




Life-threatening PPHN refractory to nitric oxide: proposal for a rational therapeutic algorithm

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Abstract

Persistent pulmonary hypertension of the neonate (PPHN) refractory to inhaled nitric oxide still represents a frequent clinical challenge with negative outcomes in neonatal critical care. Several pulmonary vasodilators have become available thanks to improved understanding of pulmonary hypertension pathobiology. These drugs are commonly used in adults and there are numerous case series and small studies describing their potential usefulness in neonates, as well. New vasodilators act on different pathways, some of them can have additive effects and all have different pharmacology features. This information has never been summarized so far and no comprehensive pathobiology-driven algorithm is available to guide the treatment of refractory PPHN.

Conclusion: We offer a rational clinical algorithm to guide the treatment of refractory PPHN based on expert advice and the more recent pathobiology and pharmacology knowledge.

What is Known:

• *Refractory PPHN occurs in 30–40% of iNO-treated neonates and represents a significant clinical problem. Several pulmonary vasodilators have become available thanks to a better understanding of pulmonary hypertension pathobiology.*

What is New:

• *Available vasodilators have different pharmacology, mechanisms of action and may provide additive effect. We provide a rational clinical algorithm to guide the treatment of refractory PPHN based on expert advice and the more recent pathobiology and pharmacology knowledge.*

Keywords Pulmonary hypertension · Prostacyclin · Prostaglandin · Endothelin · Phosphodiesterase

Background

Persistent pulmonary hypertension of the neonate (PPHN) is a severe clinical syndrome representing the most common form

of pediatric pulmonary hypertension and is usually associated with various types of respiratory failure [1]. Refractory PPHN is defined as an acutely life-threatening condition not responding to the administration of inhaled nitric oxide (iNO)

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at the classical dose of 20 ppm) and conventional measures (including mechanical ventilation (with alveolar recruitment, if needed) and inotropic support) with resulting hypoxemia and represents a significant proportion (up to 30–40% [2]) of PPHN patients. Refractoriness to iNO depends on many factors such as genetic background, gestational age, underlying conditions, and co-interventions; depending on these factors only some patients can be considered as candidate for extra-corporeal life support [3].

As the knowledge about pathobiology of pulmonary hypertension has been increasing in the last years, several pulmonary vasodilators acting on different molecular pathways have been introduced for the treatment of pulmonary hypertension in adults. These drugs have been tested in numerous studies enrolling small newborn populations, thus strong evidence is unavailable due to difficulty in designing adequately powered, explanatory trials enrolling large, and homogeneous populations. However, these small studies have been accumulating over the years suggesting clinical benefits, supported by a strong pathobiological background. Refractory PPHN may represent an indication for extra-corporeal life support, but this may not be an option for all patients and may not be available in all centers. Therefore, a large weaponry of pulmonary vasodilators is available to be used on a case-by-case scenario, considering their pharmacological features and PPHN pathobiology, when a patient cannot be candidate to extra-corporeal life support or this is unavailable. To the best of our knowledge, no comprehensive pathobiology-driven algorithm is available so far to guide the treatment of refractory PPHN. Consistently, our aim is to propose a rational clinical algorithm to guide the treatment of refractory PPHN in neonatal intensive care units (NICU).

The available weaponry

Table 1 reports the currently marketed drugs that have been used to treat refractory PPHN [4–53]. We might classify pulmonary vasodilators as primary or secondary: the former are represented by drugs primarily designed to treat pulmonary hypertension (e.g., iloprost, bosentan), while the latter consist of drugs originally used for other indications that may have a certain effect on pulmonary hypertension (e.g.: milrinone, alprostadil). Their pharmacology features are remarkably different, and the following general principles should be highlighted:

1. iNO remains the first-line therapy based on large evidence-based data and European guidelines [3] and, therefore, it is approved for neonates ≥ 34 weeks' gestation. However, many trials have demonstrated its safety also in more premature infants and, therefore, recent US consensus supports the use of iNO to treat acute hypoxia due to PPHN in preterm infants as well [54]. iNO

generally has a good safety profile without side effects, is classically used at 20 ppm, as higher doses do not provide additional advantages, while lower doses may be equally effective in some cases.[3] iNO has no absolute contra-indication, beyond neonatal methemoglobinemia.[55] For refractory PPHN, second-line drugs should be added on top of iNO, as significant additive effect may be obtained (see below).

2. Local (nebulized) pulmonary vasodilators should be generally preferred as they directly reach the site of action reducing the risk of systemic side effects. Moreover, when PPHN is secondary to a parenchymal, severely restrictive disorder (such as, for instance, neonatal acute respiratory distress syndrome (NARDS) [56]), the drug will preferentially reach lung areas that have been recruited and therefore are well ventilated. Thus, the risk to increase intrapulmonary shunt, and to worsen the ventilation/perfusion mismatch, is lower with nebulized vasodilators. This risk is less cogent in lung development disorders or pulmonary hypoplasia due to genetic anomalies,[57] but, anyway a local pulmonary vasodilator can be preferred, as there is no advantage from systemic therapies which can more frequently provide generalized side effects. Modern vibrating mesh nebulizers provide satisfactory drug delivery both in conventional and high-frequency oscillatory ventilation, if placed proximal to the endotracheal tube on the inspiratory limb of the ventilator circuit [58]. The same setting can be efficaciously used during non-invasive ventilation, as well [59].
3. In an extremely acute setting like refractory PPHN, orally administered drugs are less suitable, since they may need longer time to reach an effective systemic distribution and little to nothing is known about their intestinal absorption in neonates and particularly in preterm ones [39, 46]. Conversely, oral drugs can be useful in the weaning phase, when other vasodilators are being reduced, and a more long-lasting treatment may be needed. Some drugs are available in a pediatric syrup-like oral suspension: whenever possible, these should be preferred to those available only as tablets since these latter could not provide accurate dosing.
4. Some drugs are known to have an additive effect due to different mechanisms of action on distinct pathways. This has been observed in various animal studies or clinical reports describing patients of any age [12–14, 20, 25, 28, 29, 31, 35, 37, 38, 60–68] and is of utmost importance for the choice of drugs to treat refractory PPHN (Fig.1). Obtaining a greater pulmonary vasodilation with no or minor systemic side effects should be the first therapeutic objective in patients with refractory PPHN in order to reduce the need of extra-corporeal life support, especially in patients generally considered poor candidates for this intervention (preterm neonates <34 weeks' gestation or

	Adenosine	Alprostadil	Bosentan	iNO	Milrinone	Prostacyclin & analogues	Sildenafil/Tadalafil
Adenosine	■	?	?	+	±	±	?
Alprostadil	?	■	?	±	?	?	+
Bosentan	?	?	■	+	?	+	+
iNO	+	±	+	■	+	+	±
Milrinone	±	?	?	+	■	±	+
Prostacyclin & analogues	±	?	+	+	±	■	+
Sildenafil/Tadalafil	?	+	+	±	+	+	■

Fig. 1. Additive effect of main pulmonary vasodilators used for refractory PPHN. Drugs may show synergy in terms of vasodilation and oxygenation, as they have different molecular mechanisms of action on distinct pathway. Green cases with “+” indicate additive effect reported in pre-clinical studies and/or in clinical reports (in patients of any age; see text for more details). Yellow cases with “±” indicate that an additive effect has been inconsistently reported or that it may be expected only in some conditions (see text for more details). White cases with “?” indicates lack of data about the possible synergy between those two drugs. “Prostacyclin and analogues” refer, respectively, to epoprostenol and beraprost, iloprost or treprostinil

weighting <2500g). Once the critical phase is over, weaning should be provided by de-escalating the last introduced vasodilator and anyway avoiding any sudden interruption. Synergy is well-known for some drugs, while for others it has been inconsistently reported or may be expected only in some conditions. For instance, drugs acting on different pathways (i.e., iNO and milrinone or prostacyclins; bosentan and prostacyclins) usually ensure an additive effect, while those with the same second messenger (i.e., iNO and sildenafil or tadalafil; milrinone and adenosine or prostacyclins) may show synergy or not, depending on the pathobiology of that particular case. In other words, if acting on that pathway with a previous drug has been successful, one may argue that a second vasodilator might potentiate the effect; however, if the already used drug did not provide any benefit, it might be unlikely that adding another vasodilator on the same pathway would be efficacious. It is important to remember that PPHN is a syndrome that may be associated to several underlying conditions with a significantly different pathobiology. This is largely unknown, since clinical studies have enrolled non-homogeneous populations of neonates with PPHN secondary to different conditions, thus the clinical response is not always actually predictable. Alprostadil represents a particular

case, because it has the peculiarity to be efficacious in keeping the *ductus arteriosus* open. Alprostadil may vasodilate pulmonary vessels binding EP4 receptors, but may have an opposite (vasoconstriction) effect through EP1 and EP3 receptors [69]. Therefore, it has a weaker and less consistent pulmonary vasodilatory action compared to the other drugs. However, it may be useful if a restrictive or recently closed *ductus arteriosus* is associated with right ventricular failure or pulmonary overflow (see below) [28, 70].

The clinical algorithm

We propose a rational clinical algorithm based on the above-described considerations, according to the following priority: (1) the known synergy between some drugs and their pharmacology features, (2) the preference to nebulization over other administration routes, (3) the knowledge of biological mechanisms of PPHN and the clinical experience accumulated on the different drugs, and (4) the possible coexistence of particular hemodynamic conditions. For the algorithm application, careful monitoring is essential and should be provided with multiple vital parameters control (including perfusion index, arterial pressure, pre- and post-ductal saturation) and serial point-of-care echocardiography according to current international guidelines [71]. Some monitoring may need invasive techniques to be accurate. Additional monitoring techniques, such as electrical cardiometry or near-infrared spectroscopy might also be useful, if available.[72, 73]

Figure 2 describes the proposed algorithm in detail. As first level, the basic management is obviously composed of iNO and hemodynamic support, that is, volume filling and norepinephrine, which are administered to reduce the pulmonary-systemic arterial pressure difference, reverse the shunt through the patent *ductus arteriosus* (if any) and support peripheral perfusion. Other inotropes (notably vasopressin, dobutamine or epinephrine) may also be needed and titrated, according to point-of-care echocardiography findings and monitoring of vital parameters. The treatment of underlying conditions such as NARDS or sepsis and optimal ventilatory support (including sedation and muscle paralysis, as needed) must be considered as basic management, as well. Hydrocortisone can also be considered in this phase for some patients such as preterm neonates or infants with septic shock. In fact, hydrocortisone may increase systemic pressure in preterm infants with relative cortico-adrenal insufficiency [74] and is included in the neonatal septic shock management [75]. Moreover, there are some data suggesting that it might provide benefits by increasing intracellular cyclic guanosine monophosphate and reducing inflammation associated with PPHN and several underlying conditions [76, 77].

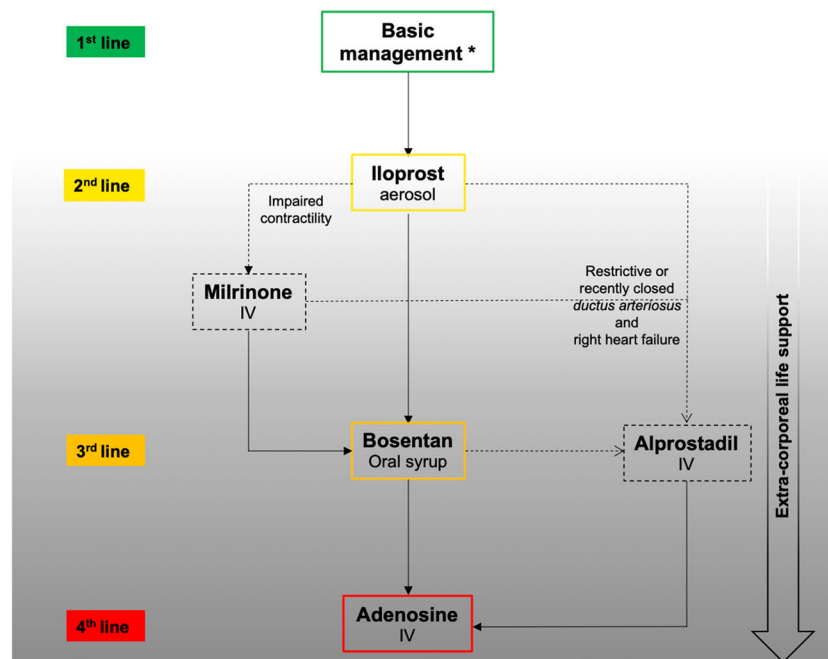


Fig. 2. Rational clinical algorithm to guide the treatment of refractory PPHN. The flow-chart is based on the principles described in the main text, considering the known synergy between the drugs, the preference to nebulization, the knowledge of biological mechanisms of PPHN, the clinical experience accumulated on the different drugs and the possible coexistence of particular hemodynamic conditions. Therapeutic interventions are categorized in 4 levels with different colors. Full lines indicate failure of the previous level treatment (i.e., persistence of life-threatening PPHN). Hatched lines indicate a therapeutic option when particular hemodynamic conditions coexist. Faded gray gradient and the big arrow depict an increasing risk of extra-corporeal life support for neonates who can be candidates to that. Extra-corporeal life support should not be delayed and instituted with the classical indications and oxygenation thresholds if the interventions proposed in the algorithm fail. The time to pass from one level to the next can be variable, however the effect of nebulized iloprost is always very quick (within minutes), while milrinone and

alprostadil also provide relatively rapid (within few hours) vasodilation and oxygenation improvement, if any. Therefore, an iloprost nebulization trial can always be quickly done without delaying the further steps or extra-corporeal life support. Serial point-of-care echocardiography as internationally recommended [71] and/or other hemodynamic monitoring are essential at any step of the algorithm. *The basic management consists of the treatment of underlying conditions and best ventilatory support together with optimized hemodynamic management including iNO and volume filling and/or inotropes infusion as needed. Norepinephrine is usually administered to reduce the pulmonary arterial/systemic pressure difference and support peripheral perfusion. Other inotropes (notably vasopressin, epinephrine, dobutamine) may be added according to hemodynamic monitoring findings. Sedation, paralysis and hydrocortisone can also be considered within the basic management phase. Abbreviations: CDH: congenital diaphragmatic hernia; IV: intravenous

Iloprost, the carbacyclin analog of prostacyclin (i.e., prostaglandin- I_2 (PGI $_2$)), is preferred as second-line treatment after iNO failure, as it is a well-known vasodilator characterized by synergy with iNO, optimal safety profile and nebulization [12]. Iloprost potency is equal to that of iNO and has a fast action so the response (if any) can be quickly detected without delaying other treatments and extra-corporeal life support [78, 79]. Due to its short half-life, the time between iloprost administration may need to be shortened or a continuous nebulization may be possible, as it has been done for epoprostenol (which is the pharmaceutical form of PGI $_2$) [23].

Milrinone, an ino-dilator able to increase myocardial contractility and reduce afterload, is considered after iloprost in case of impaired cardiac contractility, provided that related hypotension can be controlled with the basic management. As milrinone inhibits phosphodiesterase-3, it may also provide an additional synergic pulmonary vasodilation by

reducing adenosine monophosphate breakdown and increasing its intracellular levels (Fig.1) [66]. Enoximone, another ino-dilator of the same family, has been used in only two cases, when milrinone was unavailable, and should not take its place due to the very limited experience [40, 53].

Alprostadil, the pharmaceutical form of prostaglandin- E_2 (PGE $_2$) is considered for some particular conditions characterized by the presence of restrictive or recently closed *ductus arteriosus* associated with: (1) right ventricular failure, or (2) pulmonary overflow with congested pulmonary veins. These are two particular and completely different scenarios, in which, however, alprostadil might be beneficial. The first (right ventricular failure) may occur in patients with very severe refractory PPHN (such as, patients with congenital diaphragmatic hernia). The second (pulmonary overflow with pulmonary veins congestion) is typical of patients with excessively early (that is, antenatal or early after birth) closure of the

Table 1 Pulmonary vasodilators that have been used for PPHN refractory to iNO. Not all drugs are marketed in every country and their neonatal use is off-label in the majority of cases. Reported doses are the lowest and highest used in cited clinical reports. The arrows denote the mechanisms of action of the various drugs. Notes (more details in the text and references articles): [†]Nebulization can be provided with different techniques and devices, and this can significantly impact on the actual drug delivery. The use of vibrating mesh nebulizers placed on the inspiratory limb of the ventilator circuit proximal, to the endotracheal tube provides the best performance. Nebulization can be intermittent or continuous for the same total dose. [‡]The double arrow indicates that effect of PGE2 in terms of intracellular cAMP depends on the receptors and may

be variable. *Iloprost and epoprostenol have also been administered as intratracheal injection of continuous infusion (before the advent of modern nebulizers in line on the inspiratory limb). [#]Epoprostenol is dissolved in a highly basic solution; no problem has ever been reported although its effects on the lung epithelium have never been formally studied. Iloprost is conversely dissolved in a neutral and harmless solution. [°]Hypotension induced by milrinone might be milder if given continuously (without boluses). [®]Treprostinil is administered subcutaneously with particularly designed micro-infusion pumps and specific dilutions. Abbreviations: *B*: bolus; *C*: continuous infusion; *cAMP*: cyclic adenosine monophosphate; *cGMP*: cyclic guanosine monophosphate; *IV*: intra-venous; *PDE*: phosphodiesterase; *ROP*: retinopathy of prematurity; *SC*: sub-cutaneous

Drug	Route	Dose	Mechanism of action	Possible side effects
Adenosine [26, 31, 33, 34]	IV	C: 50 mcg/kg/min	cAMP precursor	None
Alprostadil (PGE ₂) [18, 27, 28, 41, 43, 50]	IV Aerosol [†]	C: 0.0125-0.05 mcg/kg/min C: 25-300 ng/Kg/min	↑↓intracellular cAMP [*] Keep the <i>ductus arteriosus</i> open	Hypo- and hypertension, respiratory arrest, fever, bleeding, ductal aneurysm, bone cortical bone proliferation (for long-term therapy), worsening inflammation.
Beraprost [25, 32, 49]	<i>Per os</i>	1 mcg/Kg/6h	Prostacyclin analog (↑intracellular cAMP)	Hypotension
Bosentan [14, 17, 25, 29, 36–38, 46]	<i>Per os</i>	1 mg/kg/12h	Endothelin pathway inhibition	None
Iloprost* [6, 12, 21, 22]	Aerosol [†] IV	1-2 mcg/kg/2-4h [#] C: 0.5-10 ng/kg/min	Prostacyclin analog (↑intracellular cAMP)	None (aerosol) Hypotension (IV)
Enoximone [40, 53]	IV	B: 0.25-5 mg/Kg slowly C: 10-23 mcg/Kg/min	PDE-3 inhibitor (↓cAMP catabolism)	Hypotension
Epoprostenol (PGI ₂)* [4, 6, 7, 17, 19, 32, 36, 45]	IV Aerosol [†]	C: 2-20 ng/kg/min C: 10-100 ng/Kg/min [#]	(↑intracellular cAMP)	Hypotension, worsening hypoxia (IV) None (aerosol)
Milrinone [7, 13, 16, 30]	IV	B: 20-50 mcg/Kg over 1h C: 0.2-0.5 mcg/Kg/min	PDE-3 inhibitor (↓cAMP catabolism)	Hypotension [°]
Sildenafil [4, 5, 9, 11, 13–15, 19, 22, 24, 39, 44, 45, 47, 48, 52]	<i>Per os</i> IV	0.5-2 mg/Kg/6h B: 0.4-2 mg/Kg/6h over 3h C: 1-2 mg/Kg/d	PDE5 inhibitor (↓cGMP catabolism)	Hypotension (especially IV), worsening hypoxia, priapism, hypertrophic pyloric stenosis, ROP, acute visual loss, bleeding, cardiovascular events and death (at high-dose for long-term treatments)
Tadalafil [91]	<i>Per os</i>	1 mg/Kg/d	PDE-5 inhibitor (↓cGMP catabolism)	None
Treprostinil [35, 51]	IV/SC	5-39 ng/Kg/min [®]	Prostacyclin analog (↑intracellular cAMP)	None

ductus arteriosus. In these two scenarios: (1) the right heart is not tolerating PPHN, or (2) lung edema occurs due to pulmonary overflow: in both cases opening the *ductus* may be helpful by downloading the right ventricle or reducing the pulmonary artery flow. Anyway, alprostadil has an inconsistent pulmonary vasodilator effect, and its use might also cause a marked increase of right-to-left shunt resulting in a worsening hypoxia, but it can help to tolerate PPHN while other drugs lower pulmonary pressures [69].

If PPHN remains life-threatening despite iNO and iloprost administration, bosentan (a potent dual endothelin receptor antagonist) is preferred as third-line treatment, despite it is only orally administered, since it shows additive effects with

iNO and prostacyclins [37]. Moreover, the inhibition of endothelin pathway is strongly supported by specific biological data, since circulating levels of endothelin-1 are significantly higher in neonates with PPHN secondary to various conditions [80–82].

Adenosine is preferred as last line treatment, since it has an ideal safety profile and can have an additive effect with iNO, although neonatal experience on its use is smaller than that accumulated about iloprost and milrinone.

The majority of the described drugs are off-label in neonates. This is not surprising since more than 95% NICU-admitted neonates receive off-label drugs during their stay [83]. An extremely acute life-threatening condition such as

refractory PPHN, justifies the use of these therapeutics, but demands a logical framework for their management and the proposed algorithm is useful to this purpose.

Sildenafil is not suggested in this context for several reasons. It is not free from side effects (Table 1) and the US Food and Drug Administration discouraged its use (especially at high dosages) in children beyond neonatal age [84]. More and above this, there are pharmacologic features making sildenafil less suitable for an extremely acute setting, such as refractory PPHN. In fact, the systemic availability of oral sildenafil in neonates is not well known and may not be reliably and quickly achieved to treat life-threatening PPHN [39]. Moreover, its renal clearance significantly increases during the first days of life and this influences the availability, as well [85]. On the other hand, the intravenous administration of sildenafil is not always available and is frequently associated with clinically significant systemic hypotension [86]. The vasodilatory potency of sildenafil is significantly lower than that of iloprost and it may not show synergy with iNO, as well as it can reduce the protective mechanism of hypoxic vasoconstriction in restrictive syndromes such as NARDS [5, 11, 22]. Conversely, sildenafil can be suitable in setting different from “acute” life-threatening refractory PPHN. For instance, short course sildenafil is useful when weaning iNO to avoid pulmonary pressure rebounds [87]. Similarly, sildenafil is valuable for chronic pulmonary hypertension due to bronchopulmonary dysplasia [88] or congenital heart disease [89] and has been associated to iloprost in non-invasively ventilated infants to spare the need of iNO and invasive ventilation [59, 90].

This algorithm is responding to an actual clinical unmet need but has also some limitations. The pathophysiology, biology, and pharmacology features of pulmonary vasodilators have not been resumed and integrated in a protocol to treat refractory PPHN so far, although these drugs are available worldwide. Randomized clinical trials are difficult to be conducted in this area, mainly because PPHN is a syndrome secondary to several underlying conditions receiving different co-interventions. Thus, while waiting for more evidence, a physiopathology and pathobiology-based approach is desirable. There is no test or tool to predict the response to any step of the algorithm and a full patient monitoring is needed. However, the effect of nebulized iloprost is always very quick (within minutes) and milrinone and alprostadil also provide rapid vasodilation and oxygenation improvement, if any. Therefore, an iloprost nebulization trial can always be quickly attempted and the algorithm can generally be applied over a short time-period (2–6 h). Therefore, the algorithm is not designed to delay extra-corporeal life support: this, or at least a prompt referral system, should always be available. For those neonates who may be candidate to extra-corporeal life support, a careful evaluation should be done by expert neonatal intensivists through each different steps of the algorithm. The

algorithm needs significant expertise in neonatal critical care, and particularly in hemodynamic monitoring, thus it may not be easily applied in settings lacking expertise or adequate monitoring tools: in these cases, a prompt referral to a more expert center must be ensured.

In conclusion, we offer a rational, integrated, pathobiology, and physiology-based protocol for the treatment of refractory PPHN. The algorithm is an example of personalized approach to a complex life-threatening problem that has a common clinical appearance (i.e., refractory hypoxia) but different possible causes. A personalized medicine strategy is likely to be more effective than a simplified “one drug fits all” approach. In our experience, the protocol has proven useful to guide the successful management to these critical cases and for teaching purposes. The protocol is based on availability of several drugs and should be adapted for those settings where not all these drugs are available. Some of them may be quite easily exchanged with others (for instance, epoprostenol or trepostinil can be used at the place of iloprost). Nonetheless, the protocol may be difficult to apply in low-resources settings where drugs and full monitoring are unavailable and specific protocols should be built for these particular settings.

Abbreviations list iNO, inhaled nitric oxide; NARDS, neonatal acute respiratory distress syndrome; NICU, neonatal intensive care units; PGE₂, prostaglandin-E₂; PGI₂, prostaglandin-I₂ (i.e., prostacyclin); PPHN, persistent pulmonary hypertension of the neonate

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