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Trust Guideline for Inhaled Nitric Oxide therapy for Neonates

A clinical guideline recommended for use

For Use in:	Neonatal Intensive Care Unit (NICU)
By:	NICU Medical and Registered Nursing Staff, ANNPs
For:	Newborn Infants with severe Hypoxic Respiratory failure
Division responsible for document:	Women and Children's Services
Key words:	Inhaled Nitric Oxide, Hypoxic Respiratory failure, Persistent Pulmonary Hypertension of the Newborn, Oxygenation index (OI)
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Assessed and approved by the:	Professional Protocols, Policies and Guidelines Chair Clinical Guidelines Assessment Panel (CGAP) If approved by committee or Governance Lead Chair's Action; tick here ☐
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Version No:	5
Compliance links: *(is there any NICE related to guidance)*	None
If Yes - does the strategy/policy deviate from the recommendations of NICE? If so why?	N/A

This guideline has been approved by the Trust's Clinical Guidelines Assessment Panel as an aid to the diagnosis and management of relevant patients and clinical circumstances. Not every patient or situation fits neatly into a standard guideline scenario and the guideline must be interpreted and applied in practice in the light of prevailing clinical circumstances, the diagnostic and treatment options available and the professional judgement, knowledge and expertise of relevant clinicians. It is advised that the rationale for any departure from relevant guidance should be documented in the patient's case notes.

The Trust's guidelines are made publicly available as part of the collective endeavour to continuously improve the quality of healthcare through sharing medical experience and knowledge. The Trust accepts no responsibility for any misunderstanding or misapplication of this document.

Version and Document Control:

Version Number	Date of Update	Change Description	Author
5	06/10/2020	Addition of flowchart and checklist	Rahul Roy

This is a Controlled Document

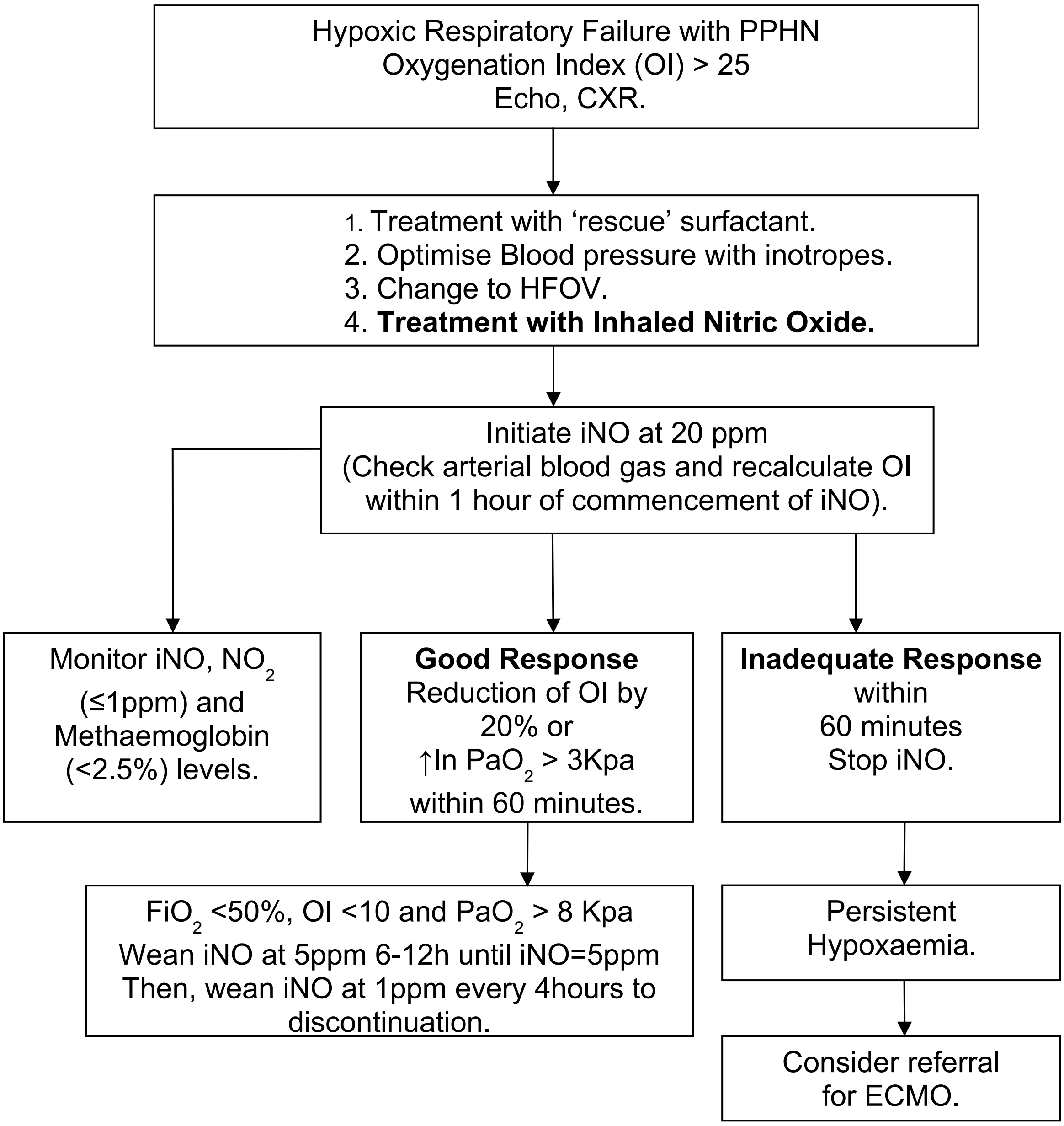
Printed copies of this document may not be up to date. Please check the hospital intranet for the latest version and destroy all previous versions.

List of abbreviations:

iNO	Inhaled Nitric Oxide
NO	Nitric Oxide
PPHN	Persistent Pulmonary Hypertension of Newborn
OI	Oxygenation Index
ECMO	Extracorporeal Membrane Oxygenation
HFO	High Frequency Oscillation
HFOV	High Frequency Oscillatory Ventilation
NO_2	Nitrogen Dioxide
ppm	parts per million
SEND	South East Neonatal Data system

Quick reference

Algorithm for Inhaled Nitric Oxide therapy for Term and Near-Term Infants (>34 weeks) with Hypoxic Respiratory failure associated with PPHN



Objectives of the Guideline

To ensure that inhaled nitric oxide (iNO) is used in a safe, effective, appropriate and cost-effective way for term or near term infants (>34 weeks gestation) with hypoxic respiratory failure associated with PPHN on the neonatal unit.

Rationale for the recommendation

Neonatal hypoxemia may result from intra-pulmonary shunting, extra-pulmonary shunting or from cyanotic congenital heart disease. Inhaled nitric oxide at present is the only selective and potent pulmonary vasodilator which has been established by prospective randomised trial to improve oxygenation in neonates born at term or near term (>34 weeks) with severe hypoxic respiratory failure associated with persistent pulmonary hypertension.

It has been shown to improve outcome by significant reduction in the combined outcome of death or need for extracorporeal membrane oxygenation (ECMO) It improves oxygenation through selectively lowering pulmonary vascular resistance, decreasing extra pulmonary shunting, improving ventilation-perfusion matching and/or reduced intrapulmonary shunt in approximately 50% of treated infants.

Use of extra ‘rescue’ exogenous surfactant and ventilatory manoeuvres, by using High Frequency Oscillation (HFO) to improve alveolar recruitment should be tried before iNO is introduced to achieve an optimum response. Inhaled nitric oxide is most likely to benefit babies with PPHN with adequately recruited lung volume.

Current evidence suggests that iNO in term or near term babies is not associated with an increase in adverse neurodevelopmental effects at 2 years of age. It is currently licensed for use in babies who are over 34 week’s gestation and have hypoxic respiratory failure.

The evidence of benefits of iNO as an effective rescue therapy for **preterm babies** (≤ 34 weeks gestation) with severe hypoxic respiratory failure is lacking. The off-label use of iNO in this population has escalated by six fold reported in a study published in 2010 .

Pilot studies reported short term improvement in oxygenation with iNO, but no significant benefit was observed in mortality or other morbidities. Meta-analysis of 14 RCTs looking at benefits of iNO in preterm concluded that it does not recommend the use of iNO in early routine, early rescue or later rescue in infants born less than 34weeks.

Treatment with iNO is expensive and can add significantly to healthcare costs. In clinical situations where iNO is used as an ‘off-label’ as judged by the clinician to be in the best interest of the patient, then document reasons for using and you may wish to record that you have discussed the issue with the parents.

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

$$\frac{\text{Mean Airway Pressure (cm } H_2O) \times FiO_2 \times 100}{PaO_2 \text{ (mmHg)}}$$

To convert from KiloPascals (KPa) to millmetres of Mercury (mmHg), multiply KPa value by 7.5

Broad Recommendations

Indication for iNO therapy

Term and near-term babies (>34 weeks) with hypoxic respiratory failure (OI >25) associated with Primary PPHN or PPHN secondary to Meconium Aspiration Syndrome, Pneumonia, Respiratory Distress Syndrome or other lung pathology.

PPHN is present when an infant with an echocardiographically confirmed structurally normal heart has: i) severe hypoxaemia ii) echocardiographic evidence of right-to-left shunting of blood across the ductus arteriosus and/or the foramen ovale secondary to pulmonary hypertension.

Indication for Inhaled Nitric Oxide (iNO) therapy

- Term and near-term babies (>34 weeks) with hypoxic respiratory failure associated with Persistent Pulmonary Hypertension of the Newborn (PPHN).

Exclusion criteria

- PPHN secondary to congenital diaphragmatic hernia.
- Cyanosis secondary to congenital heart disease.
- Preterm infants (≤34 weeks) with hypoxic respiratory failure.

Contraindications to inhaled nitric oxide therapy

- Bleeding diathesis should be corrected prior to starting iNO.
- Use of iNO may not be appropriate in babies with severe or lethal congenital or chromosomal anomalies.

Method of Delivery of iNO:

Inhaled Nitric oxide is delivered using the INOvent system supplied by INO Therapeutics AB (U.K). This system combines gas cylinders, monitoring equipment and delivery equipment in one unit. The gas mixture (INOmax) of NO in nitrogen is administered into the inspiratory limb of the ventilatory circuit. When iNO reacts with oxygen it forms Nitrogen Dioxide (NO_2) which is highly toxic. Therefore, both NO and NO_2 are monitored in the inspiratory gases. A closed circuit is maintained to prevent release of NO into the surrounding atmosphere. Details about the set up and use of the INOvent can be found in the manual attached to each system. Only staff that have been trained and assessed should set up the INOvent and nurse babies receiving iNO.

Starting Treatment:

The Neonatal Consultant must always be involved in the decision to commence iNO. Start iNO at 20 ppm and check for response by measuring the OI within 60min of commencement. Evidence is lacking for benefit of doses > 20ppm. A good response is defined by an improvement in oxygenation with a reduction of OI from baseline by at least 20% or increase in post-ductal PaO_2 of more than 3Kpa within 60minutes. If there has been no response within 60 min then iNO **should be stopped and not weaned**. Evidence is lacking for benefit of continuing iNO in patients who do not demonstrate a good response in terms of improved oxygenation.

Note: Please fill in the inhaled Nitric Oxide checklist and flow chart prior to commencing and during treatment.

Maintenance and Weaning:

The dose of iNO should be maintained at an optimal level as judged by the reduction of OI. Review the dose of iNO at least every 12 hours, with a view to weaning the dose to minimise exposure. After improvement in oxygenation, dose reduction should be attempted once ventilatory requirements are reducing and OI falls below 10 with FiO_2 below 50%.

Decrease the iNO dose slowly in steps of 5 ppm every 6 hrs to a minimum of 5 ppm. Finally wean iNO by decreasing in steps of 1 ppm every 4 hrs until dose = 1 ppm. If a worsening of OI or increase of FiO_2 by more than 20% occurs then further attempts at weaning should be deferred and the dose may need to be increased.

Discontinuation:

Stop once iNO has been weaned to 1 ppm with FiO_2 <50%. Stopping of iNO can occasionally lead to a rebound pulmonary hypertension leading to decreased oxygenation and requiring reintroduction of iNO.

Patient Monitoring

Inhaled nitric oxide can combine with oxygen to produce nitrogen dioxide (NO_2) or with haemoglobin to form methaemoglobin. NO_2 is potentially toxic to the lung and methaemoglobinaemia can reduce tissue oxygen delivery. iNO and NO2 levels in inspired gases should be monitored continuously. NO_2 levels should be kept below 1 ppm. Reduce iNO dose if NO_2 levels greater than1ppm. Blood methaemoglobin levels should be measured at 1 and 4 hours after starting iNO and at least 12 hourly thereafter. Methaemoglobin levels should be maintained below 2.5%. Reduce iNO if methaemoglobin levels are greater than 2.5% and repeat levels in 1 hour. If levels >7% at any time stop iNO therapy and consider giving intravenous methylene blue (1 mg/kg over 1 hour).The methaemoglobin level can be measured by the blood gas machine.

Inhaled NO has been associated with a prolonged bleeding time by inhibiting platelet aggregation. Ensure platelet count >50 before starting and during treatment.

Environmental Safety

Environmental NO contamination can occur from two sources during NO administration: dumped waste ventilator gas and accidental leakage of concentrated gas from the delivery system or cylinder. Scavenging of waste NO is unnecessary in well ventilated intensive care units[11]. Environmental level of NO_2 should be continuously measured using the NO_2 environmental monitor. Maintain the environmental level of NO_2 below 1.5 ppm.

Documentation

The times of starting and stopping iNO therapy should be entered in the South East Neonatal Data (SEND) system. The prescribed dose of iNO, the delivered concentrations of iNO and NO_2, and measured methaemoglobin concentrations must also be recorded as part of regular observations.

Clinical Audit Standards Derived From Guideline

1. All term and near term babies with hypoxic respiratory failure associated with PPHN should receive a trial of iNO therapy once adjunctive therapies such as surfactant and HFO have been tried.
2. Echocardiography to be performed before or within 24 hrs of initiating iNO to confirm a structurally normal heart and/or to demonstrate extrapulmonary right-to-left shunting.
3. ‘Off-label’ usage of iNO.
4. Stop iNO in non-responders within 2hrs.

Summary of Development and Consultation Process Undertaken Before Registration and Dissemination

This guideline was drafted by Dr Rahul Roy, on behalf of the Neonatal Intensive Care Unit. During its development and review it has been circulated to consultant neonatologist colleagues for comments. It has been presented and discussed at the neonatal unit clinical guidelines meeting (attended by medical, nursing and ANNP staff of the neonatal unit).

Distribution list/ dissemination method

Hospital Intranet

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Appendix 1

Checklist Prior and During Nitric Oxide Therapy	Patient Identifier label

Is the neonate Term or near term >34wks PPHN and with an OI > 25	Yes No	**If not, does the neonate fit any of the following exclusion criteria?** below	
	CDH	PREM (≤34w)	Cyanosis 2_0 CHD
	OR Trial of iNO has been initiated under consultant discretion		

Rescue Surfactant given	Yes No	*if no detail why not*
All actions to optimise blood pressure completed Trial of HFOV	Yes No	*if no detail why not*
ECHO (before or within 24hrs of initiating iNO)	Yes No	*if no detail why not*
Prior to starting iNO calculate 0I > 25	*Tick when complete*	
Check platelets > 50	*Tick when complete*	
Consultant decision to start iNO *detail*		
Discuss with parents for 'off label'use of iNO	*Tick when complete*	

Start NITRIC at 20ppm	*Tick when complete*	Date *dd/mm/yyyy* and Time *24 hours clock* started	
1hour after starting check blood gas, 0I and Methaemoglobin (below 2.5)		tick to confirm	

Good Response = Reduction in 0I by 20% or increase in PaO_2 > 3Kpa within 60 minutes	Yes Review dose at 12 hours: Time Please turn over for review chart	No Stop Nitric – Yes No Consider ECMO referral

Print name		Signature	
Designation		Date *dd/mm/yyyy*	

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Checklist
Prior and During
Nitric Oxide Therapy

Patient Identifier label

Dose should be weaned once OI falls below 10 with F 2 below 50%	Tick to confirm	NB: If worsening of OI or increase in FiO_2 by 20% stop weaning nitric and dose may need to be increased
Criteria for initiating weaning met	*Date dd/mm/yyyy and time* 24 Hours	

Print name		Signature	
Designation		Date *dd/mm/yyyy*	

Review 12 hourly					
Time *24 hours clock* and Date *dd/mm/yyyy*	Yes	No	Met Hb	Print name	Signature
	Yes	No			
	Yes	No			
	Yes	No			
	Yes	No			
	Yes	No			
	Yes	No			
	Yes	No			
	Yes	No			
	Yes	No			
	Yes	No			
	Yes	No			
	Yes	No			
	Yes	No			
	Yes	No			
	Yes	No			
	Yes	No			
OI below 10 with FiO2 below 50% / NO - OI above 10 and FiO2 above 50% do not wean					

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Checklist For Use Prior and During Nitric Oxide Therapy

Patient Identifier label

Once YES (OI falls below 10 or FiO2 below 50%), commence weaning in steps of 5 every 6 hours			
Date *dd/mm/yyyy* and Time *24 hours*	iNO Dose	Print name	Signature

Once at 5ppm reduce dose by 1ppm every 4 hours.			
Date *dd/mm/yyyy* and Time *24 hours*	iNO Dose	Print name	Signature