Providence HEALTH CARE	Department: **Respiratory Services**	Date Originated: December 1997 Date Reviewed/Revised: **May 2012**
CLINICAL GUIDELINE	Topic: Critical Care – Nitric Oxide Administration Protocol (Respiratory Therapy) Number: B-00-13-12013	Related Links: RTDM006, INOmax DS_{IR} RTDM013, Pre-Use Checkout RTDM014, INOblender

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APPLICABLE SITES:

St. Paul's Hospital

POLICY STATEMENT:

Nitric oxide gas may be administrated via inhalation upon receipt of a physician order in critical care areas which includes ICU, CSICU, CICU, ED, and the Cardiac Catheterization Lab.

ICU, CICU, ED:

- ICU Physician *only* may order nitric oxide

CSICU:

- Anaesthesia, Cardiac Surgeon, or ICU Physician may order nitric oxide

CARDIAC CATHETERIZATION LAB:

- Interventional Cardiologist may order nitric oxide for *diagnostic nitric challenge* purposes only

The gas concentrations of nitric oxide, nitrogen dioxide, and oxygen must be continuously analyzed for all patients receiving nitric oxide therapy.

INDICATIONS:

1. Acute Pulmonary Hypertension
2. Cardiac Transplantation
3. Post-operative Care for Newly Inserted Ventricular Assist Device (VAD)
4. Refractory Hypoxemia
5. Diagnostic Purposes
6. Sickle-Cell Anemia Crisis

CONTRAINDICATIONS:

1. Patients with know methemoglobin reductase deficiency, or a demonstrated intolerance to inhaled nitric oxide therapy resulting in elevated methemoglobin levels.
2. Inhaled nitric oxide may attenuate platelet aggregation, which could have an effect on bleeding times – whether this effect should be discussed when considering iNO therapy is unknown, as the effects of this phenomenon are highly variable and have not been consistently seen in healthy adults or patients with cardiopulmonary disease.

GENERAL INFORMATION:

1. Acute Pulmonary Hypertension:
- PAP_{MEAN} greater than 20 mmHg and/or PVR greater than 200 dyne/cm/s^{-5}
- Nitric oxide is a potent and selective pulmonary vasodilator
- Effects may be more variable and less pronounced with chronic hypertension, which may be due to varying degrees of vascular remodeling in the musculature of the pulmonary arteries
- Pulmonary hypertension in ARDS may be secondary to an inflammatory-mediated release of pulmonary vasoconstrictors, development of pulmonary microemboli, and localized areas of ventilation-perfusion mismatch

2. Cardiac Transplantation:
- Nitric oxide dosage and therapeutic goals are to be determined by the anesthetist
- PVR may be elevated post-transplant and may result in right ventricular failure, often a consequence of cardiopulmonary bypass due to ischemia and reperfusion injury, or resulting from recipient preoperative pulmonary hypertension

3. Ventricular Assist Device:
- Nitric oxide dosage and therapeutic goals are to be determined by the anesthetist
- LVAD function may be impaired in the presence of significant pulmonary hypertension resulting in inadequate left-sided VAD flow refractory to conventional treatment

4. Refractory Hypoxemia:
- PaO_2/FiO_2 less than 100
- Refractory hypoxemia that is unresponsive to other manipulations of mechanical ventilation
- Hypoxemia is aggravated by increased venous admixture in the lung due to perfusion of non-ventilated lung segments
- Systemic vasodilators may by enhance perfusion to non-ventilated alveoli and worsen shunt
- Nitric oxide may improve perfusion to ventilated alveoli and result in improved pulmonary blood flow and oxygenation
- The link between improved oxygenation that may be seen with nitric oxide administration has not been causatively linked to improved patient outcome

5. Diagnostic Purposes:
- Assess the reversibility of pulmonary artery hypertension

GUIDELINES:

Continuous administration of inhaled nitric oxide has been shown to demonstrate:

1. A time dependent dose-response relationship
2. Evidence of a plateau effect over time

As such, the optimal dose of inhaled nitric oxide should be determined by titration against a therapeutic target in each patient, and this target should, at minimum, be reevaluated daily.

NITRIC OXIDE ADMINISTRATION IN ICU/CICU/ED:

Use the lowest effective dose with the lowest possible FiO_2 for the shortest period of time.

Dose-Response:

- Start nitric oxide at a concentration of 10 ppm
- Nitric oxide concentration of 20 ppm may be administered if there is inadequate response at 10 ppm
- Decrease rapidly to 2 – 4 ppm while observing patient response
- Notify physician if the patient requires greater than 20 ppm
- No evidence that greater than 20 ppm NO has any further effect on oxygenation or PVR
- A different dose response is observed for enhanced ventilation-perfusion as compared to the required dose for a reduction in PAP
- Maximum response usually occurs with doses ≤ 10 ppm
- Combining iNO therapy with strategies to maximize alveolar recruitment (i.e. with HFOV and/or recruitment maneuvers) has been shown to improve the dose-response relationship of iNO

NITRIC OXIDE ADMINISTRATION IN CSICU:

Use the lowest effective dose with the lowest possible FiO_2 for the shortest period of time.

Dose-Response:

- Start nitric oxide at a relatively high concentration of 20 – 40 ppm or as per physician order
- Decrease rapidly to 2 – 4 ppm while observing patient response
- A different dose response is observed for enhanced ventilation-perfusion as compared to the required dose for a reduction in PAP
- No evidence that greater than 20 ppm nitric oxide has any further effect on oxygenation or PVR
- Maximum response usually occurs with doses less than or equal to 10 ppm

NITRIC OXIDE ADMINISTRATION IN THE CARDIAC CATHETERIZATION LAB:

Dose-Response:

- Refer to Nitric Oxide Diagnostic Challenge in the Cardiac Catheterization Lab

IDEAL TREATMENT GOALS:

Table 1. Comparison of Ideal Treatment Goals with Those Achieved by Inhaled Nitric Oxide in Adults with the Acute Respiratory Distress Syndrome (ARDS).

Ideal Treatment Goals	Physiological Effects of Inhaled Nitric Oxide
Improved oxygenation	20% Improvement in approximately 60% of patients for only 1 to 2 days in clinical trials, with no associated survival benefit[24,25]; may significantly improve oxygenation in very severe cases and buy time for the institution of other means of support
Decreased pulmonary vascular resistance	Selective pulmonary vasodilator of uncertain benefit in acute lung injury or ARDS characterized by mild pulmonary hypertension[26]; may have a supportive role in patients with acute right-sided heart failure, particularly in association with increased pulmonary vascular resistance and hypoxemia
Decreased pulmonary edema	May be influenced by effects on hemodynamics, inflammation, infection, and the alveolar-capillary membrane
Reduction or prevention of inflammation	Conflicting evidence of its antiinflammatory efficacy at multiple molecular and clinical levels
Cytoprotection	May contribute to the formation of cytotoxic reactive nitrogen species and reactive oxygen species, especially when administered with high concentrations of oxygen; conversely, may prevent the generation of reactive oxygen species by free iron and scavenge hydroxyl radicals[27]
Protection against infection	Direct antimicrobial effects,[28] but associated with an increased incidence of ventilator-associated pneumonia in one study[25]

WEANING NITRIC OXIDE:

- Wean nitric oxide concentration to less than 5 ppm
- Increase FiO_2 by 0.1 – 0.2 when the nitric oxide has been discontinued
- FiO_2 may be weaned back to previous level over 2 – 4 hours
- With ARDS, wean and discontinue the nitric oxide when the FiO_2 is less than or equal to 0.40 with the PEEP less than or equal to 10 cmH_2O
- A rebound effect may occur which may be due to decreased production of *endogenous* nitric oxide when *exogenous* nitric oxide is delivered, and may result in an increased PVR and/or decreased oxygenation when nitric oxide is discontinued; this effect can be mitigated by gradually reducing iNO concentrations (avoiding rapidly reducing or discontinuing therapy), discontinuing therapy after tolerance to low levels of iNO is observed (less than 5 ppm), and titrating iNO to a therapeutic target (avoiding longer term iNO therapy which may exacerbate rebound effect).

SPECIAL CONSIDERATIONS:

1. **NO, NO_2, O_2 Analysis:**
   - An analyzer for nitric oxide, nitrogen dioxide, and oxygen gas must be used at all times
   - Physician must be notified if concentration of NO_2 greater than or equal to 2 ppm

2. **Transports:**
   - Nitric oxide is unavailable for use during transports or transfers between areas
   - In these situations the patient will be ventilated with 100% oxygen until:
     a) The transport is complete and the nitric oxide therapy can be resumed at the patient's bedside
     or
     b) The patient is at the receiving destination (i.e. Radiology) at which point nitric oxide can be resumed temporarily for the duration of the procedure

3. **Methemoglobin:**
   - MetHb measurements must be taken within 4 hours of initiating therapy, and every 12 hours thereafter for duration of therapy
   - Physician must be notified if MetHb greater than or equal to 2%
   - Nitric oxide binds rapidly with Hb and forms MetHb
   - Symptoms of hypoxemia may result when MetHb levels increase, as MetHb is incapable of transporting oxygen
   - Half-life of MetHb is 15 – 20 hours

METHODS OF ADMINISTRATION OF NITRIC OXIDE:

Nitric oxide may be administered using the following breathing systems:

1. **Invasive:**
   - Critical care ventilator
   - High frequency oscillator

2. **Noninvasive/Spontaneous:**
   - Spontaneous breathing with non-vented mask (Nitric challenge)
   - High-flow nasal cannula (Optiflow)
   - NIV via ventilator and non-vented face mask

NOTE: *Nitric oxide should **NOT** be used with the Vision Bipap system or other single-lumen breathing systems with bidirectional flow, as over-dosing of nitric oxide or interruption of drug delivery to the patient may occur.*

Refer to RTDM006 – INOmax DS_{IR} (Delivery System) for diagrams and additional information on methods of administration.

NITRIC OXIDE DELIVERY USING THE INOMAX DS_{IR} SYSTEM:

The INOmax DS_{IR} delivery system delivers nitric oxide gas into the inspiratory limb of the ventilator through an injector module, which allows for synchronized and proportional dosing based on flow. The INOmax DS_{IR} aspirates gas from the breathing circuit which may affect flow-trigger sensitivity. The trigger sensitivity may need to be adjusted to a higher threshold, or changed to pressure-trigger.

A system purge MUST be performed prior to use as part of the pre-use checkout. If the INOmax DS_{IR} is NOT going to be used on a patient within 10 minutes of the purge,

depressurize the regulator supply line – a depressurized supply line does not need to be re-purged unless 12 hours have elapsed since the initial purge. If the INOmax DS_{IR} is NOT USED and HAS REMAINED pressurized for more than 10 minutes, the purge procedure MUST be repeated. This is necessary to clear the circuit of any nitrogen dioxide which may have formed.

The addition of nitric oxide to the circuit will have a dilution effect. Depending on nitric oxide concentration and flow, the addition of NO to the circuit may dilute the delivered oxygen concentration by up to 10%, therefore iNO should NOT be administered with 21% oxygen.

A low calibration must be completed every 12 hours while nitric oxide is being administered; this can be done without interrupting the delivery of nitric oxide while the injector module is still inline. A high calibration must be performed at minimum once per month.

For more information and specific instructions for the INOmax DS_{IR} refer to the following documents in the online manuals:

RTDM006 – INOmax DS_{IR} (Delivery System)
RTDM013 – INOmax DS_{IR} & INOblender Pre-use Checkout
RTDM014 - INOblender

REFERENCES:

1. Griffiths MJ, Evans TW. *Inhaled nitric oxide therapy in adults.* NEJM 2005; 353(25): 2683-95.
2. Germann P, Ullrich R, et al. *Inhaled nitric oxide therapy in adults: European expert recommendations.* Intensive Care Med 2005; 31:1029-1041.
3. Chien-Wei Hsu, et al. *The initial response to inhaled nitric oxide treatment for intensive care unit patients with acute respiratory distress syndrome.* Respiration 2008; 75: 288-295.