
Milrinone (IV)	PDE3 inhibitor	Loading dose of 50 µg/kg administered over 60 min, followed by 0.33-0.75 mcg/kg/min continuous IV. NOTE: loading dose is usually not used, as in neonates with PPHN and haemodynamic instability it may worsen or cause hypotension, with the harmful effects outweighing the benefits. It can be used cautiously when systemic blood pressure is at the upper limit of normal.	Inotrope + mild vasodilator (↓ PVR)	Hypotension, tachycardia, arrhythmias.
Dopamine (IV)	Vasoactive amine (dose-dependent)	2-20 mcg/kg/min continuous IV; (doses > 10-15 mcg/kg/min likely to have pulmonary vasoconstriction). NOTE: Dopamine has traditionally been the first vasopressor in many NICUs because it reliably increases systemic blood pressure. However, at high doses it may increase pulmonary vascular resistance, which is undesirable in PPHN.	Low dose: renal effect; Moderate: inotropy; High: systemic vasoconstriction.	Tachyarrhythmias, peripheral vasoconstriction, ischaemia.
Dobutamine (IV)	Beta-agonist inotrope	5-10 mcg/kg/min (2-20 mcg/kg/min) continuous IV.	Increases cardiac contractility; reduces afterload.	Tachycardia, hypotension, increased O_2 demand.
Norepinephrine (IV)	Alpha and beta agonist	0.05-1 mcg/kg/min continuous IV. Titrate to response. Correct hypovolaemia before administration.	Potent systemic vasoconstrictor (↑ BP).	Peripheral ischaemia, arrhythmias, lactic acidosis.

Continues

Table 2. Pulmonary vasodilators and vasoactive agents in persistent pulmonary hypertension of the newborn (*continued*)

Drug	Class	Dose/regimen	Primary effect	Risks/adverse effects
Epinephrine (IV)	Alpha, beta-1, beta-2 agonist	0.05-1 mcg/kg/min continuous IV. Titrate to response. Correct acidosis before administration. NOTE: Low-dose epinephrine provides both inotropic support and some vasoconstriction, and several neonatal haemodynamic experts now favour it in infants with myocardial dysfunction or catecholamine-resistant hypotension.	Increases BP, HR and cardiac output.	Hyperglycaemia, tachyarrhythmias, acidosis, ischaemia.
Vasopressin (IV)	Synthetic antidiuretic hormone	Can be commenced at 0.0001 units/kg/minute. Titrated to a maximum 0.0018 units/kg/minute.	V1-mediated vasoconstriction (↑ systemic BP, ↑ renal perfusion).	Hyponatraemia, splanchnic Vasoconstriction.
Hydrocortisone (IV)	Corticosteroid (glucocorticoid)	1-2 mg/kg/day IV, 8/8h or 12/12h; duration varies (usually 3-7 days), adjusted based on clinical response.	Restores vascular responsiveness to catecholamines; improves haemodynamic stability; anti-inflammatory effects.	Hyperglycaemia, hypertension, immunosuppression, adrenal suppression (especially with prolonged use), electrolyte imbalances (e.g., hypokalaemia), potential delayed growth.

BP: blood pressure; h: hour; HR: heart rate; IV: intravenous; NO_2: nitrogen dioxide; O_2: oxygen; PDE: phosphodiesterase; PH: pulmonary hypertension; ppm: parts per million; PVR: pulmonary vascular resistance.

iNO is typically initiated at a concentration of 20 ppm and titrated based on the clinical response and methaemoglobin levels.[13] It is particularly effective in infants with parenchymal lung disease or right-to-left shunting at the ductal or foramen ovale region.[13] The recommended initial dose of iNO is 20 ppm. Although some authors suggest that higher doses (up to 40-80 ppm) may be considered in the absence of a clinical response, the evidence supporting their efficacy and safety remains limited and insufficient to justify their adoption as standard clinical practice.[15] An adequate response to iNO is an increase in PaO_2 greater than 20 mmHg.[16,17]

Once an infant demonstrates stable haemodynamics with maintained alveolar gas exchange and pulmonary blood flow, indicated by oxygen saturations above 92%, weaning of iNO can begin.[13] Adequate oxygenation is reflected by a reduction in FiO_2 to below 0.60 while maintaining a preductal PaO_2 greater than 60 mmHg or saturations above 92%.[13] Serial echocardiograms are valuable for guiding weaning decisions, particularly by assessing the resolution of suprasystemic pulmonary artery pressures and improvement in right ventricular (RV) function. Clinically stable infants may not show overt signs of rebound pulmonary hypertension (PH), so serial echocardiograms are useful for detecting subtle changes during the weaning process.[13]

The weaning can begin by tapering the iNO dose every two to four hours until reaching 5 ppm.[13] Once at 5 ppm, the dose is further reduced by 1 ppm at similar intervals. The transition from 5 ppm to 0 ppm has been associated with episodes of hypoxaemia. Abrupt reductions in iNO can trigger rebound vasoconstriction, leading to acute hypoxaemia. This is best managed by returning to the previous effective dose and retrying weaning at lower doses on subsequent days.[13] Even withdrawal from low doses of iNO can lead to rapid haemodynamic deterioration; however, resuming therapy usually restores pulmonary blood flow and systemic perfusion.[13] In clinical trials, the average duration of iNO therapy was two to three days, with most infants successfully weaned within one week of starting treatment.[17-19] In cases of pulmonary hypoplasia, the duration of therapy may need to be extended for individual patients.[20] A prolonged need for iNO therapy with no improvement should prompt a more comprehensive evaluation to assess whether underlying developmental lung disease or cardiac abnormalities are contributing to persistently elevated PVR.[13,21]

When NO is exposed to circulating erythrocytes, it forms nitrosyl haemoglobin, which is rapidly oxidised to methaemoglobin (MetHb). At standard iNO doses, MetHb levels exceeding 2.5% are uncommon in near-term and term neonates. According to the INOmax prescribing information, methaemoglobin levels should be measured within four to eight hours after initiating iNO therapy and periodically throughout treatment.[22] However, premature neonates are at higher risk for elevated MetHb levels due to lower levels of MetHb reductase.[23] When elevated MetHb levels occur, the primary intervention is to reduce or temporarily discontinue iNO while closely monitoring MetHb concentrations and the infant's clinical status. In moderate-to-severe cases, and when clinically indicated, treatment with methylene blue may be considered, although its use requires caution in neonates, especially those with prematurity or glucose-6-phosphate dehydrogenase deficiency, and alternative strategies such as blood transfusion or exchange transfusion may be required if methylene blue is contraindicated or ineffective. Vitamin C seems to have beneficial antioxidative properties preventing the oxidation of Hb to MetHb.[24]

NO is unstable in ambient air and reacts with oxygen to form nitrogen dioxide (NO_2), with the rate of this conversion increasing at higher oxygen concentrations. Pulmonary toxicities associated with NO_2 include impaired surfactant metabolism, epithelial injury and inflammation. Despite concerns about NO_2 toxicity, the implementation of standardised real-time monitoring has minimised exposure. Notably, significant increases in NO_2 levels have been observed primarily when NO is administered at doses exceeding 40 ppm.[22,23]

NO-induced platelet dysfunction has been observed in both in vivo and in vitro studies, raising concerns about the use of iNO in preterm neonates. While bleeding time may be transiently prolonged at standard iNO doses, this effect is typically short-lived and does not result in clinically significant bleeding in most neonates.[25-28]

When the response to iNO is inadequate, additional agents such as sildenafil, a PDE-5 inhibitor, may be used.[12] Sildenafil can be administered orally or intravenously and works by augmenting cGMP-mediated vasodilation, providing a synergistic effect with iNO or serving as an alternative when iNO is unavailable. In critically ill infants, the intravenous route is preferred over the oral route. However, intravenous infusion can cause systemic hypotension, necessitating close monitoring of blood pressure. The combined use of iNO at median concentrations of 10-20 ppm with oral sildenafil has been shown to produce a complementary pulmonary vasodilatory effect in infants with PPHN. At these moderate iNO doses, sildenafil can enhance and prolong pulmonary vasodilation by inhibiting phosphodiesterase-5, thereby reducing cyclic GMP degradation and amplifying the downstream signalling of nitric oxide. This combination may facilitate lower effective doses of iNO, support more stable oxygenation and assist in weaning from iNO by preventing rebound PH. However, the interaction requires careful monitoring, as excessive vasodilation or systemic hypotension can occur, and individual patient response may vary depending on disease severity and underlying comorbidities. It may be considered as a second-line pulmonary vasodilator in infants with stable haemodynamics and good ventricular function, particularly when a right-to-left shunt is present at the patent foramen ovale and/or patent ductus arteriosus.[12,29] Also, sildenafil may aid in the weaning of iNO and help prevent rebound PH in patients who have previously failed weaning attempts.[30,31]

Prostacyclin analogues (PGI_2), such as iloprost and epoprostenol are also utilised in some centres, typically via inhalation or intravenous infusion, although their use in neonates requires caution due to systemic hypotensive effects.[32] The intravenous formulation of epoprostenol carries a substantial risk of systemic hypotension and is therefore often avoided in critically ill infants with PPHN. Iloprost, a synthetic prostacyclin, can be administered via aerosol or intravenously and has been shown to improve oxygenation in infants with PPHN.[32-34] Inhaled prostacyclin analogues may be considered as adjunctive therapy for infants with PPHN who are refractory to iNO and have an OI over 25.[14]

Prostaglandin E1 may have a role in PPHN.[12] Critically ill infants with RV failure may benefit from a patent ductus arteriosus, which can function as a "pop-off" valve in the context of severely elevated PVR.[12] In cases where the ductus arteriosus is constricting, prostaglandin E1 can be administered to reopen and maintain ductal patency. This reduces RV afterload by allowing a right-to-left shunt. The use of prostaglandin E1 should be guided by echocardiographic findings and may be particularly beneficial in infants with RV failure and a narrowing ductus arteriosus.[12,35]

Bosentan, an oral dual endothelin receptor antagonist, has emerged as a potential therapeutic option in the management of PPHN.[36] It works by blocking the effects of ET-1, a potent vasoconstrictor. By antagonising both ETA and ETB receptors, bosentan promotes vasodilation and reduces pulmonary arterial pressure.[36] Bosentan can be used as an adjuvant therapy with iNO and can be an alternative therapy option in mild-to-moderate PPHN.[36-39]

While iNO remains the first-line treatment for PPHN due to its selective pulmonary vasodilatory effect, some newborns show an inadequate response. In such cases, bosentan may serve as an adjunct therapy, especially when iNO is not available or insufficient.[37] Studies have demonstrated that bosentan can improve oxygenation and haemodynamic stability in neonates with PPHN, particularly when started early in the course of the disease.[37]

Moreover, bosentan has a convenient oral formulation, making it suitable for transitioning from intensive care settings to outpatient management in selected cases.[40,41] However, its use in neonates is still considered off-label, and more research is needed to establish standardised dosing, safety profiles and long-term outcomes.[42]

Vasoactive support

Vasoactive support is often necessary in PPHN to maintain systemic perfusion and optimise RV function.[43] Recent expert reviews and neonatal haemodynamic guidance increasingly emphasise physiology-based management using targeted neonatal echocardiography rather than recommending one universal first-line vasoactive agent.[12]

Dopamine used at low-to-moderate doses (3-10 mcg/kg/min) has traditionally been the first vasopressor in many NICUs because it reliably increases systemic blood pressure and cardiac output.[43-45] However, at higher doses it may increase PVR, which is undesirable in PPHN.[46] By elevating systemic arterial pressure, dopamine may help reduce right-to-left shunting across foetal circulatory pathways, thereby improving oxygenation. Additionally, at moderate doses (5-10 mcg/kg/min), dopamine has positive inotropic effects, which can support cardiac output and tissue perfusion.[46] However, its use in PPHN remains controversial, as higher doses may cause pulmonary vasoconstriction and potentially worsen PH.[46] Therefore, while dopamine can be beneficial in cases of PPHN associated with systemic hypotension or myocardial dysfunction, its administration should be carefully titrated and considered within the broader context of alternative therapies.[47] Dobutamine may be preferred in cases where inotropic support is needed without significant increases in afterload.[43,44,47,48]

Norepinephrine and epinephrine can be employed in more severe cases to provide both inotropic and vasoconstrictive effects, enhancing systemic vascular resistance (SVR) and improving oxygen delivery.[49,50] The goal of vasoactive support in PPHN is to maintain adequate systemic perfusion and cardiac output, guided by individualised haemodynamic assessment, including ventricular function and shunt direction. Systemic blood pressure should be optimised according to the infant's haemodynamic status rather than increased solely to reverse right-to-left shunting, as excessive vasoconstriction may impair cardiac function and organ perfusion.[49,50] Norepinephrine may be considered in the management of PPHN when associated with profound systemic hypotension, particularly in the context of vasodilatory or septic shock.[51] Its strong alpha-adrenergic vasoconstrictive effects help to increase SVR and arterial pressure, thereby improving systemic perfusion and reducing right-to-left shunting through foetal circulatory pathways. This can lead to improved oxygenation in critically unwell neonates. Although norepinephrine has minimal direct inotropic action, it may be preferable to other catecholamines in some cases due to a potentially lower impact on PVR when carefully titrated. Nevertheless, it is not a first-line agent for treating PH itself, and its use should be individualised and closely monitored to avoid excessive vasoconstriction and impaired peripheral perfusion. Epinephrine may be used in the management of PPHN in cases of severe cardiovascular instability, such as refractory shock or significant myocardial dysfunction.[51] Its potent alpha-adrenergic vasoconstrictive effects can increase SVR and arterial pressure. Additionally, its beta-adrenergic activity enhances cardiac contractility and heart rate, supporting cardiac output in critically unwell neonates. However, epinephrine is not a first-line agent for treating PH itself, as it may increase PVR and exacerbate the underlying condition. Due to the potential risks of tachycardia, arrhythmias and increased myocardial oxygen demand, its use should be carefully reserved for select cases where haemodynamic support is urgently needed.[51]

Milrinone, a PDE-3 inhibitor with both inotropic and vasodilatory effects, has shown promise in improving myocardial function and reducing PVR, particularly when iNO fails.[52] Milrinone plays an important role in the management of PPHN, particularly in cases associated with ventricular dysfunction or an inadequate response to iNO.[53] It increases intracellular cAMP, leading to pulmonary and systemic vasodilation, which helps to reduce PVR and improve oxygenation. Milrinone also has positive inotropic effects, enhancing myocardial contractility without significantly increasing myocardial oxygen consumption, making it especially beneficial in neonates with right or left ventricular dysfunction. Furthermore, milrinone may have a synergistic effect when combined with iNO, particularly in cases of partial or non-response to iNO alone. However, due to its vasodilatory properties, milrinone may cause systemic hypotension and should be administered

cautiously with close haemodynamic monitoring.[54] The combination of milrinone and dopamine or norepinephrine may be beneficial in the management of PPHN, particularly in cases with myocardial dysfunction and systemic hypotension.[54] There is a theoretical rationale for combining milrinone with epinephrine in PPHN: milrinone may lower pulmonary vascular resistance and improve ventricular function, while low-dose epinephrine can help maintain systemic blood pressure and support cardiac output. This complementary haemodynamic effect could be beneficial in selected cases. However, there is currently no clinical evidence validating this combination, and its use remains speculative.

Vasopressin has emerged as a potential rescue therapy in the management of PPHN, particularly in cases of refractory hypotension and vasodilatory shock.[55] Acting primarily through V1 receptors, vasopressin induces systemic vasoconstriction, thereby increasing SVR and improving arterial pressure without significantly affecting heart rate. Unlike catecholamines, vasopressin may reduce or preserve PVR, which is beneficial in the context of PPHN. By improving systemic blood pressure, it can help decrease right-to-left shunting and enhance oxygenation. Vasopressin is especially useful in neonates who are unresponsive or show poor tolerance to dopamine, epinephrine or norepinephrine. However, its use requires careful monitoring due to potential adverse effects such as hyponatraemia and reduced splanchnic perfusion. While promising, further research is needed to establish standardised dosing and safety profiles in the neonatal population.[55-59]

Hydrocortisone serves as an adjunctive therapy in neonates with PPHN who exhibit refractory haemodynamic instability, particularly in the context of relative adrenal insufficiency. It enhances vascular responsiveness to catecholamines by upregulating adrenergic receptor expression and modulating inflammatory pathways, thereby improving systemic blood pressure and reducing right-to-left shunting. Additionally, hydrocortisone's anti-inflammatory effects may contribute to lowering PVR. While not a primary treatment for PPHN, hydrocortisone is beneficial in cases resistant to conventional vasopressors or when relative adrenal insufficiency is suspected. Careful monitoring is essential due to potential side effects, including hyperglycaemia, hypertension and adrenal suppression with prolonged use.[60-62]

Extracorporeal membrane oxygenation (ECMO) serves as a vital rescue therapy for neonates with severe and refractory PPHN who fail to respond to conventional treatments such as optimised mechanical ventilation, iNO and haemodynamic support.[63] ECMO provides temporary cardiopulmonary support by oxygenating the blood and removing carbon dioxide outside the body, allowing the lungs and heart to rest and recover. This extracorporeal support reduces ventilator-induced lung injury and cardiac strain while giving time for PVR to decrease and myocardial function to improve. Due to its invasive nature and associated risks, ECMO requires specialised centres and multidisciplinary experienced teams. Typically, an OI threshold of 40 for at least four hours, or over 20 for 24 hours despite medical optimisation, is utilised for ECMO therapy.[63-65]

Emerging and future therapeutic approaches for PPHN

Emerging and future therapies for PPHN aim to improve pulmonary vasodilation, reduce oxidative stress and enhance long-term outcomes beyond current standards of care. Recent studies have explored the use of nebulised nitroglycerin as an alternative pulmonary vasodilator, showing promising results in improving oxygenation and echocardiographic parameters.[66] The combination of inhaled nitric oxide (iNO) with oral sildenafil, a phosphodiesterase-5 inhibitor, is under investigation for synergistic effects and the prevention of rebound hypoxaemia (NCT01558466). Other agents such as bosentan, a dual endothelin receptor antagonist, and milrinone, a phosphodiesterase-3 inhibitor, are being compared for efficacy and safety in PPHN management.[67] Additionally, novel therapies targeting oxidative stress pathways, such as recombinant superoxide dismutase and NADPH oxidase inhibitors, are being studied in preclinical models.[68] Although many of these therapies remain investigational, they represent promising directions for optimising treatment and reducing morbidity in neonates with PPHN.

Prognosis

The prognosis of PPHN has improved significantly over recent decades due to advances in neonatal intensive care, particularly the use of iNO and ECMO.[69] However, PPHN remains associated with considerable short- and long-term morbidity.[14] While many infants recover without major complications, a subset may experience chronic pulmonary issues, neurodevelopmental delays or sensorineural hearing loss. The risk of adverse outcomes is highest in cases requiring prolonged respiratory support or ECMO.[7] Early identification, optimised management and structured follow-up are essential to improve long-term outcomes in these patients. Therefore, structured follow-up after hospital discharge is essential to monitor growth, development

and potential sequelae, enabling timely interventions and support for both the child and family.[70]

Conclusion

PPHN remains a complex and challenging condition with significant morbidity and mortality despite advances in neonatal care. Early recognition and a comprehensive, multidisciplinary approach are essential for optimising outcomes. Current therapies target PVR and cardiac function. In severe, refractory cases, ECMO provides lifesaving support. Ongoing research into the pathophysiology of PPHN and novel therapeutic strategies holds promise for improving survival and long-term outcomes. Ultimately, individualised treatment protocols and timely intervention are critical to reduce complications and enhance the quality of life for affected neonates.

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Conflicts of interest

None.

Ethical considerations

Protection of human subjects and animals. The author declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. This study does not involve personal patient data, medical records, or biological samples, and does not require ethical approval. SAGER guidelines do not apply.

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