Administration of Inhaled Nitric Oxide

A Review of Canadian Hospital Guidelines and a Systematic Review of the Literature for the Canadian Association of Paediatric Health Centres (CAPHC)

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Overview

A review of hospital guidelines for administration of inhaled Nitric Oxide (iNO) was completed. Eighteen documents from eleven hospitals across Canada and a systematic review of the literature, the American Association for Respiratory Care: Evidence-Based Clinical Practice Guideline: Inhaled Nitric Oxide for Neonates With Acute Hypoxic Respiratory Failure, were analyzed. There are two documents from IWK Health Centre. The first document is a literature review and guideline from 2006 and the second is a guideline with some content based upon the first document. Two of the documents from London Health Science Centre consisted of tables used to document monitoring levels.

Two researchers extracted all the content from the documents to a platform for comparison. Due to the heterogynous nature of the documents, time was devoted to independently identify categories common among the documents. After a discussion, categories were agreed upon. Inclusion and exclusion criteria were then determined. Information was grouped using the criteria. Information within categories was summarized and standardized for ease of comparison. The researchers compared the results for similarities and differences. A conclusion was prepared for each category highlighting key results.

The document below consists of our key results by category and is followed by summary tables. It is important to note that direct comparisons were complicated by the nature of the documents which were heterogynous in their goals and target audience. For example, two of the documents provided (London Health Sciences: Inhaled Nitric Oxide Study and London Health Sciences: NICU Nitric Oxide Administration Flow Sheet) were tables for entering vitals and monitoring parameters and were not analyzed in our review.
Summary of Findings

Policy

Most documents recommend the initiation of iNO therapy follow a physician’s order, however medical orderable items noted in many documents do not reference supplementary medical directives and there are limited occasions where requesting an additional physician order is recommended. In addition to physician orders, the London Health Sciences Centre neonatal unit allows nurse practitioners and advance practice nurses to order the initiation of iNO therapy whereas McGill allows a neonatal nurse practitioner to write a medical order to begin iNO therapy. The administration of iNO is overseen by RRTs in most hospital guidelines. Only McGill assigns the role of assessment and monitoring during iNO therapy to NICU nurses.

Procedure

Most hospital documents provide a procedure list for the administration of iNO and diagnostic and monitoring practices. Exceptions include BC Women’s Hospital and CHU Sainte-Justine which provide flowcharts, and Stollery Children’s Hospital. SickKids CCU, SickKids NICU, and Hamilton Health Sciences, CHEO, and IWK recommend setting alarms for NO range and NO₂ on the iNOmax system. Of the hospitals that gave specific levels, SickKids CCU, SickKids NICU, and Hamilton Health Sciences recommend a range of +/- 5 ppm for NO and for NO₂ SickKids NICU and Hamilton Health Sciences recommend a high of 2 ppm whereas SickKids CCU recommends a high of 1.5 ppm.

Equipment

iNOmax is the standard delivery system for iNO therapy. Only IWK Health Centre and SickKids NICU document equipment and instructions on set-up and pre-use procedures. CHEO lists equipment and suggest referral to iNOmax DS Reference Manual (Delivery System), iNOmax pocket guide, and Technical Bulletin for Ventilator Applications, whereas Hamilton Health Sciences lists equipment and suggest referral to iNOmax DSIR Operation Manual, iNOmax DSIR PreUse Calibration Card, and iNOmax DSIR Pocket Guide. McGill University Health Centre refers to iNOmax DSIR manual for set-ups, troubleshooting and alarms. AARC recommends that FDA-approved iNO delivery systems should be used to assure consistent and safe gas delivery during therapy.

Conditions where iNO Therapy is Recommended

iNO therapy is recommended for PPHN is all hospitals with the exception of IWK and CHU Sainte-Justine; IWK mentions no conditions and CHU Sainte-Justine is recommended more generally in pediatric ARDS. Only London Health Science Centre recommends the use of iNO on adults, children, and neonates. BC women’s hospital notes limited evidence for use in PPROM whereas CHEO recommends use of iNO therapy for patients with PPROM in the NICU. Only Stollery and McGill (in certain cases) recommend iNO therapy for congenital diaphragmatic hernia despite many other documents listing CDH as a contraindication. Only Hamilton Health Sciences recommends iNO in preterm patients with particular oxygenation requirements. London Health Science Centre, Hamilton Health Sciences, and CHEO recognize other secondary conditions that can cause pulmonary hypertension.
Inclusion Criteria for iNO Therapy

Documents that reference age as a criteria for iNO therapy all recommend >34 weeks of gestational age for inclusion. Oxygenation index is used for inclusion criteria in most hospitals but vary between OI>15 and OI>25. Pre and post ductal saturation difference >10% and clinical or echocardiatic evidence of PPHN are also inclusion criteria for some hospitals. General hypoxemia requirements of FiO₂ >60% is also used as an inclusion criteria for iNO therapy in some hospitals.

Contraindications/Exclusions

Contraindications and exclusion criteria vary between hospitals. Contraindications include: total anomalous pulmonary venous drainage, cardiac circulation dependent on right to left shunting, presence of intraventricular hemorrhage or any other hemorrhage, methemoglobinemia (methemoglobin >5%) or lower methemoglobin reductase levels, low platelet count, gestational age <34 weeks, and congenital diaphragmatic hernia.

Recommendations prior to administration of iNO

A confirmation of PPHN by echocardiogram is recommended by most hospitals prior to initiating iNO therapy. Most hospitals recommend appropriate lung inflation and to optimize ventilatory parameters, sedation, muscle relation, and fluid resuscitation. In addition, CHEO recommends a head ultrasound for NICU patients.

Dosage

Most hospitals recommend an initial dose of iNO at 20 ppm. Only four hospitals recommend doses beyond 20 ppm: SickKids CCU (40 ppm), IWK (80 ppm maximum), Hamilton Health Sciences (40 ppm), and the Jewish General Hospital (no limit given). CHU Sainte-Justine recommends an initial dose of 10 ppm. Nearly all hospitals recommend evaluating response after 30 minutes at the initial dose before weaning or titrating iNO.

Assessment of the Response after Initiation of iNO Therapy

All hospital documents have explicit criteria for a positive response to iNO therapy measured but vary on which criteria is considered and levels. Criteria for positive response include: pulmonary vascular resistance decrease by 20%, OI ≥ 20 (with the exception of BC Women’s Hospital which uses O₂≥15), SpO₂ increase of 10% (with the exception of London Health Science Centre which has a lower threshold of 5% increase and Jewish General Hospital with no specific criteria), PaO₂ increase by ≥ 20 mmHg (measured as PaO₂/FiO₂ increase of 20% at CHU Sainte-Justine, London Health Science Centre, and McGill), or able to decrease FiO₂ by 20%. Criteria for negative response include: pulmonary vascular resistance increase by 20%, OI ≤ 10%, SpO₂ increase of <5%, and PaO₂ increase by ≤ 10 mmHg (measured as PaO₂/FiO₂ decrease of 15% at CHU Sainte-Justine and a decrease of 20% at London Health Science Centre), or able to drop FiO₂ by <10%.
Monitoring

Most hospitals recommend monitoring vital signs, ventilation and oxygenation levels, and the iNOmax equipment which continuously monitors the dose of NO, NO₂, and O₂. Stollery and the Jewish General Hospital are the only hospitals that recommend monitoring platelet levels.

Weaning

All hospitals recommend weaning iNO as soon as possible; however the weaning procedure varies by hospital. If there is a positive response to the iNO therapy, usually determined after 4-12 hours, most hospitals recommend reducing iNO at varying intervals. The most common weaning procedure is a reduction of 50% until 5 ppm and then by 1 ppm until discontinuation of iNO therapy. Timeframes for weaning from one dose to the next lowest dose vary by hospital and range from every hour to every 8-12 hours. If weaning is not tolerated it is recommend to return to last effective dose and wait prior to restarting weaning. Interestingly, CHU Sainte-Justine recommends a much longer period time before weaning (3 days), and a much fast weaning process (reduction of dose every 30 minutes).

Complications

The most common cited complications include methemoglobinemia, nitrogen dioxide poisoning, and rebound hypertension. Less common cited complications include platelet dysfunction, inadvertent hypoxic gas delivery, systemic hypertension, and direct lung toxicity.

Monitoring Schedule of Methemoglobin

All hospitals recommend measuring methemoglobin levels but vary in their monitoring schedule. All hospitals recognize the importance of measuring within the first 12 hours after initiation of iNO. Depending on the result of the initial measurement, the subsequent evaluations occur at short intervals in the case of elevated methemoglobin levels or daily or longer intervals if methemoglobin levels are within parameters.

Methemoglobin Parameters

Actions taken to address methemoglobin levels vary depending on the hospital. Methemoglobin levels deemed safe range from 2% to 5%. The response to elevated methemoglobin levels (>2.5% to >5%) varies by hospital with some recommending a reduction in dose or discontinuing treatment and all hospitals with procedures for very high levels (>10%) recommend discontinuing treatment.

IWK recommends treating patient with reducing agents such as methylene blue if methemoglobin >5%, Hamilton Health Sciences recommends methylene blue 1-2 mg/kg, or pure oxygen, or blood transfusion in pediatrics with methemoglobinemia. London Health Science Centre and London Health Science Centre Neonatal recommend the administration of reducing agents such as methylene blue be considered if methemoglobin >2.5%. McGill University Health Centre recommends treating methemoglobinemia with intravenous vitamin C, intravenous methylene blue, or blood transfusion, based upon the clinical situation.
**Monitoring of Nitrogen Dioxide**

The monitoring of nitrogen dioxide is not explicitly stated in some hospital guidelines. Specifically, IWK Health Centre, BC Women’s Hospital, CHU Sainte-Justine, IWK Health Centre Review, and London Health Science Centre do not mention NO\(_2\) monitoring or define safe levels. Of the hospitals that do recommend monitoring most do so continuously. Safe levels of NO\(_2\) vary by hospital and range from 0.5 ppm to 5 ppm.

**Management of Rebound Pulmonary Hypertension**

Of the hospitals that recommend specific action for rebound pulmonary hypertension, most warn against abrupt interruption of iNO therapy and recommend increasing FiO\(_2\) by 10% to 20%. It is also common to note that rebound pulmonary hypertension is not a reason to restart iNO therapy.
Documents Reviewed

3. The Hospital for Sick Children: Nitric Oxide Delivery in the NICU (2013)
4. The Hospital for Sick Children: Nitric Oxide Delivery in the CCU (2013)
6. IWK- Health Centre: Report Recommendations for Guidelines for the Use of Inhaled Nitric Oxide and the NICU for Term & Pre-Term Newborns (2006)
7. Mount Sinai Hospital: Respiratory Therapy, Neonatal Intensive Care Unit Policy/Procedure (2012)
8. BC Women’s Hospital: Inhaled Nitric Oxide (iNO) (2013)
10. Alberta Health Services, Stollery Children’s Hospital: Inhaled Nitric Oxide Policy (2012)
12. London Health Sciences: iNOmax (Inhaled Nitric Oxide) Administration (2010)
13. London Health Sciences: Neonatal - Nitric Oxide Therapy (Inhaled Nitric Oxide) Administration
14. London Health Sciences: Inhaled Nitric Oxide Study (Table)
16. London Health Sciences: Nitric Oxide Cheat Sheet: Recommended Guidelines for Nitric Oxide Use
18. McGill University Health Centre: Administration of Inhaled Nitric Oxide (iNO) in the NICU (2013)

All documents include a list of references except for CHU Sainte-Justine, BC Women’s Hospital, Stollery Children’s Hospital, and London Health Sciences Centre iNO Cheat Sheet.
Hospital Abbreviations

AARC  American Association for Respiratory Care
SickKids  The Hospital for Sick Children, Toronto, Ontario
IWK-HC  IWK Health Centre, Halifax, Nova Scotia
Mount Sinai  Mount Sinai Hospital, Toronto, Ontario
BC Women’s  BC Women’s Hospital & Health Centre, Vancouver, British Columbia
CHEO  Children's Hospital of Eastern Ontario, Ottawa, Ontario
Stollery  Stollery Children’s Hospital, Edmonton, Alberta
HHS  Hamilton Health Sciences, Hamilton, Ontario
CHUSJ  Centre Hospitalier Universitaire Sainte-Justine, Montréal, Québec
LHSC  London Health Sciences Centre, London, Ontario
JGH  Jewish General Hospital, Montreal, Quebec
MUHC  McGill University Health Centre, Montreal, Quebec

Technical Abbreviations

ABG  Arterial Blood Gas
ARDS  Acute Respiratory Distress Syndrome
CCM  Critical Care Medicine
CCU  Critical Care Unit
CDH  Congenital Diaphragmatic Hernia
FiO2  Fraction of Inspired Oxygen
iNO  Inhaled Nitrogen Oxide
MPAW  Mean Airway Pressure
MRSP  Medical Readiness Strategic Plan
NICU  Neonatal intensive Care Unit
NO  Nitric Oxide
OI  Oxygenation index; (FiO2 * MPAW)/ PaO2
OR  Operating Room
PaO2  Partial Pressure of Oxygen in Arterial Blood
PICU  Pediatric Intensive Care Unit
PPHN  Persistent Pulmonary Hypertension of the Newborn
PPROM  Preterm Premature Rupture of Membranes
PVR  Pulmonary Vascular Resistance
RDS  Respiratory Distress Syndrome
RRT  Registered Respiratory Therapist
SaO2  Arterial Oxygen Saturation
SpO2  Saturation of Peripheral Oxygen
SvO2  Venous Oxygen Saturation
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Summary Tables

Policy
Policies include orders proposed by the institutions and specific responsibilities of health care providers.

<table>
<thead>
<tr>
<th>Policy</th>
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<tbody>
<tr>
<td><strong>SickKids NICU</strong></td>
</tr>
<tr>
<td>• Registered Respiratory Therapists are responsible for the safe and effective delivery of iNO.</td>
</tr>
<tr>
<td>• Initiate iNO therapy with written medical order.</td>
</tr>
<tr>
<td>• Verify physician’s order to begin iNO. Changes to the prescribed iNO dosage require a physician’s order to follow the iNO guideline or to follow an alternate dosing strategy.</td>
</tr>
<tr>
<td>• The medical team should be notified immediately of any deterioration in hemodynamic or oxygenation status following the initiation of iNO or following any dosage changes.</td>
</tr>
<tr>
<td>• A medical team discussion (including MRSP when available) will ensue to determine response and ongoing plan of care.</td>
</tr>
<tr>
<td><strong>SickKids CCU</strong></td>
</tr>
<tr>
<td>• iNO administration requires a written medical order cosigned by two physicians (CCM Fellow and Attending Staff) reassessed daily and with any change to the dosage. The physician should be notified immediately of any change in patient condition associated with changes in iNO therapy.</td>
</tr>
<tr>
<td>• Registered Respiratory Therapists are responsible for the safe and effective delivery of iNO to patients in the CCU.</td>
</tr>
<tr>
<td>• iNO is to be directed by CCU physician in patients with a relative contraindication.</td>
</tr>
<tr>
<td><strong>IWK Health Centre</strong></td>
</tr>
<tr>
<td>• Adjust NO to appropriate dosage in consultation with physician.</td>
</tr>
<tr>
<td><strong>IWK Health Centre Review</strong></td>
</tr>
<tr>
<td>• No mention</td>
</tr>
<tr>
<td><strong>Mount Sinai Hospital</strong></td>
</tr>
<tr>
<td>• No mention</td>
</tr>
<tr>
<td><strong>BC Women’s Hospital</strong></td>
</tr>
<tr>
<td>• Start iNO with physician’s orders</td>
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</table>
| • A team meeting with 2 neonatologists and a cardiologist take place at 5-7 days of treatment to
Inhaled Nitric Oxide Review

### Policy

- Decide to wean or discontinue iNO, consider other vasodilators, or continue iNO and re-evaluate every 7 days.
- Neonatologist to document decision in chart.

### CHEO

- Initiate iNO therapy with physician order.
- The delivery and initiation of iNO to patients via nasal cannula or mechanically ventilated patients will be initiated by the RRT.
- The RRT is required to complete the competency based assessment for INOMax DSIR equipment prior to using the equipment to deliver iNO to the patient.

### Stollery Children’s Hospital

- Initiate iNO therapy with physician order.

### Hamilton Health Sciences

- Inform the physician of any patient meeting the criteria and having one ABG with an OI greater than or equal to 15.
- Initiating, weaning and discontinuing iNO therapy is only done as ordered by the attending physician.
- Safety guidelines and toxicity checks must be strictly followed.
- The RT is responsible for setting up all INOMax® equipment and supplies and must be present if required.
- If the infant is a partial/non-responder, be discussed with the NICU physician.
- Follow documentation policy.

### American Association for Respiratory Care

- No mention

### Centre Hospitalier Universitaire Sainte-Justine

- No mention

### London Health Sciences Centre

- iNO is administered only upon an order from the following physicians:
  - MSICU/CCTC/CSRU/PCCU: Critical Care Consultant
  - OR: Cardiovascular Anesthetist in conjunction with Cardiac Surgeon
- iNO is administered only in the following clinical areas: Operating Room (OR), Cardiac Investigation Unit (CIU), and Critical Care Units (Medical Surgical Intensive Care Unit (MSICU), Cardiac Surgery
Policy

**Recovery Unit (CSRU), Critical Care Trauma Unit (CCTC), Pediatric Critical Care Unit (PCCU), Pediatric Transport).**

- Only Registered Respiratory Therapists (RRT) are permitted to initiate and adjust therapy and to discontinue the delivery device and associated supplies from clinical use.
- Ensure that the ordering physician and the patient’s nurse are aware of this dosage once the most effective dose of INOmax has been determined and documented.
- Weaning may commence upon a physician’s order.

**London Health Sciences Centre Neonatal**

- iNO therapy will be initiated on the order of a physician/NNP/APN.
- iNO will be administered and titrated by RRTs.

**London Health Sciences Centre iNO Cheat Sheet**

- Obtain iNO order from Critical Care Consultant or Anesthesiologist (in OR).

**Jewish General Hospital**

- Under the written order from the intensivist of record or ICU Fellow the RRT may institute NO Therapy to a patient.
- The Registered Respiratory Therapist assigned to the appropriate High Care Area (ICU I & II, NICU, Emergency Resuss, CCU) will test, initiate iNO therapy, or change the concentration of iNO, according to department Policy and Procedure and the written order from the intensivist of record or ICU Fellow. As corollary, while the RRT can provide suggestions to the medical team regarding iNO management, he/she cannot change the concentration on his/her own.
- No iNO order will be accepted from a rotating resident unless he/she has had explicit agreement for that intervention with one of these 2 people.
- Monthly calibration must be documented on the calibration sticker posted on top of the INOmax DS control box. Low range calibration must be documented daily. All patient information must be documented on the Depts. flowsheet.

**McGill University Health Centre**

- Respiratory Therapists who have successfully completed an orientation session (at RVH or MCH NICU) or attended the teaching session for the use of iNO therapy.
- NICU nurses responsible for patient assessment and monitoring during iNO therapy.
- Neonatologists responsible for patient assessment and prescription of iNO therapy as per indications described in this protocol.
- A respiratory therapist will remain in the NICU at all times when iNO is in use.
- The neonatologist, fellow, resident, or neonatal nurse practitioner (NNP) will write a medical order for the starting iNO concentration.
Policy

on the respiratory therapy ventilation order flowsheet to begin iNO as per protocol.
Procedure

The procedure includes series of actions conducted in a certain order. Direct comparisons between documents were difficult as there were differences in the purpose and audience.

<table>
<thead>
<tr>
<th>Procedure</th>
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<tbody>
<tr>
<td><strong>SickKids NICU</strong></td>
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- Do not decrease the infant’s FiO\textsubscript{2} to room air as this will inadvertently deliver a hypoxic mixture while on iNO.
- The low FiO\textsubscript{2} alarm should never be set to lower than 0.23 given the +/- accuracy of the Ikaria oxygen analyzer.
- All documented FiO\textsubscript{2} s should be read from the Ikaria delivery system.
- Arterial access if possible (pre ductal location preferred)
- Continuous monitoring of SpO\textsubscript{2}, TcPCO\textsubscript{2} / end-tidal CO\textsubscript{2}, vital signs
- Optimize ventilation strategies (i.e. Optimal PEEP, optimal MAP, frequent CXRs, HFV etc...)
- Optimize perfusion (pulmonary and peripheral)

Nitric Oxide Therapy Initiation:
1. Obtain arterial blood gas prior to starting iNO (for baseline and OI)
2. Record readings of non-invasive monitors, FiO\textsubscript{2} and ventilator settings
3. Initiate iNO at 20 ppm
4. Obtain an arterial blood gas within 30-60 minutes of initiating iNO
5. A positive response to iNO will be defined on the basis of an increase in PaO\textsubscript{2} above baseline 30 minutes post delivery of the prescribed dosage. Every effort should be make to avoid ventilator parameter changes including FiO\textsubscript{2} from initiation of iNO and the first arterial blood gas (approximately the first 30-60 minutes of therapy)
6. Initiation of pharmacological treatment and/or alkalinizing agents during the first 30-60 minutes of initiating iNO should be avoided
7. If a full response is determined clinically, document and maintain the iNO at 20 ppm establish optimal FiO\textsubscript{2} and leave iNO at 20 ppm for 4 hours
8. Prepare delivery system by performing pre-use procedure checks (refer to procedure card on unit)
9. Prepare delivery circuit/sampling line and assemble into ventilator circuit (replace connectors used in NO kits in RT room)
10. Check for and correct any leaks in the system
11. Perform and document baseline assessments:
   - Arterial blood gases
Inhaled Nitric Oxide Review

### Procedure

- Vital signs
- Oxygen index calculation: OI > 15 on arterial blood gas suggests need for iNO

12. Once the prescribed dosage is achieved (as per measured NO via iNO delivery system), the alarm limits should be set as follows:
   - High / low NO dosage +/- 5 ppm
   - High NO₂ 2 ppm

13. Document initiation and dosage of iNO and tank serial number in computerized patient chart

14. After 30 – 60 minutes of iNO therapy at the prescribed dosage, arterial blood analysis should be performed and the physician should be notified of the results. If this exceeds 1 hour or when the infant has already been started on iNO in transport. A medical team discussion (including MRSP when available) will ensue to determine response and ongoing plan of care

15. Methemoglobin should be measured within 1 hour of initiating iNO, particularly if nitric oxide dosage > 20 ppm. Methemoglobin measurements should be done daily (q24h). The physician should be notified of methemoglobin results > 2.5 % and appropriate weaning done on iNO.

16. When iNO is weaned to off, ensure to turn tank off completely displaying hash marks on regulator (---) and document in computerized patient chart.

### SickKids CCU

1. Verify medical orders to begin iNO therapy.
2. Prepare and assemble appropriate delivery circuit.
3. Complete the pre-use check-out procedure and calibration of the iNOmax DSᵊ. Alarms should be set on the iNOmax DSᵊ for monitoring: High/Low NO (dosage +/- 5 ppm of set value) and High NO₂ (1.5 ppm).
4. Clearly label all circuit components of the iNO system.
5. Ensure that the patient condition has been optimized and there is steady state prior to initiating iNO (if feasible).
6. Obtain arterial and mixed venous blood gases (baseline and to determine OI). Perform and document baseline assessments:
   - Vital signs
   - Relevant hemodynamic measurements
   - Relevant parameters as identified by the team prior to initiation of iNO
   - FiO₂
   - Ventilator settings
7. Initiate iNO at 40 ppm to determine responses
8. Identify and document the patient’s response to iNO therapy and notify the physician if a positive response is not recognized.
Inhaled Nitric Oxide Review

**Procedure**

9. After 20-60 minutes at 40 ppm conduct an arterial blood gas analysis. The physician should be notified of the results.
   - Attempts should be made not to make changes to ventilator parameters or the FiO₂ during the 30-60 minutes until response to therapy is determined. Other changes to pharmacological therapies, fluid resuscitation and sedation/muscle relaxation should be limited to appropriately identify the response to iNO.

10. If a positive response is determined clinically, iNO can be decreased and maintained at 20 ppm until weaning criteria are determined by the team.

11. If no response or only a partial response is determined at 40 ppm after one hour of therapy, inhaled nitric oxide should be discontinued. (note: rebound does not generally occur when iNO is discontinued within a short period of time after initiation, i.e. < 4 hours)

**IWK Health Centre**

- Pressure level in tanks must be monitored carefully and tanks changed to ensure consistent delivery of NO.
- Empty water trap when half full to prevent discontinuation of NO delivery. System will alarm and stop delivery if water trap is allowed to fill.
- Low range calibration must be done every 12 hours or once per shift. This can be completed while patient is receiving therapy but NO concentration is not monitored during this time.
- Back up delivery system can be activated through the backup switch on the front panel. The INOmax dose should be turned off. A flow of at least 5L per minute should be present in the ventilator circuit to avoid concentrations of NO> 40 ppm. The back up is used for short term NO delivery when electronic delivery system fails.
- When administering NO, O₂ will be decreased due to the dilution of O₂ by NO. This may result in delivery of sub atmospheric O₂ concentrations.

**Nitric Oxide with Ventilator**

1. Set up ventilator as appropriate for patient clinical status.

2. Insert the injector module proximal to the humidifier.

3. Attach sample tee 24 inches from injector site to ensure proper gas mixing, ensuring that the sample tee is pointing upward.

   NOTE: After connecting the INOmax DS the trigger sensitivity may need to be adjusted due to the removal of gases from the system.

4. Adjust NO to appropriate dosage in consultation with physician.

5. Adjust alarms to appropriate levels.

6. Monitor hemodynamics and oxygenation.

Nitric Oxide Administration via High Frequency Ventilator (Sensormedics 3100 A and B)

1. Set up HFO as appropriate for patient status.
2. Insert the injector module proximal to humidifier.
3. Ensure that one-way valve is situated between injector and humidifier
4. Attach sample tee 24 inches from injector site to ensure proper gas mixing, ensuring that the sample tee is pointing upwards
   
   NOTE: Omission of one-way valve may result in high NO delivery
5. Adjust NO to appropriate dosage in consultation with physician.
6. Adjust alarms to appropriate levels.
7. Monitor hemodynamics and oxygenation.

Nitric Oxide Administration via Anesthesia Machine

1. Set-up anesthesia machine as appropriate for patient status.
2. Insert injector module between absorber inspiratory port and inspiratory tubing.
3. Place sample tee at least 6 inches away from the injector to ensure proper mixing of gas and no more than 12 inches to ensure proper measurement of nitrogen dioxide (NO₂)
4. Adjust NO to appropriate dosage in consultation with physician.
5. Adjust alarms to appropriate levels.
6. Monitor hemodynamics and oxygenation.
7. Document on patient ventilator flow sheet and the Nitric Oxide administration flow sheet
   
   NOTE: Avoid recirculation of gases to prevent high nitrogen dioxide (NO₂) levels; higher than desired NO levels and reduction in oxygen levels.
   
   NOTE: Use only Sodasorb in combination with Isofluorane or Desfluorane. Other anesthetic agents and CO₂ absorbents have not been evaluated for reactive by-products.

Nitric Oxide Administration via NIPPV (Nasal CPAP or Non-invasive ventilation)

1. Set up NIPPV as appropriate for patient status.
2. Insert the injector module proximal to the humidifier.
3. Attach sample tee 24 inches from injector site to ensure proper gas mixing, ensuring that the sample tee is pointing upward.
4. Adjust NO to appropriate dosage in consultation with physician. Tee
Procedure

5. Adjust alarms to appropriate levels.
6. Monitor hemodynamics and oxygenation.

**Nitric Oxide Administration via High Flow Nasal Prongs**

1. Set up high flow as appropriate for patient status.
2. Insert injector module proximal to the humidifier.
3. Attach sample tee at the distal end of the heated wire circuit. Ensure tee is pointing upward.
4. Attach nasal prongs to sample tee with O₂ sample tee.
5. Adjust NO to appropriate dosage in consultation with physician.
6. Adjust alarms to appropriate levels.
7. Monitor hemodynamics and oxygenation.

NOTE: Low flow nasal prongs may also be used for NO administration provided a minimum gas flow of two litres per minutes is delivered. High flow prongs provide a more consistent concentration of NO as the flow rates are higher.

**Nitric Oxide Administration via Flow-Inflating Resuscitator**

1. Set up bagging unit.
2. Adjust NO to appropriate dosage in consultation with physician.
3. Adjust alarms to appropriate levels
4. Monitor hemodynamics and oxygenation.

NOTE: A self-inflating bag is not recommended when bagging with the injector, as fresh gas flow cannot be guaranteed. This may result in delivery of high concentrations of NO and NO₂.

**Nitric Oxide Administration via flow-inflating resuscitator using INOBlender**

NOTE: Pre-use checkout of INOBlender must be completed before use as instructed in INOBlender manual.

1. Connect oxygen tubing to flow inflating resuscitator.
2. Connect tubing to INOBlender.
   a. Set INOBlender NO setting to desired concentration.
   b. Set oxygen flowmeter at appropriate flow.

   NOTE: If using a self-inflating resuscitator (not recommended) squeeze the bag 3-4 times to purge
Inhaled Nitric Oxide Review

Procedure

- any NO₂ from the system.
  - When finished turn flow on INOBender off
  - Document on patient ventilator flow sheet and the Nitric Oxide administration flowsheet.

IWK Health Centre Review

- Due to the review nature of the document, no procedure is given.

Mount Sinai Hospital

1. Ensure airway is cleared with suctioning prior to starting iNO (I include this because you do not want any disconnection after starting for 30min to evaluate effectiveness)
2. Always start at 20 ppm
3. Document onto patient flow sheet start time of iNO
4. DO NOT make any ventilatory/FiO₂ changes or disconnect infant from ventilator for at least 30 minutes (or less provided a positive response is established) after iNO has been started to be able to establish patient’s responsiveness to treatment. In cases of no response it might be appropriate to continue ‘trial’ of therapy to a maximum of 1 hour.
5. The iNO responsiveness must be reassessed within 30-60 minutes following initiation. It is preferable to obtain another ABG and establish response using PaO₂ but in cases where arterial access is not available post-ductal TcO₂ or SpO₂ may be used.

Consider structural heart defects for nonresponders with the following:
- Lack of symptoms of respiratory distress
- Lack of lability
- Hemodynamic stability in spite of extreme hypoxemia of prolonged duration
- Pre-ductal SpO₂ lower than post-ductal
- Presence of a heart murmur or abnormal cardiac silhouette on CXR.

Be aware that cyanotic heart lesions like TAPVD and TGA are commonly associated with PPHN at the time of initial presentation.

BC Women’s Hospital

- No mention

CHEO

1. Wash Hands and Identify Appropriate patient.
2. Verify Physician’s order to begin Inhaled Nitric Oxide (iNO)
3. Prepare Delivery Circuit and Assemble equipment into Ventilator Circuit or Nasal Cannula set up.
4. Check for, and correct, any leaks in the system.
5. Clearly Label all circuit components of the INO system.
Procedure

6. Perform and document baseline assessment Document: Arterial Blood Gases (ABG), consecutive blood gases performed 30 minutes apart, vital signs (HR, mean B/P, RR, pre/post SpO₂), Oxygen Index (OI), Methemoglobin, sedation vs. muscle relaxant.

7. Initiate INO at 20 ppm, unless specifically ordered otherwise,

8. Once prescribed dosage is achieved set alarms.

9. Continue monitoring pre/post SpO₂, TcCO₂/ETCO₂, HR, B/P and perform ABG 30 minutes after initiation of therapy.

10. Assess patient response.

11. If there is no response to therapy within 30 minutes discontinue therapy.

12. FOR External Transport ONLY:
   If the patient responds to 20 ppm INO and the FiO₂ < 0.60, maintain this dosage for the duration of the transfer. If the FiO₂ >0.60 on 20 ppm, repeat an ABG. If there are no mechanical or clinical reasons for the increased oxygen requirements then increase the INO dosage by 20 ppm to 40 ppm and determine the response via arterial blood gas sampling.

13. Measure methemoglobin q24 hours.

14. If NO₂ exceeds 5 ppm, wean NO. Ensure that circuit has been purged, patient should be taken off and manually ventilated, if NO₂ exceeds 7 ppm, discontinue therapy. Wean INO as per weaning guidelines.

15. Document all interventions on appropriate record.

16. Wean INO as per weaning protocols

Stollery Children’s Hospital

- Do not disconnect or interrupt the ventilator circuit unless necessary.
- “In-line” suction catheters should be used.

Hamilton Health Sciences

- Mechanical Ventilator Circuit disconnects must be avoided as much as possible.
- Suctioning must be done with “In-line” type technology as much as possible.
- An echocardiogram should be done whenever possible to determine pulmonary pressures and rule out cyanotic congenital heart defects. If an echocardiogram is not possible, pre and post ductal pressure of oxygen saturations (PO₂s) and/or pre and post ductal transcutaneous pressure of oxygen (tcPO₂ s) may be useful to document.
- An OI is calculated on all patients with oxygenation difficulties, and requires:
  - An indwelling post-ductal arterial line [Umbilical Arterial Catheter (UAC)], or blood sample from lower limbs.
  - An ABG to be drawn.
- Inform the physician of any patient meeting the criteria and having one ABG with an OI greater than
2. Ensure both the manual bagging system and a high pressure oxygen (O₂) source are set up and attached to the INO blender, as per the INOMax® DSᵢᵣ Pocket Guide. Note: The desired iNO dose set on the INO blender should match the dose the patient is currently receiving.

3. Ensure the necessary equipment is calibrated and ready for use should the next ABG again have an OI greater than or equal to 15.

4. Refer to the INOMax® DSᵢᵣ Operation Manual, INOMax® DSᵢᵣ Pocket Guide or INOMax® DSᵢᵣ PreUse Calibration Card and perform the calibration procedure for the INOMax® DSᵢᵣ as required:
   - Prior to use - a pre-use system check/cylinder leak test/low range calibration/purge/alarm verification/backup and iNO blender delivery test (see INOMax® DSᵢᵣ Pocket Guide)
   - Every 24 hours while in use - a Low range Calibration (see INOMax® DSᵢᵣ Operation Manual and INOMax® DSᵢᵣ PreUse Calibration Card)
   - Every 30 days - a High range Calibration (see INOMax® DSᵢᵣ Operation Manual and INOMax® DSIᵣ PreUse Calibration Card).

5. Should a second ABG qualify the infant for iNO therapy:
   - Inform the physician
   - Await an order for initiation of iNO therapy.

6. Perform an iNO trial upon receiving an order for the initiation of iNO from the NICU Physician:

7. Insert the INOMax® DSIᵣ injector module in the Mechanical Ventilator/High Frequency Oscillator (HFO) to establish a good mixing reservoir for the iNO:
   - At the ventilator outlet or
   - In the circuit just before the humidifier chamber (dry side).

8. When used with High Frequency Oscillator (HFO), place a one way valve between the humidifier and the injector module (see pp 24-25 of INOMax® DSᵢᵣ Pocket Guide).

9. Insert an iNO sample line (iNO Delivery System specific):
   - At least 30 cm downstream from the humidifier chamber
   - In the inspiratory limb of the mechanical ventilator/HFO circuit.

   Refer to “Circuit connection diagrams” pp 21-35 of the INOMax® DSIᵣ Pocket Guide for specific circuit set up."

10. Collaborate with the RN and determine who will draw the ABGs during iNO Therapy

11. Obtain a baseline ABG

12. Start iNO as ordered at 20 ppm

13. Ensure no changes are made in ventilation or FiO₂ for 30 minutes, and

14. Do a follow-up ABG.
Note: The team must attempt to avoid changes in patient position or interventions during initiation to determine the patient response to iNO.

15. Assess the infant’s response to iNO:
   • If full response is noted, move to weaning procedure. Monitor toxicity.
   • If partial response or no response is noted, move to Escalation Procedure
   • Document the INOMax® cylinder contents in pounds per square inch gauge (psig) at least every 4 hours to determine when the cylinder needs to be changed (INOMax® cylinder empty “red zone” is 200 psig).
   • To prevent inadvertent NO₂ delivery to the patient:
      – Perform a pre-use system check/purge/calibration prior to patient use (see INOMax® DSₘᵢᵣ Operation Manual).
      – Ensure there is a full back up INOMax® cylinder on the back of the INOMax® DSᵢᵣ, ready for use.
      – Replace empty cylinders immediately.
      – Purge the low-pressure line, prior to connecting a new INOMax® cylinder.
   • When HFO is used, place a one-way valve between the humidifier chamber and the INOMax® DSᵢᵣ Injector module to prevent inadvertent overdoses of iNO to the patient.
   • Ensure the INOMax® DSᵢᵣ alarms are set appropriately:
      – High/Low iNO plus or minus 5 ppm of set dose, or as clinically determined by the RT
      – High NO₂ is set at 2 ppm
      – High/Low O₂ set plus or minus 10%, or as clinically determined by the RT.
   • Record dose and response with full details described including:
      – Cylinder lot number
      – OI results
      – Initiation time and dose of iNO
      – Patient response
      – Vital signs, saturation and transcutaneous monitor readings
      – All ventilator changes
      – iNO and NO₂ levels
      – INOMax® cylinder contents in psig
      – Any further care or treatment.
   • Record on Nitric Oxide Tracking Sheet as indicated:
      – Every new initiation of iNO
      – Any cylinder change
### Procedure

- Upon discontinuation of iNO therapy.

#### American Association for Respiratory Care

- Scavenging of exhaled and unused gases during INO therapy is not necessary.
- Response to a short trial (30–60 min) of INO should be judged by an improvement in PaO₂ or oxygenation index (OI); if there is no response, INO should be discontinued.
- During conventional mechanical ventilation, the INO gas injector module should be placed on the dry side of the humidifier.
- During conventional ventilation, sampling port be placed in the inspiratory limb of the ventilator, downstream from the site of injection, no greater than 15 cm proximal the patient connection/interface.
- FiO₂ be measured downstream from the injection of INO into the circuit.
- The patient/ventilator system be continuously monitored for changes in ventilation parameters, with adjustments to maintain desired settings during INO therapy.

#### Centre Hospitalier Universitaire Sainte-Justine

- ABG pre and post NO (15-30 minutes) and with any change in dosage.
- Keep iNO therapy for 3 days, then wean.

#### London Health Sciences Centre

- Insertion of a pulmonary artery catheter is required if INOMax administration is for treatment of pulmonary hypertension.

The Respiratory Therapist will:

1) Obtain an order from appropriate physician for iNOMax (inhaled nitric oxide and for methemoglobin testing).

2) Assemble required equipment and supplies. Refer to iNOvent Set Up Procedure (also available with the INOMax delivery unit).

3) Prior to the initiation of therapy, record all relevant baseline values as indicated on the “Nitric Oxide Study Sheet”, including baseline level of methemoglobin (metHgb).

4) Initiate therapy at 20 ppm, unless otherwise ordered by the physician. Use appropriate Personal Protective Equipment (PPE) as required.

5) If no effect is noted within 30 minutes then the therapy is to be discontinued. To determine that a therapeutic effect has been achieved, the following criteria must be met:

- An increase of 20% or more in the ratio of partial pressure of oxygen to the fraction of inspired oxygen (PaO₂/FiO₂) and/or
- An increase in SpO₂ of 5% or more and/or
Procedure

- A 20% decrease in pulmonary vascular resistance.
- Evidence of decreased Right Ventricular Systolic Pressure by cardiac echo or reduction in pre and post oxygen saturation difference that appears within 20 minutes after initiation.

6) If a positive effect is observed then the administration of iNOmax is continued.

7) Once a positive response has been confirmed, reduce iNOmax to 10 ppm for 15 minutes and determine effect using criteria listed above. If a reduction of positive effect is noted, increase iNOmax level back to 20 ppm. Note observations on the Nitric Oxide Study Sheet.

8) If positive effect is maintained at 10 ppm, reduce iNOmax to 5 ppm for 15 minutes and determine effect using criteria listed above. If there is a reduction in positive effect noted, increase iNOmax dose back to 10 ppm. If positive effect is maintained, continue iNOmax administration at 5 ppm. Note observations on the Nitric Oxide Study Sheet.

9) Once the most effective dose of iNOmax has been determined and documented, ensure that the ordering physician and the patient’s nurse are aware of this dosage.

10) Complete/document all relevant information on the “Nitric Oxide Administration Flow Sheet”.

11) After 60 minutes of continuous use, a methemoglobin level is to be measured and compared to the baseline methemoglobin. If the level is >2.5% the iNOmax dose should be decreased and methemoglobin levels redrawn every 60 minutes until it drops below 2.5%. The administration of reducing agents such as Methylene Blue may need to be considered. Methemoglobin levels are to be determined once daily during continuous administration of nitric oxide.

12) Each day, unless otherwise ordered, the RRT will attempt a dose response test to assess the patient’s required dosage and need for continued iNOmax administration.

Refer to weaning / discontinuation of inhaled nitric oxide listed below.

13) Once the iNOmax administration has been discontinued the RRT will ensure the iNOmax cylinder has been turned off and its metering device’s red locking mechanism is properly reinserted.

14) Remove all equipment from the patient area and clean as per the manufacturer’s guidelines.

15) Return all equipment to the department and prepare for the next patient.

London Health Sciences Centre Neonatal

The Respiratory Therapist will:

1. Obtain an order for Nitric Oxide therapy.

2. Assemble required equipment and supplies; ensure delivery unit has been calibrated. Ensure that Masimo oximeter with MetHb measuring ability and appropriate probe is attached to patient pre-ductal, with standard probe post-ductal, prior to initiation of therapy.

3. Initiate therapy start at 20 ppm, unless otherwise ordered by the physician. Ideally 20 ppm should be no longer than 4 hours.

4. If no effect is noted within 30 minutes then the therapy is to be discontinued.

5. If a positive effect is observed then the administration of Nitric Oxide therapy is continued.

6. Once dosing level is achieved, SpO₂ has increased and stabilized for X hours, commence weaning of
Inhaled Nitric Oxide Review

**Procedure**

FiO₂ until < 0.50 with oxygen saturation appropriate for gestation age and disease process as determined by the attending physician.

7. Once a positive response has been confirmed, FiO₂ has been weaned and SpO₂ stable, aggressive attempts to lower the dose to 5 ppm, should be maintained until underlying oxygen saturation has been resolved but no more than 96 hours of therapy (at which time the neonate should be weaned from Nitric Oxide Therapy).

8. After 60 minutes of continuous use a methemoglobin level is to be measured and compared to the methemoglobin measurement on the Masimo Rainbow oxygen saturation monitor w/MetHb.

9. Each day, unless otherwise ordered, the RRT will attempt a dose response test to assess the patient’s required dosage and need for continued Nitric Oxide Therapy administration. Refer to weaning/discontinuation of inhaled nitric oxide listed below.

10. If iNO Therapy has been > 24 hours there is a risk of rebound from down-regulated endogenous NO production. Once 5 ppm has been achieved and duration of therapy has been > 24 hours, allow the patient to stabilize for 4 hours.

11. Once the iNO Therapy administration has been discontinued the RRT will ensure the iNO cylinder has been turned off and its metering device’s red locking mechanism is properly reinserted.

12. Complete/document all relevant information on the “Nitric Oxide Administration Flow Sheet”.

**London Health Sciences Centre iNO Cheat Sheet**

- Document on/off times and tank changes on the VH Nitric Usage Data Collection Form for billing purposes. Start/Stop times must also be entered into Critbase.

**Jewish General Hospital**

1. When given via mechanical ventilator, the VTe may be lower than the VTi (depending on the size of the Vt) due to a constant sampling rate of 230 ml/min from the inspiratory limb of the circuit through the sample line. The addition (NO flow) and subtraction (230 ml/min) may balance out, and is fairly insignificant with larger VT (ped, adult). In neonates, when very small tidal volumes are used, this may be significant. In these situations, pressure ventilation modes are recommended.

2. Trigger sensitivity of the ventilator might be compromised, especially if the patient is on an assisted mode of ventilation. If ventilator auto-triggers, slightly decrease sensitivity.

3. The set FiO₂ in the breathing circuit will be reduced with increases in the NO concentration due to the dilution effect. You are adding a gas that doesn’t contain oxygen into the breathing circuit; therefore it will dilute the FiO₂. The maximum dilution is seen when using 80 ppm of iNO and FiO₂ of 1.0 = FiO₂ of 92%

   - A ventilator INOmax DS system check (pre-use procedure) should be done upon initiation of NO therapy. This verification ensures that:
     1. There are no leaks (High pressure test)
     2. The low calibration zero’s the electrochemical cells for accuracy (Low cal)
     3. The purging is done to prevent giving the patient a bolus of NO₂ from NO+O₂ gas that has been
Inhaled Nitric Oxide Review

Procedure

stagnant in the device (Purging)

4. The back-up delivery test is to insure that the back-up system is functional. The back-up system is ensuring that in a event that the INOmax DS system fails, the patient will received NO from the back-up delivery system when turned ON. A constant flow of 250 ml per minute of 800 ppm of NO will be injected into the patient circuit. This fixed flow will provided 20 ppm of NO when the ventilator has a continuous flow of 10 lpm. This back-up delivery system is meant for short term use until a replacement INOmax DS system is available.

5. The electrochemical cells are reading properly. (Performance check)

6. The INOblender is connected and performing well. (INOblender system check)

7. In addition to an initial check, a patient verification check should be done:
   - every 2 hours
   - following any changes in ventilator and / or INOmax DS delivery system settings

McGill University Health Centre

Neonates with congenital heart disease and CDH

- A consultation with cardiology and an echocardiogram is recommended prior to initiation to assure for no severe left ventricular dysfunction or ductal-dependent lesion.

Suctioning should be done as per VAP protocol
1. RT to be present at the bedside during intervention.
2. Pre-oxygenate patient as needed, and proceed to suction as per protocol.
   - PS: If RT not present on unit, the bedside nurse will page the RT

During weaning:

Respiratory Therapist (RT) will:
1. RT will document ventilator parameter settings and arterial blood gas (if available) prior to weaning iNO. RT will notify nurse and neonatologist/fellow/NNP that neonate is ready to wean and follow procedure below.

Nurse will:
1. Continue to monitor and document vital signs, and ventilator settings as stated above.
2. Continue to monitor and document patient’s comfort/sedation status as stated above.
3. Advocate for pain management, minimal handling while maintaining close observation and grouping of patient’s care.
4. Do not wean FiO₂ below 30% while patient remains on iNO.

Emergency Measures:

- Procedures for neonates with significant oxygen desaturation and bradycardia will follow NICU OWL protocol, which includes assessing patient and responding to needs such as suctioning, positioning, and increasing FiO₂ on ventilator, depending on SpO₂ targets.
**Procedure**

- If case of a severe deterioration of bradycardia and desaturation, requiring bagging, then the flow-inflating resuscitator attached to the iNO blender will be used by the RT.
- iNO should not be stopped abruptly.
- If the patient gets accidentally extubated, manual ventilation via flow-inflating bag and mask on the same concentration of iNO should be immediately started by the RT.

**Emergency Intervention for Sudden Deterioration:**

- Procedures for oxygen desaturation will follow NICU OWL protocol, which includes assessing patient and responding to needs such as suctioning, positioning, and increasing FiO\textsubscript{2} on ventilator, depending on SpO\textsubscript{2} targets.
- If RT not present on unit the nurse will have RT paged 22389 – 911 (MCH) or 35107 (RVH), identify bed location, and simultaneously have a second nurse notify the responsible Physician.
- If unable to stabilize patient and RT not present, the nurse should begin to manually bag as per NRP guidelines.
- Use bedside flow inflating bag and FiO\textsubscript{2} at 100%. Place ventilator circuit end tubing downward away from personnel. Once at bedside, RT will proceed to manually bag patient using iNO flow inflating bag.

Note: this is in extreme circumstance as iNO should not be stopped abruptly.
Equipment

List of Equipment

SickKids NICU

- Nitric oxide gas source and delivery unit (see iNO delivery system manual)
- Second MIE bag, pressure manometer and oxygen tubing for iNO blender system so that iNO will not be interrupted should the patient require manual ventilation
- Appropriate circuit connectors and one-way valves (when required) for introduction of injector module into current ventilator circuit and for sampling line.

IWK Health Centre

- INOMax DS
- Ventilator, if required
- High flow system, if required
- Nasal Prongs, if required
- NIPPV system, if required
- Manual Resuscitator, if required
- Anesthesia Machine, if required
- High Frequency Oscillator, if required

CHEO

- INO max DS$_{IR}$
- Regulator connections
- iNO blender connections
- Nitric Oxide tanks
- Sample line/filter
- Water trap bottle
- Injector module cable and connections
- Injector module tubing
- Oxygen source
- Manual resuscitation bag
- Cardiovascular/saturation monitoring system

Hamilton Health Sciences

- Two INOMax® cylinders
- INOMax® DS$_{IR}$ with INOMax® DS$_{IR}$ Pocket Guide (attached to cylinder)
Inhaled Nitric Oxide Review

- Manual resuscitator
- NO and Nitrogen Dioxide (NO₂) Calibration gas cylinders and regulators – as per INOMax® DS\textsubscript{IR} Operation Manual

American Association for Respiratory Care

- FDA-approved INO delivery systems should be used to assure consistent and safe gas delivery during therapy.

London Health Sciences Centre

- Nasal Cannula (1–6 lpm) (limited from 5–40 ppm)
- Face Mask (6–15 lpm)
- Critical Care Ventilator
- Anesthetic Delivery Unit
- Manual Resuscitator
- INOvent Set Up Procedure (also available with the INOMax delivery unit).

London Health Sciences Centre Neonatal

iNO may be used in conjunction with:
- conventional mechanical ventilation
- high frequency oscillation ventilation
- high frequency jet ventilation

iNO will not be used with non-invasive ventilation.

Jewish General Hospital

- INOMax DS delivery system with one 800 ppm nitric oxide gas cylinders
- Appropriate ventilator
- Pulse oximeter
- Pulmonary artery catheter (optional in Neonatal Unit)
- Arterial line (optional in Neonatal Unit)
- Purge and performance set-up equipment

McGill University Health Centre

- iNO delivery device and blender – INOMax DS\textsubscript{IR}.
- Connectors for sampling line and injector module to insert into ventilator circuit.
- Two flow-inflating resuscitator bags (500ml or 1L depending on patient size), one attached to INOMax DS\textsubscript{IR}, the other attached to the bedside blender.
- In-line suction.

Stability and storage recommendations:
- The shelf life of INOMax is 36 months. Cylinders should be stored at 25°C (77°F) with excursions
Inhaled Nitric Oxide Review

permitted between 15-30 °C (59-86°F) [see USP controlled room temperature].

- All regulations concerning handling of pressure vessels must be followed.
- Protect the cylinders from shocks, falls, oxidizing and flammable materials, moisture, and sources of heat or ignition.
### Conditions where iNO Therapy is Recommended

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<tr>
<th>Conditions</th>
<th>SickKids NICU</th>
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<tr>
<td></td>
<td>• Neonates with PPHN if extra pulmonary right to left shunting (foramen ovale and/or ductus arteriosus) is present</td>
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<td>• Term and near term infants with hypoxic respiratory failure</td>
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<th>SickKids CCU</th>
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<td>• PPHN</td>
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<th>IWK Health Centre</th>
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<td>• No mention</td>
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#### IWK Health Centre Review

- Term and near term infants with PPHN

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<th>Mount Sinai Hospital</th>
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<td>• PPHN</td>
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<th>BC Women’s Hospital</th>
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<tr>
<td>• Hypoxic respiratory failure associated with persistent high pulmonary vascular pressure and resulting right to left shunting</td>
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<tr>
<td>• Limited Evidence for preterm infants with PPROM resulting in oligohydramnios, pulmonary hypoplasia and pulmonary hypertension</td>
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<tr>
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<tr>
<td>• PPHN (NICU)</td>
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<td>• Pulmonary hypertension (PICU) (OR) (cardiac catheterization lab)</td>
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<td>• Acute on chronic pulmonary hypertension (NICU)</td>
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<td>• PPROM (prolonged premature rupture of membranes) (NICU)</td>
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<td>• Sickle cell chest crisis (in consultation with Hematology) (PICU)</td>
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<td>• ARDS unresponsive to conventional therapy (PICU)</td>
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<td>• Right ventricular failure (OR)</td>
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<th>Stollery Children’s Hospital</th>
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<tr>
<td>• Persistent pulmonary hypertension,</td>
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<td>• Respiratory failure,</td>
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<tr>
<td>• Congenital diaphragmatic hernia,</td>
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<td>• Pulmonary hypoplasia,</td>
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Conditions

- Cardiac disease

Hamilton Health Sciences

- Any infant with refractory hypoxemia, and with a diagnosis Persistent Pulmonary Hypertension of the Newborn (PPHN), secondary to:
  - Respiratory Distress Syndrome (RDS)
  - Perinatal aspiration syndromes (meconium, blood, amniotic fluid)
  - Pneumonia
  - Sepsis
  - Pulmonary hypoplasia may be considered for iNO.
- Preterm patients with continually high oxygenation requirements, despite surfactant administration, optimized ventilation and optimal clinical management.

American Association for Respiratory Care

- Term and near-term neonates with hypoxemic respiratory failure associated with clinical or echocardiographic evidence of pulmonary arterial hypertension.

CHU Sainte-Justine

- Pediatric Acute Respiratory Distress Syndrome (ARDS)

London Health Sciences Centre

**Adult:**

- Primary and secondary pulmonary hypertension
- Rescue therapy for life threatening hypoxemia secondary to ARDS/Acute Lung Injury (ARDS/ALI) that is unresponsive to maximal ventilatory support
- Acute Right Ventricular Failure with associated cardiogenic shock

**Children:**

- Acute progressive hypoxic respiratory failure (FiO₂ > .50) and SpO₂ saturation <92% and documented evidence of pulmonary hypertension on echo (right ventricular systolic pressure of systemic pressure)
- Congenital heart defects with known history of pulmonary hypertension
- Persistent Pulmonary Hypertension of the Newborn (PPHTN).

**Neonatal/Infant:**

- Acute progressive hypoxic respiratory failure (FiO₂ > .50 and SpO₂ saturation levels <92%) on mechanical ventilation, with clinical or echocardiographic evidence of persistence of pulmonary hypertension (PPHN), as documented by frequent desaturations, right to left shunting, in absence of CHD (excluding PDA and ASD).

London Health Sciences Centre Neonatal

- PPHN with clinical or echocardiography evidence
### Conditions

- Refractory hypoxemia. (FiO₂ > 0.50 and Hb saturation levels < 92%)

### London Health Sciences Centre iNO Cheat Sheet

- No mention

### Jewish General Hospital

- To reduce severely elevated pulmonary artery pressures and pulmonary vascular resistance due to reactive pulmonary hypertension from various clinical settings (i.e.: post-cardiopulmonary bypass, post-lung resection, pulmonary embolism, sickle-cell disease, lung transplantation-grade C recommendation)
- To enhance oxygenation
- As adjunctive therapy in the treatment of ARDS
- Increased pulmonary artery pressures (PPHN) (PH)

### McGill University Health Centre

- PPHN
- Some CDH infants with persistence of pulmonary vascular hyperactivity in spite of parenchymal improvement may benefit
- Congenital heart disease (consult with Pediatric cardiology before initiation)
- Any neonate with hypoxic failure and diagnosis of PPHN secondary to RDS, aspiration (amniotic fluid or meconium), pneumonia, sepsis and pulmonary hypoplasia.
Inclusion Criteria for iNO Therapy

**Inclusion Criteria**

**SickKids NICU**

- Differential diagnosis of PPHN/Hypoxic Respiratory Failure (HRF) associated with:
  - Primary PPHN
  - Surfactant deficiency
  - Perinatal aspiration syndromes (meconium, blood, amniotic fluid)
  - Pneumonia/Sepsis
  - Pulmonary hypoplasia
  - Cases of right heart failure and/or compromise

- PPHN unresponsive to optimization of ventilation and perfusion as outlined in the agreed upon guidelines for PPHN management.

- Presence of significant hypoxemia requiring FiO₂ >0.60, moderate to severe illness as defined by an oxygen index (OI) of >15 on arterial blood gas.
  - iNO therapy is recommended at an OI of ≥20; however, consideration should be given to commencing at an OI of 15-20

- Pre and post ductal saturation difference of >10%

- Echocardiography prior to starting iNO (or as early as feasible after commencement) is recommended to evaluate the presence of extra pulmonary shunting and congenital cardiovascular malformations

- Gestational age > 34 weeks

**SickKids CCU**

- Neonate (Gestational age ≥ 34 weeks)

- Hypoxemia requiring FiO₂ > 0.60 defined by OI >25 on two consecutive arterial blood gases, at least 20 minutes apart, and significant A-a gradient on same arterial blood gases.

- Pre and post ductal saturation difference of >10% and arterial access if possible (post ductal location preferred).

**IWK Health Centre**

- No mention

**IWK Health Centre Review**

- PPHN >34 weeks gestation with:
  - OI >25 OR
  - Pre-ductal SpO₂ Sat >10% higher than post-ductal SpO₂ Sat OR
  - Post-ductal PaO₂ <55 mmHg on 100% O₂ OR
### Inclusion Criteria
- Echo evidence per cardiology of PPHN

### Mount Sinai Hospital
- Can be attempted in patients with severe chronic lung disease (CLD) with associated pulmonary hypertension provided the following conditions are met:
  - Pulmonary hypertension is confirmed by echocardiography
  - Clear clinical goals are defined prior to initiation of iNO therapy (for example: acute stabilizing while infant is being started on intravenous steroids; therapy for a predefined period in an attempt to reverse pulmonary hypertension)
  - iNO therapy should only be continued if infant responds positively and for as long as the responsiveness is maintained
- iNO may be used as rescue treatment (using principles & procedures mentioned above) for preterm infants in hypoxic respiratory failure if there is a high probability of PPHN (history of oligohydraminos plus clinical signs suggesting PPHN – pre & post-ductal SpO2 difference, presence of lability &/or confirmation of PPHN on echocardiography)

### BC Women’s Hospital
- OI ≥ 15

### CHEO

**NICU:**
- PPHN unresponsive to the optimization of ventilation and perfusion (ideally confirmed by echocardiography in consultation with Cardiology) as outlined in the following agreed upon treatment guidelines for PPHN:
  - Intubation and ventilation
  - FiO2 > 60 %
  - Adequate lung volumes on anterior-posterior CXR as defined by expansion of the R hemi diaphragm to the 7th – 9th rib.
  - Normalized acid base status as per arterial blood gases:
    - pH > 7.30
    - PaCO2 < 50 mmHg
  - Consideration of surfactant replacement therapy
  - Sedation and muscle relaxation
  - Adequate skin perfusion as defined by a capillary refill time of <3 seconds
  - Normalized systolic blood pressure with appropriate support such as volume expansion and inotropic support
  - Correction of anemia
- Moderate to severe illness as defined by an OI of >20 on two consecutive arterial blood gases, at least 20 minutes apart.
Inhaled Nitric Oxide Review

Inclusion Criteria

- Gestational age > 34 weeks
- Pre and Post ductal saturation difference >10%
- Weight >1500g
- The following infants will be considered for a trial of iNO:
  - Infant born after PPROM before 25 completed weeks
  - PPROM for at least 5 days before delivery
  - Respiratory Failure in the first 48 hours of life that is persistent despite full medical treatment* and where pulmonary hypertension is documented by echocardiogram, if possible (review of echo by cardiologist is recommended)

*Full medical treatment includes all below:

- Surfactant
- Optimized ventilation
- Open lung strategy (Peep 5 to 8 cm)
- HFV or HFJV
- Target pH> 7.30 to 7.35
- Optimized perfusion
- Inotrop support to maintain adequate blood pressure as appropriate
- Adequate preload
- Adequate hemoglobin
- Optimized oxygenation
- FiO₂ > 80 % to keep SaO₂ 88- 92%
- Adequate sedation plus /minus muscle relaxation

PICU:

- Pulmonary hypertension unresponsive to optimization of care as suggested
- Oxygen Index of > 20 on at least two consecutive gases at least 20 minutes apart in FiO₂ > than 80%.
- Sickle cell chest crisis (in consultation with Hematology)
- ARDS unresponsive to conventional therapy.

NICU and PICU

- Acute on chronic pulmonary hypertension. In the event that a patient with known pulmonary hypertension is experiencing an acute exacerbation of pulmonary hypertension, iNO via nasal cannula can be used with the idea that this would be a short-term therapy to get over the acute process and prevent respiratory failure.

Stollery Children’s Hospital
### Inclusion Criteria

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Hamilton Health Sciences</th>
<th>American Association for Respiratory Care</th>
<th>CHU Sainte-Justine</th>
</tr>
</thead>
<tbody>
<tr>
<td>• OI &gt; 25</td>
<td>• ≥ 34 weeks gestation</td>
<td>• ≥ 34 week gestation</td>
<td>• OI &gt; 20</td>
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<tr>
<td></td>
<td>• OI ≥15 on 2 consecutive ABGs</td>
<td>• &lt; 14 d of age with PaO₂ &lt; 100 mmHg on FiO₂ 1.0 and/or an oxygenation index (OI) &gt;25</td>
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<tr>
<td><strong>London Health Sciences Centre</strong></td>
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<td><strong>London Health Sciences Centre</strong></td>
<td><strong>London Health Sciences Centre iNO Cheat Sheet</strong></td>
</tr>
<tr>
<td>• No mention</td>
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<td>• No mention</td>
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<tr>
<td><strong>London Health Sciences Centre Neonatal</strong></td>
<td></td>
<td><strong>Jewish General Hospital</strong></td>
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<tr>
<td>• No mention</td>
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<td>• No mention</td>
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<tr>
<td><strong>London Health Sciences Centre iNO Cheat Sheet</strong></td>
<td></td>
<td><strong>McGill University Health Centre</strong></td>
<td></td>
</tr>
<tr>
<td>• No mention</td>
<td></td>
<td>• Term and late preterm infants (≥34 weeks)</td>
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<td></td>
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<td>• OI &gt; 40</td>
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<td>• OI &gt; 25 with evidence of PPHN by echocardiogram or a pre/post ductal SpO₂ difference &gt; 5% or</td>
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<tr>
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<td></td>
<td>• Pre-ductal SpO₂ &lt; 92% on FiO₂ 1.0 in patients with respiratory distress AND adequate lung inflation and</td>
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<td></td>
<td></td>
<td>cardiac output</td>
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</tr>
</tbody>
</table>
Contraindications and Exclusion Criteria

Contraindications and Exclusions

**SickKids NICU**
- Known or suspected Total Anomalous Pulmonary Venous Drainage and TGA
- Lethal congenital anomalies
- Preterm infants with respiratory failure

**SickKids CCU**
- Known or suspected Total Anomalous Pulmonary Venous Drainage
- Cardiac Circulation dependent on Right to Left shunting
- Left atrial hypertension
- Intraventricular hemorrhage grade III or higher
- Active pulmonary or gastrointestinal hemorrhage

**IWK Health Centre**
- None indicated

**IWK Health Centre Review**
- Short-term use of iNO cannot be considered an effective rescue therapy for pre-term infants with profound respiratory failure
- Pending the results of further trials, iNO in the pre-term infant should be avoided in the first week of life.
- There is no evidence to support the routine use of iNO in infants with developing nor established severe BPD
- Congenital Diaphragmatic Hernia

**Mount Sinai Hospital**
- Should not be routinely used to prevent Chronic Lung Disease (CLD) in preterm infants
- Congenital Diaphragmatic Hernia (CDH) as these infants require urgent stabilization and transfer to HSC

**BC Women’s Hospital**
- None indications

**CHEO**
Relative:
- Methemoglobinemia >5%
- Evidence of intraventricular hemorrhage or stroke
- Gestational age <32 weeks
Contraindications and Exclusions

Exclusion:

- Suspicion of active intracranial bleed
- Platelet count less than 50000
- Evidence of septic shock

Stollery Children’s Hospital

- None indicated

Hamilton Health Sciences

The use of in the preterm population is still controversial and further studies are required before clear criteria for its use can be implemented.

Caution:

- Preterm (<34 weeks)
- Patients <26 weeks gestation, or less than 750g (risk of IVH).

Exclusion:

- Absence of methemoglobin reductase
- Complex congenital cardiac physiology with risk of pulmonary over circulation
- Congenital diaphragmatic hernia.

American Association for Respiratory Care

- Newborns with congenital diaphragmatic hernia
- Newborns with cardiac anomalies dependent on right-to-left shunts, congestive heart failure, and those with lethal congenital anomalies
- Insufficient data for postoperative management of hypoxic term or near-term infants with congenital heart disease

CHU Sainte-Justine

- None indicated

London Health Sciences Centre

- Neonates known to be dependent on right-to-left shunting of blood.
- Precaution for neonates with diminished methemoglobin reductase activity compared to adults.
- PPHN with CHD

London Health Sciences Centre Neonatal

Contraindications: Neonates known to be dependent on right-to-left shunting of blood.

Precautions: Neonates have diminished methemoglobin reductase activity compared to adults.

London Health Sciences Centre iNO Cheat Sheet

- None indicated
Contraindications and Exclusions

Jewish General Hospital

Absolute contraindication:

- Patients with congenital or acquired methemoglobinemia reductase deficiency

Relative contraindication:

- Patients with bleeding diathesis
- Intracranial hemorrhage
- Severe left ventricular failure or babies dependent on right-to-left shunting

McGill University Health Centre

- Not be routinely used for preterm infants
- In patients with ductal-dependent cardiovascular defect or severe left ventricular dysfunction, the use of iNO has the potential to be fatal.
- Warning: Treatment with iNO might aggravate cardiac insufficiency in a situation with left-to-right shunting. Therefore, it is recommended that prior to the administration of iNO, cardiology consultation and echocardiographic examination of central hemodynamics should be performed.
Recommendations prior to administration of iNO

**SickKids NICU**
- Echocardiography
- Perform and document baseline assessments:
  - Arterial blood gases
  - Vital signs
  - Oxygen index calculation: OI > 15 on arterial blood gas suggests need for iNO

**SickKids CCU**
- Echocardiography prior to starting iNO is recommended. Echocardiography must be completed immediately after initiation of iNO if not completed prior.
- Appropriate lung inflation, sedation, muscle relaxation, fluid resuscitation, and normocapnia.
- Perform and document baseline assessments:
  - vital signs
  - post ductal arterial blood gases
  - relevant hemodynamic measurements
  - oxygen index calculation
  - relevant parameters as identified by the team prior to initiation of iNO

**IWK Health Centre**
- None given

**Mount Sinai Hospital**
- Mean airway pressure is adjusted to provide adequate lung inflation confirmed by chest X-ray. This might mean using high frequency ventilation (HFOV/HFJV) particularly if patient also has high PaCO₂ and parenchymal lung disease. HFV & iNO should not be started simultaneously. HFV if deemed appropriate should precede iNO and settings adjusted to correct hypercapnia. Time should be given to adjust/assess its impact before iNO is started.
- Ensure correct acidosis and hypercapnia. Ensure PaCO₂ (not TcCO₂) and pH are in clinically acceptable range. In most situations the aim should be for PaCO₂ to be 35-45 mmHg (not more than 50 mmHg) and for pH to be between 7.30-7.40 (not less than 7.25).
- Optimize sedation with or without muscle relaxant to ensure patient is as comfortable as possible
### Recommendations prior to administration of iNO

and agitation is not a significant contributor to high PVR.

- Correct hypopfusion if present by appropriate fluid resuscitation.
- Establish an arterial access and obtain an arterial blood gas (ABG) stat before starting iNO. This should preferably be post-ductal (umbilical artery or post-tibial artery).
- PPHN is confirmed before or as soon as possible after starting iNO by echocardiography infants with hypoxic respiratory failure (especially those not responding to iNO) be carefully evaluated for a possibility of cyanotic heart disease. Urgent structural echocardiography.
- Ensure airway is cleared with suctioning.

### BC Women’s Hospital

- Optimized clinical conditions (ventilation, cardiovascular support and sedation)
- Consult Cardiology

### CHEO

**NICU:**

- Head ultrasound

**PICU:**

- Confirm clinical judgment of pulmonary hypertension by echocardiography in consultation with Cardiology (strongly recommended but not mandatory)
- Optimize Ventilation
  - Review recent chest x-ray
  - Target improved alveolar recruitment via optimal PEEP, increased mean airway pressure, alveolar recruitment maneuvers, and different modes of ventilation
  - Respiratory Alkalosis - pH > 7.4: consider the use of sodium bicarbonate
  - FiO₂ 100 %
  - High Frequency Oscillation Ventilation (excluding transport)
  - Prone positioning
  - Surfactant Therapy
- Optimize perfusion
  - Ensure adequate pre-load/circulating volume
  - Inotropic support
- Optimize Sedation
  - Ensure muscle relaxation

### Stollery Children’s Hospital

- None indicated

### Hamilton Health Sciences
Recommendations prior to administration of iNO

- Echocardiogram should be done whenever clinically possible to determine pulmonary pressures
- Mechanical ventilation and Right Ventricular (RV) preload and/or afterload should be optimized

American Association for Respiratory Care

- For the newborn with parenchymal lung disease, it is recommended that optimal alveolar recruitment be established.

CHU Sainte-Justine

- Conventional ventilation, sedation, prone position

London Health Sciences Centre

- Record baseline values for FiO₂, PEEP, SpO₂, Pulmonary Artery Pressure and PVRI at current level of therapy.

London Health Sciences Centre Neonatal

- Optimize ventilation. Possible optimization strategies include: optimal positive end expiratory pressure, inspiratory time, high frequency oscillation, high frequency jet ventilation and prone positioning.

London Health Sciences Centre iNO Cheat Sheet

- Initiate an Inhaled Nitric Oxide Study to obtain baseline data including baseline methemoglobin.

Jewish General Hospital

- None indicated

McGill University Health Centre

- For the newborn with parenchymal lung disease, it is recommended that optimal alveolar recruitment should be established prior to initiation of iNO therapy.
- The physician, nurse and respiratory therapist should optimize mechanical ventilation, cardiovascular stability, and patient comfort through sedation.
- It is highly suggested to obtain cardiology consultation and insert an indwelling arterial line in place.
- Optimize mechanical ventilation
- Optimize sedation
- Optimize cardiac output
Dosage

**SickKids NICU**

Initial starting dose is 20 ppm. Evaluate response after 30-60 minutes.

**SickKids CCU**

Initial starting dose is 40 ppm for 30 min, if response less than criteria discontinue.

- If a positive response is recognized titrate to 20 ppm until weaning criteria are met.
- If there is no positive response iNO should be discontinued.

**IWK Health Centre**

Initial starting dose is 20 ppm. Wait 30 min and assess response.

- If patient has no, or partial response, double iNO dose Q30 minutes until full response is seen or maximum dose of 80 ppm is reached. If patient then responds, maintain iNO dose at lowest level that elicits full response. If at 80 ppm for at least 30 minutes and patient still does not respond, use weaning guidelines to discontinue iNO.
- If patient responds at 20 ppm iNO and PaO₂ ≥60 mmHg, then decrease iNO to 5 ppm. If unable to decrease iNO to 5 ppm, return to 20 ppm and try to decrease to 5 ppm Q4h for first 24 hours. If unable, maintain treatment at 20 ppm iNO.

**IWK Health Centre Review**

Same as IWK Health Centre

**Mount Sinai Hospital**

Initial starting dose is 20 ppm for 30 min.

- If positive response or partial response, adjust to lowest effective dose.
- If no response it might be appropriate to continue ‘trial’ of therapy to a maximum of 1 hour then iNO therapy should be discontinued and details of response documented.

It is extremely important that during the trial period of iNO, no additional ventilator changes are made as it can make interpretation of ‘response to iNO therapy’ difficult.

**BC Women’s Hospital**

Initial starting dose is 20 ppm. Evaluate response at 30 minutes and begin weaning.

**CHEO**

Initial starting dose is 20 ppm. If there is no response to therapy within 30 minutes discontinue therapy.

For External Transport only:

If the patient responds to 20 ppm iNO and the FiO₂ < 0.60, maintain this dosage for the duration of the transfer. If the FiO₂ >0.60 on 20 ppm, repeat an ABG. If there are no mechanical or clinical reasons for the increased oxygen requirements then increase the iNO dosage by 20 ppm to 40 ppm and determine the response via ABG.
Dosage

Stollery Children’s Hospital

Initial starting dose is 20 ppm; titrate to lowest effective level as soon as possible.

Hamilton Health Sciences

Initial starting dose is 20 ppm.

If the patient is a non-responder and as per physician orders, wean the iNO off within 2 hours or increase iNO to 30 ppm, and if ordered again, increase to 40 ppm. Repeat an ABG 30 minutes after each iNO increase.

After escalation:

- If no response:
  - Inform the physician
  - Decrease iNO to 20 ppm.
  - Continue to wean to 0 ppm within 2 hours of initiating therapy. Note: This patient is considered a non-responder.

- If partial or full response:
  - Inform the physician
  - Maintain at the effective ppm for 12 hours prior to commencing weaning.

American Association for Respiratory Care

iNO therapy should be instituted early in the disease course, which potentially reduces the length of mechanical ventilation, oxygen requirement, and stay within the intensive care unit.

The recommended initial starting dose is 20 ppm and a short (30-60 minutes) trial run followed by weaning to the lowest effective dose.

It is suggested that the lowest effective doses of iNO and O₂ be used, to avoid excessive exposure to NO, NOₓ, and methemoglobinemia

CHU Sainte-Justine

Initial starting dose is 10 ppm. If there is no response, increase to 20 ppm. Try for minimal effective dose. Draw ABG 15-30 min after increase in dose. If positive response from ABG follow positive response guideline. If continued negative response, stop iNO without weaning, retry after 3 days, if still no response then patient is not responding to iNO.

London Health Sciences Centre

Initial starting dose is 20 ppm. If positive response titrate to the lowest effective dosage. If no response within 30 minutes then discontinue.

London Health Sciences Centre Neonatal

Initial starting dose is 20 ppm, unless otherwise ordered by the physician. Ideally 20 ppm should be no longer than 4 hours. If no effect within 30 minutes then discontinue.

London Health Sciences Centre iNO Cheat Sheet

Initial starting dose is 20 ppm (unless otherwise ordered) If no effect within 30 minutes discontinue. If a
### Dosage

Positive effect goal is to obtain iNO at 5 ppm within 4-24 hours if tolerated.

**Jewish General Hospital**

Initial starting dose is 20 ppm. If there are concerns about producing harm may start at 5-10 ppm. Increase by 5-10 ppm increments q15 minutes until satisfactory response (adequate homeostasis between systemic perfusion, pulmonary hemodynamics and gas exchange). Patients remain on iNO therapy until their hemodynamic status improves.

**McGill University Health Centre**

Initial starting dose is 20 ppm. Evaluate patient response after 30 minutes.
### Assessment of the Response after Initiation of iNO Therapy

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Positive/Full Response</th>
<th>Partial Response</th>
<th>Negative Response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SickKids NICU</strong></td>
<td>PaO$_2$ ≥ 20 mmHg or SpO$_2$ by 10% (or able to drop FiO$_2$ by at least 0.2)</td>
<td>PaO$_2$ 10-20 mmHg &gt; SpO$_2$ between 5-10% (or able to drop FiO$_2$ by 0.1–0.2)</td>
<td>Either no change or rise in PaO$_2$ &lt;10 mmHg or SpO$_2$ by 5% (or able to drop FiO$_2$ by &lt;0.1)</td>
</tr>
<tr>
<td><strong>SickKids CCU</strong></td>
<td>• ↓ in PVR by ≥ 20% (measured by ECHO or reflected in vital signs)</td>
<td></td>
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<tr>
<td></td>
<td>• ↓ in OI ≥ 20%</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>• ↑ Cardiac Output ≥ 20% (Measured of reflected by SvO$_2$)</td>
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<tr>
<td></td>
<td>• ↑ in SpO$_2$ &gt; 10%</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>• ↑ in PaO$_2$ &gt; 20%</td>
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<tr>
<td></td>
<td>• Marked changes evident upon echocardiography.</td>
<td></td>
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</tr>
<tr>
<td><strong>IWK</strong></td>
<td>PaO$_2$ ↑ by 20 mmHg or OI ↓ 20%</td>
<td>PaO$_2$ ↑ by 10-20 mmHg or OI ↓ 10-20%</td>
<td>PaO$_2$ ↑ by ≤10 mmHg or OI ↓ ≤10%</td>
</tr>
<tr>
<td><strong>IWK Review</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Mount Sinai</strong></td>
<td>Rise in post-ductal PaO$_2$ ≥20 mmHg or TcO$_2$ ≥ 20 mmHg or ≥ SpO$_2$ by 10% (or able to drop FiO$_2$ by at least 0.2)</td>
<td>Rise in post-ductal PaO$_2$ 10-20 mmHg or TcO$_2$ 10-20 mmHg or &gt; SpO$_2$ between 5-10% (or able to drop FiO$_2$ by 0.1–0.2)</td>
<td>Either no change or rise in post-ductal PaO$_2$ &lt;10 mmHg or TcO$_2$ &lt;10 mmHg or SpO$_2$ by &lt;5% (or able to drop FiO$_2$ by &lt;0.1)</td>
</tr>
<tr>
<td><strong>BC Women’s</strong></td>
<td>OI ≥15</td>
<td>↑ PaO$_2$ 10-20 mmHg from baseline</td>
<td>PaO$_2$ &lt; 10 mmHg from baseline</td>
</tr>
<tr>
<td></td>
<td>↑ PaO$_2$ &gt; 20 mmHg from baseline</td>
<td>↓ FiO$_2$ 0.10-0.20 from baseline if no arterial line</td>
<td>FiO$_2$ &lt; 0.10 from baseline if no arterial line</td>
</tr>
<tr>
<td></td>
<td>↓ FiO$_2$ &gt; 0.20 from baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CHEO</strong></td>
<td>PaO$_2$ ↑ &gt; 20 mmHg after 30 minutes</td>
<td>PaO$_2$ ↑ of 10 to 20 mg Hg after 30 minutes</td>
<td>PaO$_2$ ↑ of &lt;10 mmHg after 30 minutes</td>
</tr>
<tr>
<td><strong>Stollery</strong></td>
<td>↑ in PaO$_2$ 20 mmHg or greater after 30 minutes</td>
<td></td>
<td>PaO$_2$ rise &lt;10 mmHg over baseline after 30 minutes</td>
</tr>
<tr>
<td><strong>HHS</strong></td>
<td>PaO$_2$ improves by greater than 20 mmHg</td>
<td>PaO$_2$ improves 10-20 mmHg</td>
<td>PaO$_2$ improves &lt;10 mmHg or does not improve</td>
</tr>
<tr>
<td><strong>AARC</strong></td>
<td></td>
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<tr>
<td><strong>CHUSJ</strong></td>
<td>PaO$_2$/FiO$_2$ ↑ 15-20%</td>
<td></td>
<td>PaO$_2$/FiO$_2$ ↓ 15%</td>
</tr>
<tr>
<td><strong>LHSC</strong></td>
<td>• ↑ of 20% or more in PaO$_2$/FiO$_2$ and/or</td>
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<td></td>
<td>• ↑ in SpO$_2$ of 5% or more and/or</td>
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<tr>
<td></td>
<td>• A 20% ↓ in PVR</td>
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</tbody>
</table>
### Inhaled Nitric Oxide Review

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Positive/Full Response</th>
<th>Partial Response</th>
<th>Negative Response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Evidence of decreased Right Ventricular Systolic Pressure by cardiac echo or reduction in pre and post oxygen saturation difference that appears within 20 minutes after initiation.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• LHSC Neonatal</td>
<td>• ↑ of 20% or more in PaO₂/FiO₂ and/or</td>
<td>• ↓ of 20% or greater in PaO₂/FiO₂ and/or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• ↑ in SpO₂ of 5% or more and/or</td>
<td>• ↓ in SpO₂ of &gt;5 % and/or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• A 20% ↓ in PVR.</td>
<td>• 20% ↑ in PVR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Evidence of decreased Right Ventricular Systolic Pressure by cardiac echo or reduction in pre and post oxygen saturation difference that appears within 20 minutes after initiation.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• LHSC Cheat Sheet</td>
<td>• ↑PaO₂/FiO₂ &gt; 20% and/or</td>
<td>• ↓PaO₂/FiO₂ &gt; 20% and/or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• ↑ SpO₂ by 5% and/or</td>
<td>• ↓ in SpO₂ &gt; 4% and/or</td>
<td></td>
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<tr>
<td></td>
<td>• ↓ PVRI by 20% and/or</td>
<td>• ↑ PVRI by 20%</td>
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</tr>
<tr>
<td></td>
<td>• Positive response on cardiac echo within 20 minutes</td>
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<tr>
<td>• JGH</td>
<td>• Improved SpO₂</td>
<td></td>
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<tr>
<td></td>
<td>• ↑PaO₂</td>
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<td></td>
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<tr>
<td></td>
<td>• ↓ Pulmonary artery pressures.</td>
<td></td>
<td></td>
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<tr>
<td>• MUHC</td>
<td>• ↑PaO₂/FiO₂ of 15-20%</td>
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</table>
Inhaled Nitric Oxide Review

Monitoring
Monitoring includes measures of patient condition during the administration of iNO therapy.

<table>
<thead>
<tr>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SickKids NICU</strong></td>
</tr>
<tr>
<td>• Arterial access if possible (pre ductal location preferred)</td>
</tr>
<tr>
<td>• Continuous monitoring of SpO2, TcPCO2 / end-tidal CO2, vital signs</td>
</tr>
<tr>
<td>• The circuit allows for continuous monitoring of NO, NO2 and O2 and for control of the dose of iNO delivered to the patient.</td>
</tr>
</tbody>
</table>

| **SickKids CCU** |
| • Indwelling arterial catheter |
| • Indwelling CVP or PA |
| • Continuous Monitoring of SaO2, EtCO2, vital signs |
| • Mixed venous oxygen saturation monitoring |
| • Echocardiography to document response to iNO and guide decision making |
| • Daily methemoglobin measurement (>4% may require decrease in iNO) |
| • Daily calibration of NO, NO2 and FiO2 sensors (low end calibration) |

| **IWK Health Centre** |
| Hemodynamics and oxygenation. |

| **IWK Health Centre Review** |
| No mention or summarized in separate table |

| **Mount Sinai Hospital** |
| • Hourly checks and documentation of iNO reading onto patient flow sheet. |
| • A pre-ductal saturation probe be applied on right hand and post-ductal should be on a foot. Left hand should NOT be used to monitor saturations in this scenario. Pre and post ductal saturations can be a useful tool for semi-qualitative monitoring of the extent of right to left ductal shunting. This is only applicable if infant has a large unrestrictive PDA. Only pre-ductal saturations should be used for titrating FiO2. |

| **BC Women’s Hospital** |
| No mention or summarized in separate table |

| **CHEO** |
| • The circuit allows for continuous monitoring of NO, NO2 and O2 and for control of the dose of iNO delivered to the patient. |
| • Continue monitoring pre/post SpO2, TcCO2 ETCO2, HR, B/P and perform ABG 30 minutes after initiation of therapy. Ventilator settings and FiO2 changes should not be made within this 30 minute
### Monitoring

<table>
<thead>
<tr>
<th>Stollery Children’s Hospital</th>
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<tbody>
<tr>
<td>• Continuous arterial blood pressure monitoring is required.</td>
</tr>
<tr>
<td>• Platelet function may be inhibited so bleeding from punctures, stomach, etc. should be monitored. Monitor platelet levels q24h.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Hamilton Health Sciences</th>
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<table>
<thead>
<tr>
<th>American Association for Respiratory Care</th>
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<tbody>
<tr>
<td>It is suggested that continuous pulse oximetry and hemodynamic monitoring be used to assess patient response to iNO therapy</td>
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<thead>
<tr>
<th>CHU Sainte-Justine</th>
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<tr>
<td>Monitor FiO2.</td>
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<table>
<thead>
<tr>
<th>London Health Sciences Centre</th>
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</thead>
<tbody>
<tr>
<td>Record baseline values for FiO2, PEEP, SpO2, Pulmonary Artery Pressure and PVRI at current level of therapy and after each change in dose.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>London Health Sciences Centre Neonatal</th>
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</thead>
<tbody>
<tr>
<td>• Cardiorespiratory monitoring</td>
</tr>
<tr>
<td>• Masimo Rainbow technology with MetHb software placed pre-ductal</td>
</tr>
<tr>
<td>• Oximeter post-ductal</td>
</tr>
<tr>
<td>• Blood pressure (invasive or non-invasive)</td>
</tr>
<tr>
<td>• A baseline arterial blood gas should be drawn prior to initiation of therapy and correlated with transcutaneous O2 and CO2 values. (Post iNO therapy this combined probe will continue to be used on the patient although it may iNO longer be necessary to monitor SpMetHb, it will measure just SpO2. The probe will be replaced as per routine replacement practice; i.e. due to soiling, etc.).</td>
</tr>
<tr>
<td>• Continuous monitoring of gas delivery must consist of NO, NO2 and O2.</td>
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<tr>
<td>• iNO tank pressures should be monitored each shift to ensure an adequate supply of gas is on hand.</td>
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<table>
<thead>
<tr>
<th>London Health Sciences Centre iNO Cheat Sheet</th>
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<td>No mention or summarized in separate table</td>
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<table>
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<tr>
<th>Jewish General Hospital</th>
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<tbody>
<tr>
<td>Respiratory Therapist:</td>
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<tr>
<td>• FiO2</td>
</tr>
<tr>
<td>• Tidal Volume (and routine ventilator parameters)</td>
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<tr>
<td>• Trigger sensitivity</td>
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<tr>
<td>• Oxygen saturation</td>
</tr>
</tbody>
</table>
Monitoring

- Arterial Blood gases (optional in Neonatal Unit)
- Baseline
- Post initiation
- Each hour or PRN as needed for 6 hours
- 30 mins after each NO concentration adjustment
- at any time when clinically needed
- Pulmonary artery pressures
- Platelet count
- NO parameters as per NO protocol
- NO₂ levels (maintain < 2 ppm)

ICU Bedside Nurse:
- Vital signs & SaO₂ q1h
- PA catheter: PA Pressures q2h, Cardiac Index q4h (optional: right ventricular stroke work index (RVSWI))
- ABG:
  - Routine:
    - On initiation of iNO, then q1h X 6, then q shift
    - q30 min after NO concentration adjustment
  - Methemoglobin level: qshift (< 5%)
- Blood work: CBC: q daily

McGill University Health Centre

Respiratory Therapist will:
1. Assure that an optimal ventilatory strategy with adequate lung recruitment is in place.
2. Assure that the patient has one of the inclusion criteria (see iNO initiation)
3. Document mode of ventilation and ventilatory settings, arterial blood gas, OI, and patient assessment (including pulmonary auscultation).
4. Set up and test the iNO delivery system (INOmax DS₂₁) at the bedside as per iNO Ikaria manual.

Nurse will:
1. Verify functioning of flow inflating bag and suction equipment at bedside as per MUHC guidelines.
2. Verify that FiO₂ on oxygen blender is set at 100%, unless otherwise ordered by physician.
3. Advocate for best practice guidelines, for both a central line and an arterial line access.
**Monitoring**

5. Advocate for pain management to improve patient's overall status.


7. Assess and document patient's respiratory status, including pulmonary auscultation, work of breathing, suctioning if needed.

8. Document mode of ventilation and ventilator settings (PEEP/PIP, mean airway pressure, rate, inspiratory time, and frequency – if on high frequency ventilation).

RT and nurse will monitor and document the patient’s pre/post SpO₂ every 30 minutes for the first 2hr and every 2hr afterwards unless during the weaning phase. The FiO₂ will not be weaned for the first 30 minutes of iNO therapy.

Nurse will:

1. Continue to monitor and document vital signs, and ventilator settings as stated above.

2. Continue to monitor and document patient's comfort/sedation status as stated above.

3. Continue to advocate for pain management, minimal handling while maintaining close observation and grouping of patient's care.

4. Wean FiO₂ needs in accordance with SpO₂ parameters ordered by physician.

5. While patient receiving iNO, do not wean FiO₂ below 30%.
Weaning

The table includes the procedure for weaning iNO.

<table>
<thead>
<tr>
<th>Weaning Procedure</th>
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</thead>
<tbody>
<tr>
<td><strong>SickKids NICU</strong></td>
</tr>
</tbody>
</table>

When the infant is clinically stable and $\text{FiO}_2 < 0.60$, begin weaning iNO unless otherwise directed by medical staff.

Reduce the iNO from 20 ppm to 10 ppm, and within 2 hours if no deterioration occurs, wean to 5 ppm.

At 5 ppm, consider a stepwise reduction of iNO by 1 ppm every 1-2 hours until discontinuation is possible (see special note on discontinuation)

If at any point in the weaning process, there is significant deterioration in oxygenation status $\text{SpO}_2$ decrease by $>5\%$ or return of pre/post ductal difference $<10\%$ and/or an increase in $\text{FiO}_2 > 0.20$, stop weaning iNO and consider returning to the previous iNO dosage. Ensure optimization of care in all other areas and modalities. Consider CXR to rule out correctible causes.

| **SickKids CCU** |

Wean as soon as possible by 50% every hour until 5 ppm then by 1 ppm every hour until discontinued. If wean not tolerated, return to last effective dose.

| **IWK Health Centre** |

Once patient’s oxygenation is stable with $\text{PaO}_2 \geq 60 \text{ mmHg}$ wean iNO. Reduce iNO approximately 20% per hour until 5 ppm then decrease by 1 ppm every four hours until discontinued. If wean not tolerated ($\text{PaO}_2 \leq 60 \text{ mmHg}$), return to last effective dose and attempt weaning again in 4 hours.

| **IWK Health Centre Review** |

When discontinuing iNO, once very low levels are reached, weaning should occur gradually.

- Once patient’s oxygenation is stable with $\text{PaO}_2 \geq 60 \text{ mmHg}$ consider weaning iNO.
- Reduce iNO gradually, approximately 20% per hour until you reach 5 ppm.
- If $\text{PaO}_2 \downarrow \leq 60 \text{ mmHg}$, return iNO to previous level and attempt weaning again after 4 hours.
- Once down to 5 ppm iNO, $\downarrow$ by 1 ppm Q4H.
- When iNO gets discontinued, $\text{FiO}_2$ may need to be increased by up to 20% to prevent transient hypoxemia.

| **Mount Sinai Hospital** |

After a stable period of 6-12 hours, the patient should be assessed for suitability for weaning iNO. Weaning of iNO should commence when $\text{FiO}_2 < 0.4$. Wean iNO by 5 ppm every hour until 5 ppm followed by one of the following:

- If total duration of iNO $> 24$ hours: leave on 5 ppm for 4 hours and then wean by 1 ppm every 4 hours.
- If total duration of iNO therapy $< 24$ hours: wean by 1 ppm every hour until discontinued.

Discontinue weaning if:
**Weaning Procedure**

- FiO₂ rise by > 0.2 or
- Return of pre-ductal saturation higher than post-ductal by > 10%.

If weaning had to be discontinued then increase iNO by one step at a time till infant returns back to pre-deterioration status and then leave for at least 12 hours before recommencing weaning. This time weaning strategy should be slower than earlier attempt and should be decided on an individual basis by the attending team.

If there is a negative response after 30 minutes, there is no need to wean.

It is recommended that if iNO therapy is needed for longer than 7 days than alternate diagnosis should be considered (like alveolar capillary dysplasia; pulmonary hypoplasia; congenital heart disease).

- Inability to wean iNO should prompt a functional echo consult and consideration of alternate therapies/ diagnosis.

After a sustained positive response and oxygenation improvement, wean FiO₂ to minimum required concentration to maintain SpO₂ around 95% (acceptable range 92–97% which is equivalent to PaO₂ of 60–80 mmHg). For premature infants it may be appropriate to aim for ‘normal preterm saturations’ as per unit policy. ‘Super-saturating’ patients with pulmonary hypertension on iNO do not provide any additional benefits and may potentially be harmful.

**BC Women’s Hospital**

Three hours after full response (FiO₂ < 0.40 or decrease FiO₂ > 0.10) begin weaning procedure. Every subsequent 3 hours reassess for full response prior to proceeding one step in the weaning process. Weaning schedule: 10 ppm, 5 ppm, 3 ppm, 1 ppm, discontinue. If there is not a full response (FiO₂ ≥40 or increase in FiO₂ > 0.10) return to previous iNO dosage.

It is recommended that if wean is unsuccessful, notify physician

- Optimize clinical condition
- Increase to previous level or restart iNO
- Consider repeat echocardiogram
- Wean iNO every 6 hours after re-stabilization

**CHEO**

Attempt to wean every 6 hours if the SpO₂ is >88 %. Ventilator settings and FiO₂ should not be changed during the 30 minute assessment period or after weaning. Weaning is considered successful if the saturation remains > 88 % in any amount of oxygen. All weaning is achieved by decreasing the concentration of iNO by 50% until 5 ppm and then by 1 ppm to off.

**Stollery Children’s Hospital**

iNO should be weaned rather than discontinued abruptly. Non-responders should have iNO stopped within one hour of determining non-responder status. The weaning protocol for responders is as follows:
Weaning Procedure

- Decrease iNO at 4 hours by 50% if PaO₂ >59 and pH <7.52
- Decrease iNO every 4 hours by 50%, if criteria met
- Decrease iNO by 1 ppm q4h when at 5 ppm and below, if criteria met
- Maximum of 24 hours on 20 ppm.

**Hamilton Health Sciences**

12 hours after establishing the initial doses for Full Responders, and then every 8-12 hours as tolerated:

- Wean the iNO by 50% every 8-12 hours until a dose of 5 ppm is reached
- Once at 5 ppm, wean in 1 ppm decrements every 6-12 hours as needed.

Note: The greatest clinical deterioration in oxygenation is from 1 ppm to 0 ppm

If rebound is noted after weaning from 1 ppm to 0 ppm:

- Discuss with physician
- Increase iNO again to at least 1 ppm (based on patient need) until the infant has stabilized.
- Subsequent weaning attempts:
  - Discuss with physician beforehand
  - Decrease the iNO from 1 ppm to 0.50 ppm before 0 ppm.

In patients where dependency has been identified by a failed weaning attempt:

- Discuss with physician beforehand
- Increase the FiO₂ by 10% for a period of 30 minutes both pre- and post-wean.

**American Association for Respiratory Care**

For newborns with a response to INO therapy, wean to the lowest dose that maintains that response.

iNO should not be discontinued until there is an appreciable clinical improvement; that the INO dose should be weaned to 1 ppm before an attempt is made to discontinue; and that the FiO₂ should be increased prior to discontinuation of INO therapy.

**CHU Sainte-Justine**

If there is no evidence of pulmonary hypertension decrease iNO every 30 min until stopped by following the subsequent doses: 20-10-5-4-3-2-1-0.5 ppm.

Monitor FiO₂. If weaning is causing deterioration in condition necessitating increase in FiO₂, do an ABG. Weaning is considered failing if decrease PaO₂/FiO₂ of 15-20%, return to minimum effective dose for 24 hours, then try weaning again. Non-respondents do not need weaning.

**London Health Sciences Centre**

- iNO should not be abruptly discontinued if it has been administered for >2 hours as it may result in an increase in pulmonary artery pressure (PAP) and/or worsening of blood oxygenation (PaO₂).
- Wean to 5 ppm as soon as possible and within 4-24 hours of therapy provided that arterial
Inhaled Nitric Oxide Review

**Weaning Procedure**

- Oxygenation and/or PAP are adequate at this lower dose.
- If two attempts to discontinue iNO have failed, do not attempt further weaning for 24 hours or as ordered by the physician.
- If a positive response has been confirmed, reduce iNO to 10 ppm for 15 minutes and determine effect. If a reduction of positive effect is noted, increase back to 20 ppm.
- If positive effect is maintained at 10 ppm, reduce iNO to 5 ppm for 15 minutes and determine effect. If there is a reduction in positive effect noted, increase iNO back to 10 ppm. If positive effect is maintained, continue iNO at 5 ppm.
- If the patient’s PVRI and/or PaO2/FiO2 ratio and/or SpO2 return to acceptable levels for a minimum of 2 hours:
  - Increase FiO2 by .10
  - Decrease iNO to 2 ppm and repeat measurements.
  - If there is no deterioration, then decrease iNO to 1 ppm.
  - If a decrease of 20% or greater in PaO2/FiO2 ratio and/or a decrease in SpO2 of >5% and/or a 20% increase in pulmonary vascular resistance occurs, then restart iNO at 5 ppm. Return FiO2 to previous level
- Once at 1 ppm, discontinue, while monitoring the pulmonary vascular resistance, PaO2/FiO2 ratio and SpO2:
  - If a decrease of 20% or greater in PaO2/FiO2 ratio and/or a decrease in SpO2 of 5% and/or a 20% increase in pulmonary vascular resistance occurs then restart iNO at 5 ppm. Wait 4 – 6 hours before attempting further weaning.

**London Health Sciences Centre Neonatal**

iNO Therapy should not be discontinued abruptly as it may result in an increase in pulmonary artery pressure (PAP) and/or worsening of blood oxygenation (PaO2).

Upon a physician’s order, weaning may commence over a period of several hours or days depending on patient response. Starting as soon as possible and within 4 - 24 hours of therapy:

- If on 20 ppm wean by 5 ppm q1h until down to 5 ppm. Note observations on the Nitric Oxide Sheet, and ventilation parameter sheet.
- If positive effect is maintained at 5 ppm, reduce to 1 ppm for 15 minutes and determine effect. If there is a reduction in positive effect noted, increase dose back to 10 ppm. If positive effect is maintained, attempt reduction to 5 ppm and maintain iNO at 5 ppm for 4-6 hours before attempting wean to 1 ppm.
- If the duration of iNO therapy is greater than 24 hours, after stabilizing at 5ppm for 4 hours wean iNO 1-2ppm Q6H. If the duration of iNO therapy is less than 24 hours, once 5 ppm is achieved wean iNO 1ppm Q1H.
- Reduce iNO to 1 ppm for 30 - 60 minutes. If there is iNO change in SpO2, the FiO2 should be increased by 10%
- Discontinue iNO, while monitoring the SpO2. If a decrease of 20% in SpO2 then restart iNO at 5 ppm.
**Weaning Procedure**

- Wait 4 - 6 hours before attempting further weaning of iNO

The dose should be:

- Discontinue weaning if oxygen saturations decrease > 5% or the pre-ductal and post-ductal saturation gradient increases > 10%. Confirm with TcPO₂ and/or ABG.
- Weaned to 5 ppm provided that arterial oxygenation is adequate at this lower dose.
- Maintain at 5 ppm until there is improvement in the neonate’s oxygenation such that the FiO₂ < 0.60.

**London Health Sciences Centre iNO Cheat Sheet**

Every 30 minutes decrease iNO until optimal therapeutic dose is obtained and document on Inhaled Nitric Oxide Study sheet and Respiratory Parameter Record.

If the iNO level is greater than 5 ppm the RRT will attempt a dose response test daily.

To wean from 5 ppm increase FiO₂ by 0.10, wait 30 minutes then d/c iNO. Compare PaO₂/FiO₂ ratio, SpO₂ and pulmonary vascular resistance to baseline and assess for tolerance (see note below).

If patient does not tolerate, return to 5 ppm and previous FiO₂ for a minimum of two hours.

After patient stable for at least 2 hours then increase FiO₂ to .10, decrease iNO to 2 ppm and repeat measurements. If tolerated then decrease to 1 ppm. If tolerated then d/c iNO while monitoring patient.

If two attempts to d/c iNO fail return iNO to 5 ppm and do not wean for 24 hours.

**Jewish General Hospital**

- Decrease by 5 ppm q1-4 hrs until 5 ppm, then by 1 ppm q 1-4 hrs until 1 ppm, then by .1-.2 ppm q 1-4 hrs until d/c’ed.
- An increase in FiO₂ by 10% is recommended while weaning iNO
- In situations where iNO cannot be weaned and systemic BP & perfusion are adequate, alternative therapies should be entertained (milrinone, nitroglycerin, calcium-channel blockers, prostacyclin (systemic or inhaled), sildenafil (Viagra), bosentan (endothelin-receptor antagonist) etc.).

**McGill University Health Centre**

After 30 minutes of initiating the iNO, if SpO₂ increases ≥ 5% from baseline and SpO₂ is ≥ 92%, begin weaning FiO₂ until it is ≤ 0.5. The FiO₂ should be weaned by 2-5% every 30 minutes to achieve a pre-ductal SpO₂ ≥ 92%, and PaO₂ between 50-80 mmHg (if available), and pre/post ductal SpO₂ difference < 5%. If the weaning process takes longer than 2 hours to achieve 0.50 O₂, it is advisable to obtain an arterial blood gas to monitor the PaO₂ (50-80 mmHg).

RT will adjust iNO as per the following:

- Once the FiO₂ is ≤ 0.5 begin weaning iNO.
- If FiO₂ cannot be weaned below 0.5 after 4 hours an attempt to wean may be considered in a case by case basis.

RT will adjust iNO to 10 ppm. Remain at 10 ppm for 30 minutes and then assess pre-ductal SpO₂. If pre-ductal SpO₂ decreases more than or equal to 5%, return to 20 ppm, and notify nurse and neonatologist/fellow/NNP. iNO weaning should be reconsidered after 12 to 24 hours.
Weaning Procedure

Following this procedure, continue reducing iNO doses: 5-4-3-2-1 ppm. If criteria are not met return one step.

If preductal SpO₂ stays within 5%, STOP iNO.

After 60 minutes, assess patient and restart iNO at 1 ppm if:

- FiO₂ needs > 0.60 or
- PaO₂ < 50 mmHg or
- Pre-ductal SpO₂ < 92%

RT will discontinue INOmax DS if iNO remains off for at least 60 minutes.
List of Common Complications

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Methemoglobin</th>
<th>Nitrogen Dioxide</th>
<th>Rebound Pulmonary Hypertension</th>
<th>Systemic Hypotension</th>
<th>Platelet Dysfunction</th>
<th>Inadvertent hypoxic gas delivery</th>
<th>Direct Toxicity</th>
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</thead>
<tbody>
<tr>
<td>SickKids NICU</td>
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<td>√</td>
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<td>SickKids CCU</td>
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<td>IWK Review</td>
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<td>Mount Sinai</td>
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<td>BC Women’s</td>
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*notes caution for deficiency in methemoglobin reductase activity
<table>
<thead>
<tr>
<th>Institution</th>
<th>Monitoring Schedule of Methemoglobin Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>SickKids NICU</td>
<td>Within 1 hour of initiating iNO and daily for the duration of iNO delivery</td>
</tr>
<tr>
<td>SickKids CCU</td>
<td>Daily</td>
</tr>
<tr>
<td><strong>Mount Sinai Hospital</strong></td>
<td>Within 1 hour post-initiation of iNO therapy and then daily post-initiation if iNO ≤ 20 ppm or every 8 hours post initiation if iNO &gt; 20 ppm. If both the 1 hour and 24 or 8 hour methemoglobin &lt;2.5% then repeat every 7 days until discontinuation of treatment. If 2.5-5% consider monitoring daily.</td>
</tr>
<tr>
<td><strong>IWK Health Centre</strong></td>
<td>No mention</td>
</tr>
<tr>
<td><strong>IWK Health Centre Review</strong></td>
<td></td>
</tr>
<tr>
<td><strong>CHEO</strong></td>
<td>Baseline and daily. If methemoglobin &gt;5% repeat the methemoglobin within 1 hour after decrease in iNO.</td>
</tr>
<tr>
<td><strong>BC Women’s Hospital</strong></td>
<td>Every 12 hours</td>
</tr>
<tr>
<td><strong>Stollery Children’s Hospital</strong></td>
<td>Measured on all ABG samples on the co-oximeter with no time frame given.</td>
</tr>
<tr>
<td><strong>Hamilton Health Sciences</strong></td>
<td>Within the first 6 hours of therapy and every 12 hours thereafter. If methemoglobin &gt;2% repeat level in 30 minutes after decrease in iNO</td>
</tr>
<tr>
<td><strong>American Association for Respiratory Care</strong></td>
<td>Approximately 8 hours and 24 hours after therapy initiation and daily thereafter</td>
</tr>
<tr>
<td><strong>CHU Sainte-Justine</strong></td>
<td>6 hours post-initiation and every 12 hours</td>
</tr>
<tr>
<td><strong>London Health Sciences Centre</strong></td>
<td>Baseline and after 60 minutes. If methemoglobin &gt;2.5% levels redrawn every 60 minutes after decrease in iNO until methemoglobin &lt;2.5% then measured daily.</td>
</tr>
<tr>
<td><strong>London Health Sciences Centre Neonatal</strong></td>
<td>After 60 minutes and compared to the measurement on the Masimo Rainbow oxygen saturation monitor w/MethHb. If the level is &gt;2.5% monitored by the Masimo unit until it drops below 2.5%.</td>
</tr>
</tbody>
</table>
### Monitoring Schedule of Methemoglobin

Methemoglobin then measured daily.

### London Health Sciences Centre iNO Cheat Sheet

Baseline and again 1 hour after optimal dose is set. If <2.5%, measure daily and when iNO dose is increased. If >2.5% measure again in 1 hour.

### Jewish General Hospital

With ABG at initiation of treatment then every hour for 6 hours, then every shift. Measured 30 minutes after iNO concentration adjustment.

### McGill University Health Centre

With every blood gas.
**Methemoglobin Parameters**

The table includes actions taken in response to methemoglobin levels.

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Methemoglobin levels</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>SickKids NICU</td>
<td>&gt; 10%</td>
<td>Discontinue iNO</td>
</tr>
<tr>
<td></td>
<td>2.5–10%</td>
<td>Decrease iNO by 50%</td>
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<tr>
<td></td>
<td>&lt; 2.5%</td>
<td>Safe</td>
</tr>
<tr>
<td>SickKids CCU</td>
<td>&gt; 10%</td>
<td>Discontinue iNO and repeat methemoglobin levels. Keep decreasing iNO until &lt;5%.</td>
</tr>
<tr>
<td></td>
<td>5–10%</td>
<td>Reduce iNO by 50% and repeat methemoglobin level</td>
</tr>
<tr>
<td></td>
<td>&lt;5%</td>
<td>Considered safe</td>
</tr>
<tr>
<td>IWK</td>
<td>&gt;5%</td>
<td>Decrease iNO by 50% and repeat methemoglobin levels. Keep decreasing iNO until &lt;5%.</td>
</tr>
<tr>
<td></td>
<td>2.5-5%</td>
<td>Inform physician and consider decreasing dose of iNO.</td>
</tr>
<tr>
<td>IWK Review</td>
<td>&lt;5%</td>
<td>Does not require treatment.</td>
</tr>
<tr>
<td>Mount Sinai</td>
<td>≥ 3%</td>
<td>Medical team should be notified and weaning of iNO should be considered</td>
</tr>
<tr>
<td></td>
<td>≥ 5%</td>
<td>Should prompt discontinuation</td>
</tr>
<tr>
<td>BC Women’s</td>
<td>≥2.5%</td>
<td>Notify physician</td>
</tr>
<tr>
<td>CHEO</td>
<td>&gt;10%</td>
<td>Discontinue iNO</td>
</tr>
<tr>
<td></td>
<td>&gt;5%</td>
<td>Attempt to wean the iNO by 50%</td>
</tr>
<tr>
<td>Stollery</td>
<td>&gt;5%</td>
<td>Wean iNO by 50%</td>
</tr>
<tr>
<td></td>
<td>&gt;10%</td>
<td>iNO should be discontinued after the physician/designate is notified.</td>
</tr>
<tr>
<td>HHS</td>
<td>&gt;2%</td>
<td>Inform physician and wean the concentration of iNO by 50% immediately.</td>
</tr>
<tr>
<td></td>
<td>&gt;10%</td>
<td>Discontinue iNO and inform the physician</td>
</tr>
<tr>
<td>AARC</td>
<td>&gt; 5%</td>
<td>Wean or discontinue iNO</td>
</tr>
<tr>
<td>CHUSJ</td>
<td>&lt;5%</td>
<td>Target</td>
</tr>
<tr>
<td>LHSC</td>
<td>&gt;2.5%</td>
<td>Decrease iNO</td>
</tr>
<tr>
<td>LHSC Neonatal</td>
<td>&gt;10%</td>
<td>Discontinue iNO. If needed, restart at lesser of ≤20 ppm or 50% of iNO at discontinuation.</td>
</tr>
<tr>
<td></td>
<td>5–10%</td>
<td>Reduce iNO by 50% and repeat level 2 hours later until &lt;5%.</td>
</tr>
<tr>
<td></td>
<td>&lt; 5%</td>
<td>No action required.</td>
</tr>
<tr>
<td></td>
<td>&gt; 2.5%</td>
<td>Notify the responsible physician, and the iNO dose should be decreased.</td>
</tr>
<tr>
<td>LHSC Cheat Sheet</td>
<td>&gt; 2.5%</td>
<td>Attempt to decrease iNO</td>
</tr>
<tr>
<td>JGH</td>
<td>&gt;5%</td>
<td>Considered elevated</td>
</tr>
<tr>
<td>MUHC</td>
<td>&gt; 2.5%</td>
<td>iNO dose should be decreased</td>
</tr>
</tbody>
</table>
### Monitoring of Nitrogen Dioxide

The table includes actions taken in response to nitrogen dioxide levels.

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Monitoring</th>
<th>NO₂ Levels</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>• SickKids NICU</td>
<td>Continuously</td>
<td>&gt;2 ppm</td>
<td>Maintain levels</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;5 ppm</td>
<td>Discontinue iNO</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3-5 ppm</td>
<td>Check ventilator circuit, wean iNO by 50 % every 15 minutes until &lt; 3 ppm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;3 ppm</td>
<td>Considered safe</td>
</tr>
<tr>
<td>• SickKids CCU</td>
<td>Continuously</td>
<td>&gt;5 ppm</td>
<td>Discontinue iNO</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3-5 ppm</td>
<td>Wean iNO by 50% every 15 minutes until safe</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;2 ppm</td>
<td>Safe</td>
</tr>
<tr>
<td>• Mount Sinai</td>
<td>Continuously</td>
<td>&lt;2 ppm</td>
<td>Ensure levels</td>
</tr>
<tr>
<td>• CHEO</td>
<td></td>
<td>&gt;5 ppm</td>
<td>Wean iNO</td>
</tr>
<tr>
<td>• Stollery</td>
<td>Continuously</td>
<td>&gt;5 ppm</td>
<td>Wean by 50%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;7 ppm</td>
<td>Discontinue</td>
</tr>
<tr>
<td>• HHS</td>
<td>4 hours minimum</td>
<td>&lt;3 ppm</td>
<td>Maintain level</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;3 ppm</td>
<td>Check ventilator circuit and ensure a purge has been performed; If unresolved, wean iNO by 50% as ordered, every 15 minutes until &lt; 3 ppm Discuss with physician and discontinue iNO</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;5 ppm</td>
<td></td>
</tr>
<tr>
<td>• AARC</td>
<td></td>
<td>2 ppm</td>
<td>The high NO₂ alarm be set at this level on the delivery system to prevent toxic gas exposure to the lungs</td>
</tr>
<tr>
<td>• LHSC Neonatal</td>
<td>Continuously</td>
<td>&lt;0.5 ppm</td>
<td>Maintain levels</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;0.5 ppm</td>
<td>The delivery system should be assessed for malfunction, analyzer recalibrated, and the iNO therapy and/or FiO₂ should be reduced if possible Set high alarm at this level Ideal level</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 ppm</td>
<td>Recalibrate analyzer; replace iNO delivery system for system free of NO₂; Ensure NO₂ delivered is &lt;3 ppm No action required</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;1 ppm</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥3 ppm</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;3 ppm</td>
<td></td>
</tr>
<tr>
<td>• LHSC Cheat Sheet</td>
<td></td>
<td></td>
<td>Document NO₂</td>
</tr>
<tr>
<td>• JGH</td>
<td>Continuously</td>
<td>&lt;2 ppm</td>
<td>Maintained levels</td>
</tr>
<tr>
<td>• MUHC</td>
<td>2 hours</td>
<td>&lt;0.5 ppm</td>
<td>Remain below level</td>
</tr>
</tbody>
</table>
Management of Rebound Pulmonary Hypertension

- This table includes specific management for rebound pulmonary hypertension.

<table>
<thead>
<tr>
<th>Rebound Pulmonary Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SickKids NICU</strong></td>
</tr>
</tbody>
</table>

Acute rebound of pulmonary hypertension may occur in patients who receive therapy for >1 hours. Be aware that some infants may develop a transient hypoxemia once iNO therapy is discontinued. The hypoxemia is usually moderate (needing increase in FiO₂ by <0.2) and transient (generally lasting <1 hour). This should not be a reason to restart iNO therapy but should be treated or pre-empted by increasing FiO₂ by up to 0.2. Only if a FiO₂ increase by >0.2 is required should consideration be given to recommencing iNO (at 1-2 ppm). Rule out other correctable causes for hypoxemia, if persistent.

| **SickKids CCU**               |

If iNO therapy >4 hours, wean appropriately over given time period.

- Increase FiO₂ briefly.
- Adjust mechanical ventilation
- Consider alternate pharmacological treatments.

| **IWK Health Centre**         |

When discontinued, FiO₂ may need to be increased by up to 20%

**IWK Health Centre Review**

Abrupt withdrawal of iNO resulting in rebound hypoxemia has been reported in the literature. Rebound pulmonary hypertension has been reported in children placed on iNO after surgery for congenital heart disease. An increase in the FiO₂ by 20% of the time of cessation of iNO was noted to avoid the decrease in PaO₂.

**Mount Sinai Hospital**

Some infants may develop a transient hypoxemia once iNO therapy is discontinued. The hypoxemia is usually moderate (needing increase in FiO₂ by 0.2) and short lasting (up to an hour). This should not be a reason to restart iNO therapy but should be treated by increasing FiO₂.

Be aware that if iNO trial was longer than 30 minutes then patient might experience deterioration in oxygenation in spite of a negative response. This deterioration is usually transient (from 30 minutes to 4 hours) and is secondary to suppression of endogenous NO production. This should NOT be considered as an indication for restarting iNO therapy if there was a confirmed negative response. A full structural echocardiogram should be obtained as early as possible to rule out a cyanotic heart defect if hypoxic respiratory failure is not responsive to iNO therapy and hyperoxia test is abnormal (PaO₂ < 150 mmHg after 10 minutes of 100% oxygen therapy).

**BC Women’s Hospital**

No mention

**CHEO**

Patients who respond to iNO therapy may have a rebound effect of pulmonary hypertensive crisis if
Inhaled Nitric Oxide Review

Rebound Pulmonary Hypertension

removed from therapy abruptly. Consider Sildenafil for PICU only patients that are difficult to wean (discuss with cardiology).

Stollery Children’s Hospital

No mention

Hamilton Health Sciences

Prior to discontinuation of iNO, verify with physician if FiO₂ should be increased by 10% to prevent acute desaturation, for a period of 30 minutes both pre and post-discontinuation. Note: This has been demonstrated to improve the odds of discontinuation.

Upon discontinuation of iNO, closely monitor pulse oximetry and notify the physician immediately of any clinical deterioration. Obtain an ABG within 2 hours of discontinuation of iNO

American Association for Respiratory Care

No mention

CHU Sainte-Justine

No mention

London Health Sciences Centre

No mention

London Health Sciences Centre Neonatal

No mention

London Health Sciences Centre iNO Cheat Sheet

No mention

Jewish General Hospital

In order to avoid rebound PA HTN, slowly wean iNO from the patient.

McGill University Health Centre

The iNO dose should not be discontinued abruptly as it may result in an increase in pulmonary artery pressure (PAP) and/or worsening of blood oxygenation (PaO₂). Rapid rebound reactions such as intensified pulmonary vasoconstriction and hypoxemia after sudden withdrawal of iNO therapy have been described, precipitating cardiopulmonary collapse, even in patients without substantial oxygenation improvement. The patient should be treated with increased FiO₂ and/or by re-installment of therapy with iNO. Deterioration in oxygenation and elevation in PAP may also occur in neonate with no apparent response to iNO.