Approved by Quality & Patient Care Committee
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INHALED NITRIC OXIDE (iNO)

This Local Operating Procedure is developed to guide safe clinical practice in Newborn Care Centre (NCC) at The Royal Hospital for Women. Individual patient circumstances may mean that practice diverges from this Local Operating Procedure.

INTRODUCTION

The use of iNO as a pulmonary vasodilator is well established in term & near term infants with Persistent Pulmonary Hypertension of the Newborn (PPHN)[1]. The benefits of iNO in preterm infants are not proven and it should be used with caution in this group. There may be a place for iNO in the subgroup of preterm infants (< 34 weeks) with severe PPHN associated with prolonged preterm rupture of membranes (PPROM), prolonged oligohydramnios and pulmonary hypoplasia.

1. AIM

- To determine a neonate's need for iNO treatment, to implement this treatment and wean in a timely and appropriate mannner

2. PATIENT

- Newborns

3. STAFF

- Medical and nursing staff

4. EQUIPMENT

- INOMax DS IR (there is a NCC nursing guide for iNO set-up)

5. CLINICAL PRACTICE

Procedure:

1. <u>General Indications for iNO in Term Infants and Preterm Infants > 32 weeks gestation</u>
   - Any infant with severe hypoxic respiratory failure: ie. PaO2 < 50 mmHg or O2 saturation < 90% despite optimal ventilation (see below) with FiO2 > 80% (consider iNO in patients with an oxygenation index (OI) of 15-20 or greater)
   - Any ventilated infant with > 60% O2 requirement and echocardiographic evidence of PPHN (ie. pulmonary artery pressures close to or above systemic pressures)
   - Early use of iNO can be considered in infants with respiratory failure born after prolonged oligohydramnios or congenital diaphragmatic hernia or congenital pulmonary airway malformation as these infants may have severe PPHN. Those with a history of oligohydramnios frequently have a good response to iNO.[2-7]

2. <u>General Indications for iNO in Term Infants and Preterm Infants < 32 weeks gestation</u>
   - Any ventilated preterm infant with severe hypoxic respiratory failure: ie. PaO2 < 50 mmHg or O2 sats < 90% despite moderate ventilatory requirements (Moderate ventilator requirements are defined as Mean Airway Pressure 12-14 cmH2O with FiO2 > 60%)

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3. Relative Contraindications[8]
   - Caution with iNO in infants < 26 weeks gestation (lower dose suggested)
   - Known intraventricular haemorrhage
   - Evidence of coagulopathy (particularly in preterm infants < 32 weeks)

NOTE:
It is important to optimise respiratory and circulatory management prior to initiation of iNO therapy. For example, target mean arterial systemic blood pressure to be equal to or greater than measured or anticipated pulmonary arterial pressures.

4. Starting Dosage
   - Infants > 32 weeks gestation: Start at 20 ppm (higher doses are unlikely to be of benefit; doses > 40 ppm are associated with methaemoglobinaemia)
   - Preterm infants ≤ 32 weeks gestation: Start at 10 ppm (can increase to a maximum of 20 ppm depending on response)

5. Prescribing iNO
   - iNO is now a registered drug with the Australian Therapeutic Goods Administration (TGA)
   - As a fully registered drug, iNO must be prescribed on NCC Fluid/Gas Prescription Chart
   - Start and stop time and dose changes must be charted accurately

6. Evidence of Response to iNO therapy
   - Response within 30 minutes with a PaO2 increase > 10 mmHg
   - FiO2 should fall by 10% or more while maintaining the desired pre-ductal saturation range with or without changes to ventilation strategy (it is advised to avoid any changes in therapy while the response to iNO is being evaluated)
   - Normalisation of pre/post-ductal SaO2 difference

7. iNO Lack of Response or Dose Response
   - iNO should be discontinued if no response is observed within 1 hour
   - Attempts should be made to wean iNO dose to the minimal effective dose
   - If a trial of increasing nitric dose fails to improve oxygenation or haemodynamics then decrease dose back to original dose
   - If there is no response and/or the OI is > 25, consider whether the infant is an appropriate candidate for ECMO (see Educational Notes below for indications/considerations for ECMO)

8. Weaning iNO
   - Weaning from iNO should be carried out when an infant shows clinical improvement and is stable for a 4 hour period with FiO2 < 60%
   - If starting at 20 ppm, decrease iNO to 10 ppm for 1 hour then reduce to 5 ppm for 1-2 hours, followed by decreases of 1 ppm every 1-2 hours until ceased
   - If weaning from 20 ppm to 10 ppm results in failure, weaning can be carried out more slowly at the discretion of the medical team
   - The aim is to deliver the minimum dose compatible with normal oxygenation and haemodynamics
   - In term infants there may be an advantage in maintaining a low dose of iNO (2-5 ppm) while O2 and ventilator pressures are weaned, particularly if there is echocardiographic evidence of persistently elevated pulmonary artery pressures
   - In preterm infants the aim should be to wean off iNO as soon as possible

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9. Failure or difficulties with iNO weaning
   - While there is no clear definition for failure, iNO weaning can be considered unsuccessful if FiO2 increases by ≥ 20% and/or persistent requirements of FiO2 > 60% (Consider referral for ECMO if appropriate) [See Appendix 1; Appendix 2]
   - If weaning or discontinuation of iNO results in a clinically evident return of PPHN and hypoxaemia (as per criteria above), iNO therapy should be returned to the last effective dose

10. Methaemoglobin monitoring
    - If methaemoglobin levels rise above 5% iNO should be reduced or stopped
    - Methaemoglobin levels should be checked regularly (this is already included on blood gas analysis)

6. DOCUMENTATION

- eMR nursing notes
- Daily Care Plan
- Neonatal Observation Chart
- NICUS database

7. EDUCATIONAL NOTES

General Notes

- In term or near term infants with hypoxic respiratory failure, iNO has reduced the incidence of death or use of ECMO; (typical risk ratio (RR) 0.66, 95% CI 0.57-0.77; 859 infants in 8 RCT's).[1] This reduction was due to less use of ECMO, mortality was not affected. It did not reduce length of hospitalisation or risk of neurodevelopmental impairment. There is no evidence of adverse effects, either in the short- or long-term.[8]
- The benefits of iNO in preterm infants are not proven. A Cochrane review of 8 trials of early rescue treatment based on oxygenation criteria demonstrated no effect on mortality or BPD (RR 0.94, 95% CI 0.87-1.01; 958 infants).[9] In addition iNO was associated with a non-significant 20% increase in severe IVH.
- Despite this iNO is widely used in preterm infants with hypoxic respiratory failure and it has a good safety profile. Kinsella et al and others[2-7,10-12] argue using several case series[2-7,11,12] that there may be a place for iNO in the subgroup of preterm infants (< 34 weeks) with severe PPHN associated with PPROM, prolonged oligohydramnios and pulmonary hypoplasia. It is important in these cases that PPHN is identified on Echocardiography.[7]
- Peliowski et al reported 8 premature newborns of 24-31 weeks gestation with severe PPHN associated with prolonged rupture of membranes and suspected pulmonary hypoplasia.[3] All infants had improvement in pH and oxygenation, and 6 infants survived. Chock et al reported on a subset of 12 premature newborns enrolled in the Preemie Inhaled Nitric Oxide (PiNO) Trial with pulmonary hypoplasia after preterm premature rupture of membranes (PPROM).[4] Infants were treated with iNO with a mortality rate of 33% compared with 67% mortality for the infants in the placebo control group. Shah and Kluckow described outcomes for infants following PPROM, and reported that survival improved from 62% to 90% after the introduction of iNO and high frequency oscillatory ventilation in the management.[5] More recently, Semberova et al published a series of 22 premature infants with a history of PPROM, pulmonary hypoplasia, and PPHN who were treated with iNO with a survival rate of 86%.[6] It is important to note the peak gestation for responsiveness to iNO is 31-32 weeks and that responsiveness reduces at lower gestations.[13]

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- Common to all of these reports – severe hypoxemic respiratory failure and PPHN presenting on the first day of life that had marked improvement in oxygenation after treatment with iNO, similar to the response typically seen in term newborns with idiopathic PPHN.
- iNO therapy while not recommended routinely for RDS in premature neonates is safe and it can be considered in cases with a concurrent diagnosis of PPHN where it should be considered carefully.[7]
- The Pediatric Pulmonary Hypertension Network has proposed the following recommendations for the role of iNO in premature newborns:[10]
    - iNO therapy should not be used in premature infants for the prevention of BPD, as multicentre studies data have failed to consistently demonstrate efficacy for this purpose.
    - iNO therapy can be beneficial for preterm infants with severe hypoxemia that is primarily due to PPHN physiology rather than parenchymal lung disease, particularly if associated with PPROM and oligohydramnios.
    - iNO is preferred over other pulmonary vasodilators in preterm infants based on a strong safety signal from short and long term follow-up of large numbers of patients from multicentre randomised clinical trials for BPD prevention.
- iNO needs to be used appropriately and safely in both term and preterm infants and it is important the dose and duration of treatment is minimised.[14]
- Echocardiography can assist in directing appropriate use of iNO. The best response is often seen in infants with a relatively normal CXR but ECHO evidence of marked PPHN suggesting primary PPHN.

ECHO features of PPHN include	
DA shunt pattern	R → L > 30% (moderate) R→ L > 50% (severe)
Pulmonary blood flow	RVO < 150ml/kg/min (PA velocity < 0.25cm/sec)
RV pressure	TR jet > 30mmHg LPA pattern Septum deviation
RV function	RVO < 150ml/kg/min
LV function	LVO < 150ml/kg/min

- Toxicity of NO may result from direct inhibitory effects on platelet function, or via its products and reactive metabolites, including methaemoglobin, nitrogen dioxide, and peroxynitrite.[15,16] At the dose range applied clinically (20 ppm), iNO rarely causes clinically significant bleeding, or leads to potentially toxic levels of either methaemoglobin or nitrogen dioxide. iNO has not been demonstrated to increase peroxynitrite formation in the lungs or other tissues of human newborns.[15,16]
- iNO can theoretically cause methaemoglobinaemia although none of the RCTs using doses of 20 ppm or less have reported any increase in the incidence of methaemoglobinemia.[8]
- Preterm infants are more susceptible because of relatively low levels of the enzyme methaemoglobin reductase.

Oxygenation Index

- The severity of respiratory failure can be estimated by calculating the Oxygenation Index (OI).

$$\text{Oxygenation Index (OI)} = \frac{\text{Mean Airway Pressure (cm } H_2O\text{) x } FiO_2 \text{ (as a fraction) x 100}}{PaO_2 \text{ (mmHg)}}$$

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Consideration for referral for ECMO

- The Cochrane review of 4 RCT's shows strong benefit of ECMO on mortality (typical RR 0.44; 95% CI 0.31 to 0.61), especially for babies without congenital diaphragmatic hernia (typical RR 0.33, 95% CI 0.21 to 0.53).[17]
- Criteria for ECMO referral was initially very stringent and required infants to have severe respiratory failure and be ventilated with an Oxygenation Index (OI) of > 40 and underlying disease process which is likely to be reversible. A strategy of early institution of ECMO therapy is likely to result in the best outcomes for newborns with hypoxemic respiratory failure.[18] At present, there are few markers that predict which infants need ECMO therapy and which can be safely managed with non-ECMO therapies.[19] One UK centre's criteria for referral includes newborns with acute respiratory failure with an OI of > 25, systemic hypotension requiring treatment with moderate to large doses of inotropes, the presence of air leaks, and cardiorespiratory instability.

Consideration for ECMO	**ECMO Exclusion Criteria**	
	Absolute	Relative
• Birth weight >2000 g • Gestation ≥34+0 weeks • Potentially reversible disease • Failing conventional treatment • Oxygenation Index >25 • Uncompensated hypercapnoea (pCO_2 >90 mmHg with pH <7.25) • Less than 10 days ventilation • No reason to stop treatment	• Major congenital/chromosomal anomaly • Irreversible lung disease • Major intracranial bleed (grade 3-4 IVH) • Severe encephalopathy • Cardiac arrest (other than at birth) • Severe non-treatable congenital heart disease	• Gestation <34 weeks • Birth weight <2 kg • Ventilation >10-12 days

8. RELATED POLICIES/PROCEDURES/CLINICAL PRACTICE LOP

- Nil

9. RISK RATING

- Medium

10. NATIONAL STANDARD

- Standard 1 Governance for Safety and quality in Health Service Organisation
- Standard 4 Medication Safety
- Standard 9 Recognising and Responding to Clinical Deterioration in Acute Health Care

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11. ABBREVIATIONS AND DEFINITIONS OF TERMS

iNO	Inhaled Nitric Oxide	OI	Oxygenation Index
NCC	Newborn Care Centre	ppm	Parts per Million
PPHN	Persistent Pulmonary Hypertension of the Newborn	TGA	Therapeutics Goods Administration
PPROM	Prolonged Preterm Rupture of Membranes	ECMO	Extra Corporeal Membrane Oxygenation

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13. AUTHOR

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REVISION & APPROVAL HISTORY
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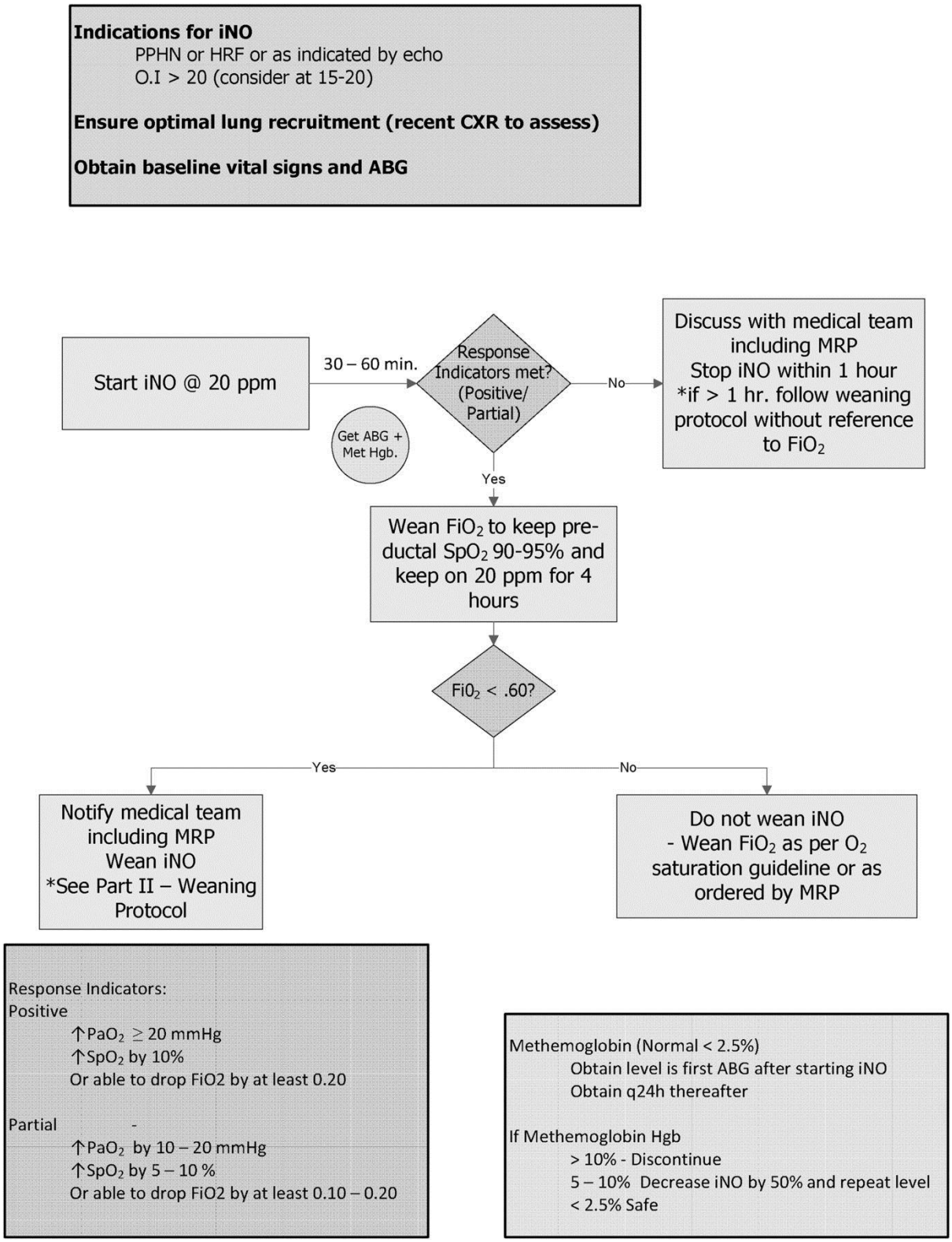
Appendix 1. Example Flowchart for Initiation of iNO[14]. ABG, arterial blood gas; CXR, chest x-ray; FiO2, fraction of inspired oxygen; Hgb, haemoglobin; MRP, most responsible physician; OI, oxygenation index; SpO2, pulse oxygen saturation. See text of LOP for RHW initiation plan.



Appendix 2. Example Flowchart for Weaning iNO[14]. FiO2, fraction of inspired oxygen; SpO2, pulse oxygen saturation. See text of LOP for RHW weaning plan.