### Inclusion Criteria
- Patients meeting criteria* to initiate iNO with one or more of the following:
  - Pulmonary hypertension
  - Low cardiac output syndrome
  - Persistent hypoxemia

*See policy on CHILD for details (for SCH only)

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## iNO Usage and Weaning

### iNO for Pulmonary Hypertension and/or Low Cardiac Output Syndrome

- NICU iNO Usage
- NICU iNO Wean Challenge
- iNO for Hypoxemia
- iNO Wean for Hypoxemia

## Appendix

- Summary of Findings
- Evidence Syntheses Statements (ESS), p1
- ESS, p2
- ESS, p3

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For questions concerning this pathway, contact: CSWINOPathway@seattlechildrens.org

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Inhaled Nitric Oxide (iNO) Pathway v1.0: iNO for Pulmonary Hypertension and/or Low Cardiac Output Syndrome

Inclusion Criteria
- Patients meeting criteria* to initiate iNO with either
  - Pulmonary hypertension
  - Low cardiac output syndrome
*See policy on CHILD for details (for SCH only)

Evaluate for response in discussion with CICU attending using the following criteria:
1. Capillary refill time decrease
2. Blood pressure increase by SBP = 10mmHg
3. Lactate decrease by = 1
4. MvO₂ saturation increase by = 10%
5. Heart rate decrease by = 10 bpm from baseline
6. CVP decrease by = 2mm Hg
7. Oxygenation (PaO₂) increase by >20 mmHg
8. Measured Pap decrease by = 2mmHg (if PA catheter in place)
   Or
   Echocardiographic evidence of improved RV/PA pressure

Has patient shown clinical response by above set criteria?
- Yes
- No

Wean iNO by 50% q1 hour until 5ppm, then by 1ppm q1 hour until discontinued
- *See policy on CHILD for details (for SCH only)

Weaning failure for 2V patient

Weaning failure for 1V patient

Weaning failure for 2V patient (any 1 of the following):
- CVP increase >5mmHg
- PaO₂ decrease >20 mmHg
- PaO₂ <60 mmHg
- SpO₂ <92%
- Clinical deterioration (worsening capillary refill, liver distention, lactate, blood pressure, MVO₂ saturation, tachycardia)

Weaning failure for 1V patient (any 1 of the following):
- PAP/CVP increase >2mmHg
- PaO₂ decrease >20 mmHg
- PaO₂ < 30 mmHg
- SpO₂ <75%
- Clinical deterioration (worsening capillary refill, liver distention, lactate, blood pressure, MVO₂ saturation, tachycardia)

Consider alternate pulmonary vasodilator therapies:
Sildenafil 0.4mg/kg enterally x 1 dose 60 minutes prior to repeat iNO discontinuation attempt

- If multiple failures at weaning attempts are noted provider may choose to discontinue the weaning protocol via order placed in the patient’s electronic medical record (EMR)
- Obtain pulmonary hypertension service consult if patient on iNO > 48 hours

Discontinue iNO therapy

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Inhaled Nitric Oxide (iNO) Pathway v1.0: NICU iNO Usage

**Inclusion Criteria**
- Patients meeting criteria* to initiate iNO with either
  - Pulmonary hypertension
  - Low cardiac output syndrome

*See policy on CHILD for details (for SCH only)

**iNO Responses**
- **Positive**
  - ↑ PaO₂ ≥ 10mmHg or ≥ SpO₂ by 5% and/or resolution of pre/post-ductal difference
  - Consider follow-up echocardiogram to assess improvement in ductal/atrial level shunting, right ventricular function, septal flattening or other measures of PPHN
- **Negative**
  - Either no change in PaO₂ (10mmHg) or SpO₂ (5%) and/or unchanged evidence of PPHN on follow-up echocardiogram

- **Q4 Hours**
  - Evaluate patient’s response
  - FiO₂ ≤ 0.4 and respiratory care remains stable?
    - Yes: Continue to Wean Challenge regardless of FiO₂
    - No: Has it been > 96 hours since starting iNO in NICU?
      - Yes: Consult Cardiology PHTN service, if appropriate
      - No: Continue iNO at 20ppm and monitor clinical indicators

- **Implementation Wean Challenge**
  - Discontinue iNO
  - Off Pathway

**Stop and Review**

For questions concerning this pathway, contact: CSWNOPathway@seattlechildrens.org
Inhaled Nitric Oxide (iNO) Pathway v1.0: NICU iNO Wean Challenge

**NICU Wean Challenge**
Decrease iNO from 20-10 ppm and hold for 2-4 hours to ensure patient maintains in Wean Response Criteria

Reduce iNO to 5 ppm, continue iNO and reassess clinical indicators within 1-2 hours

**Patient response at 5 ppm**

Positive
- Decrease iNO by 1 ppm every 1-2 hours
  - Within 2 hours
    - Patient response
      - Positive
        - Return to 10 ppm and re-challenge dose of 5 ppm within 4 hours
        - Within 4 hours
          - Patient response at 5 ppm
            - Positive
              - Return to previous ppm and assess patient in 4 hours
            - Negative
              - Number of negative response from 10 ppm to 5 ppm
                - ≥ 3 failed attempts
                  - Consult Cardiology PHTN service if appropriate
                - < 3 failed attempts
                  - Negative
                    - 4 hours
                      - Positive
                        - Patient off iNO?
                          - Yes
                            - Off Pathway
                          - No
                            - Decrease iNO by 1 ppm within 1-2 hours. Patient assessment in 4 hours until iNO is D/C’d

Negative
- Increase iNO by 1 ppm within 1-2 hours
  - Within 4 hours
    - Patient response at 5 ppm
      - Positive
        - Return to previous ppm and assess patient in 4 hours
      - Negative
        - Number of negative response from 10 ppm to 5 ppm
          - ≥ 3 failed attempts
            - Consult Cardiology PHTN service if appropriate
          - < 3 failed attempts
            - Decrease iNO by 1 ppm within 1-2 hours. Patient assessment in 4 hours until iNO is D/C’d

**Wean Response Criteria**
- FiO₂ ≤ 0.4 and respiratory care remains stable?
- Optimal Lung inflation
- SpO₂ stable
- Hemodynamically Stable

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Inhaled Nitric Oxide (iNO) Pathway v1.0: iNO for Hypoxemia

**Inclusion Criteria**
Patients meeting criteria* to initiate iNO with
- \( \text{SpO}_2 < 85\% \) on \( \text{FiO}_2 \geq 80\% \) despite
- Ventilator adjustment
- Neuromuscular blockade trial
- Prone positioning if patient is an appropriate candidate
OR
- Hypoxemia with evidence of right heart dysfunction

*See policy on CHILD for details (for SCH only)

**Trial of iNO**
20 ppm x 30 minutes

**Patient response**

- Positive
  - \( \text{SpO}_2 \) increases by \( \geq 10\% \)*
  - *absolute value
  - Attempt weaning

- Negative/None
  - Discontinue iNO

- Stop and Review

**Return to Table of Contents**
Inhaled Nitric Oxide (iNO) Pathway v1.0: iNO Wean for Hypoxemia

**Wean FiO2 Before iNO**
Decrease FiO2 Q30 minutes for goal SpO2 90-92%

**Candidacy for Trial of iNO Weaning**
Decrease iNO when SpO2 > 90% and FiO2 ≤ 60% for 4 hours

- Decrease iNO incrementally every 4 hours based on patient response
- Recommended increments: 20→10→5→4→3→2→1→off

**Patient response**

**Success**
Goal SpO2 maintained at FiO2 ≤ 60% for each incremental wean

- Continue weaning iNO to off Q4 hours

**Failure**
FiO2 > 60% to maintain SpO2

- Return iNO to last effective dose
- Assess for weaning again in 4 hours

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For questions concerning this pathway, contact: CSWINOPathway@seattlechildrens.org

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## Summary of Findings

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Level of evidence</th>
<th>Search strategy</th>
<th>Population</th>
<th>Setting</th>
<th>Data extraction</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcome</th>
<th>Duration of follow-up</th>
<th>Results</th>
<th>Number of Participants</th>
<th>Number of studies</th>
<th>GRADE score</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. Graham, P. Olander, J. Weertman, A. Altmann</td>
<td>2016</td>
<td>RCTs</td>
<td>Cochrane, Medline, Embase, CDSR, N大纲, WHOI, DMB</td>
<td>Adults and children with Acute Respiratory Distress Syndrome (ARDS): Rescuing lives of any age and duration. Observations were a permitted if they were administered to both groups.</td>
<td>Intensive care units, worldwide</td>
<td>Two review authors independently abstracted data and reached disagreements by discussion.</td>
<td>Standard care</td>
<td>Standard care</td>
<td>Intervention: 2-4 days, up to day 20</td>
<td>MD: 0.87 (95% CI: 0.80 to 0.94)</td>
<td>804</td>
<td>3</td>
<td>+4 High</td>
<td></td>
</tr>
<tr>
<td>W. Sando, S. Oms, F. Amsden, F. Prabhu, S. L. Rees, C. J. Burt, D. A. Harmer</td>
<td>2018</td>
<td>RCTs</td>
<td>Cochrane Central Register of Controlled Trials (CENTRAL), Embase, and MEDLINE for RCTs</td>
<td>Cardiac surgery population (adult or pediatric), treatment with IV or vs some comparator, at least one relevant outcome (ICU LOS, duration of mechanical ventilation, mortality, discasefree survival)</td>
<td>Operating rooms and intensive care units</td>
<td>Two authors with a third as the referee, additional data queried if not present in paper</td>
<td>Standard care</td>
<td>Comparator</td>
<td>Duration of mechanical ventilation: 12 vs 18 hours</td>
<td>RR: 0.80 (95% CI: 0.67 to 0.95)</td>
<td>805</td>
<td>2</td>
<td>+4 High</td>
<td></td>
</tr>
<tr>
<td>M. Ricceri, I. Gros, F. T. Barbosa</td>
<td>2016</td>
<td>RCTs</td>
<td>CENTRAL, the Cochrane Library, MEDLINE, Embase</td>
<td>Children age 1 to 15 years with CVS: General surgery complicated by pulmonary hypertension</td>
<td>2 reviewers</td>
<td>Standard management of pulmonary hypertension: No difference</td>
<td>MD: 1.09 (95% CI: 0.92 to 1.30)</td>
<td>210</td>
<td></td>
<td></td>
<td></td>
<td>4</td>
<td>+1 Very Low</td>
<td></td>
</tr>
</tbody>
</table>
Evidence Synthesis Statements (ESS)

Clinical Question #1: Is iNO beneficial for Postop Cardiac Transplant Patients?

Evidence Synthesis Statement
No evidence that answered this clinical question was found

Clinical Question #2: Is iNO beneficial for postop congenital heart disease patients with pulmonary hypertension, reactive pulmonary vasculature or low systemic O2 saturations?

Evidence Synthesis Statement
Sardo (2018) compared compared iNO (4-40 ppm) vs. various comparators (Standard care (5 studies), Milrinone (3 studies), Iloprost (3 studies), 1-PGE-1 (1 study), 2-Nitroprusside (1 study), 1-PGI2 (1 study), 2 intravenous vasodilators (1 study), oxygen (1 study)).

Outcome: ICU length of stay. A systematic review of 9 RCTs totaling 560 adult or pediatric cardiac surgery patients compared iNO (4-40 ppm) vs. comparator (see above). The setting was operating rooms and intensive care units. The intervention was favored [Mean difference (MD), -0.38 days (95%: CI -0.65 to -0.11)]. [Level of Evidence: +3 Moderate quality (Sardo, Osawa, Finco 2018)]

Outcome: Mechanical ventilation duration. A systematic review of 11 RCTs totaling 596 adult or pediatric cardiac surgery patients compared treatment with iNO (4-40 ppm) vs. comparator (see above). The setting was operating rooms and intensive care units. The intervention was favored. [MD, -4.81 hours (95% CI: -7.79 to -1.83)] [Level of Evidence: +2 Low quality (Sardo, Osawa, Finco 2018)]

Outcome: Mortality. Inhaled Nitric Oxide (4-40 ppm) was compared to 1-PGI2 (1 study); 1-PGE-1 (2 studies); oxygen (1 study); placebo (2 studies); standard care (1 study); and Iloprost (1 study) (n = 569 participants) to evaluate mortality over the longest follow-up follow-up period. There was no difference (3.9%) between groups [event rates 3.4% versus 3.7%, OR 1.33 (95% CI: 0.52 to 3.39)]. The study is powered to 3.9% (alpha = 0.05) which means that if a significant difference between the intervention and control existed, there is a 96.1% chance the study failed to detect it. An absolute risk difference of 1% (95% CI: -2 to 7) means that there will be between 20 fewer and 70 excess cases of mortality per 1000 subjects receiving the intervention. This assumes a control group risk of 3.4%. This outcome is downgraded for the following reasons: The study is underpowered (type II error) and the CI includes both appreciable harm and benefit. (RR < 0.75 or > 1.25) [Level of Evidence: +2 Low certainty (Sardo 2018)].

Outcome: Mortality. A systematic review of 4 RCTs totaling 210 infants and children (age range: 1 day to 17 years) with CHD requiring surgery complicated by pulmonary hypertension in the post-operative period compared iNO (Intervention) vs. placebo and/or conventional management (Comparator). There was no difference between groups [OR, 1.67 (95% CI: 0.38 to 7.3)]. [Level of Evidence: +1 Very low quality (Bizarro, Gross, Barbosa 2014)]

Outcome: Number of pulmonary hypertensive crises. A systematic review of 4 RCTs totaling 210 patients infants and children with CHD requiring surgery complicated by pulmonary hypertension in the post-operative period compared iNO (Intervention) with placebo and/or conventional management (Comparator). There was no difference between groups [OR, 0.8 95% CI (0.15-4.18)]. [Level of Evidence: +1 Very low quality (Bizarro, Gross, Barbosa 2014)]
Evidence Synthesis Statements (ESS) p2

Clinical Question #3: Is iNO beneficial for patients with heart failure without VAD (Ventricular Assist Device)?

Evidence Synthesis Statement:
No evidence that answered this clinical question was found.

Clinical Question #4: Is iNO useful for patients with severe ARDS/AHRF/ALI to avoid the use of ECMO?

Outcome: Ventilator free days over a 30-day follow-up period. A systematic review of 5 RCTs totaling 804 adults and children with ARDS compared iNO (any dose or duration) (intervention) with standard care (comparator). Co-interventions were permitted if they were administered to both groups. The setting was intensive care units, worldwide. There was no difference between groups [MD -0.57 (95% CI: -1.82 to 0.69)] [Level of Evidence: +4 High quality (Karam 2016)]

Outcome: Oxygenation Index over a 24 hour follow-up period. A systematic review of 5 RCTs totaling 368 adults and children with ARDS compared iNO (intervention) with standard care (comparator). Co-interventions were permitted if they were administered to both groups. The setting was intensive care units, worldwide. The intervention was favored [MD -2.31 (95% CI: -2.73 to -1.89)]. Two studies reported no statistically significant difference at 48 hours and two studies reported statistically significant differences at 72 hours. [Level of Evidence: +3 Moderate quality (Karam 2016)]

Outcome: Overall Mortality. Inhaled Nitric Oxide (1-80 ppm) was compared to control in 13 RCTs (n = 1243 participants) to evaluate mortality over the longest follow-up period. There was no difference between groups [event rates 37.52% versus 38.23%, RR 1.04 (95% CI: 0.9 to 1.19)]. The study is powered to 4.4% (alpha = 0.05) which means that if a significant difference between the intervention and control existed, there is a 95.6% chance the study failed to detect it. An absolute risk difference of 1.51% (95% CI: -3.75 to 7.13) means that there will be between 38 fewer and 71 excess cases of mortality per 1000 subjects receiving the intervention. This outcome is downgraded for the following reasons: The study is underpowered (type II error); the width of the pooled effect diamond may be wider than the truth. [Level of Evidence: +3 Moderate certainty (Gebistorf 2016)]

Outcome: Renal impairment defined as new renal replacement therapy ± new increase in creatinine over the duration of the inpatient stay. Inhaled Nitric Oxide (1-80 ppm, up to 28 days) was compared to control in 4 RCTs (n = 945 participants) to evaluate renal impairment (new renal replacement therapy ± new raised creatinine concentration (> 300 ?mol/L) or creatinine concentration > 177 ?mol/L or >= 265 ?mol/L over the duration of therapy. The comparator was favored [event rates 11.54% versus 18.09%, RR 1.59 (95% CI: 1.17 to 2.16)]. An absolute risk difference of 6.81% (95% CI: 1.96 to 13.38) means that there will be between 20 and 134 excess cases of renal impairment per 1000 subjects in the group receiving iNO compared to the group receiving control. The NNTH is 15 (95% CI: 7 to 51). Assuming a control group event rate of 11.54%, for every 7 to 51 patients given iNO instead of control one additional patient would experience renal impairment. Note that this confidence interval does not incorporate uncertainty around the control group risk. These absolute effects would occur over the duration of therapy. [Level of Evidence: +4 High certainty (Karam 2016)].
Clinical Question #5: Is iNO beneficial for trialing patients off ECMO?

Evidence Synthesis Statement:
No evidence that answered this clinical question was found.
Summary of Version Changes

- **Version 1.0 (11/17/2020):** Go live.
Approved by the CSW iNO Pathway team for November 17, 2020, go-live

CSW iNO Pathway Team:

Critical Care, Owner
Respiratory Care, Team Member
Respiratory Care, Team Member
Respiratory Care, Team Member
PICU, Team Member
PICU, Team Member
Neonatology, Team Member
Quality and Safety, Stakeholder

Monique Radman, MD, MAS
Dave Crotwell, RRT
Robert diBlasi, RRT
Gulroop Gill, RT
Silvia Hartmann, MD
John McGuire, MD
Robert DiGeronimo, MD
Paul Sharek, MD

Clinical Effectiveness Team:

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Project Manager
Data Analyst
Librarian
Program Coordinator

Darren Migita, MD
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John Salyer
Sue Groshong, MLIS
Ivan Meyer, PMP

Clinical Effectiveness Leadership:

Medical Director
Operations Director

Darren Migita, MD
Jaleh Shafii, MS, RN, CPHQ

Retrieval Website: [https://www.seattlechildrens.org/pdf/iNO-pathway.pdf](https://www.seattlechildrens.org/pdf/iNO-pathway.pdf)

Please cite as:
Evidence Ratings

This pathway was developed through local consensus based on published evidence and expert opinion as part of Clinical Standard Work at Seattle Children’s. Pathway teams include representatives from Medical, Subspecialty, and/or Surgical Services, Nursing, Pharmacy, Clinical Effectiveness, and other services as appropriate.

When possible, we used the GRADE method of rating evidence quality. Evidence is first assessed as to whether it is from randomized trial or cohort studies. The rating is then adjusted in the following manner (from: Guyatt G et al. J Clin Epidemiol. 2011;4:383-94, Hultcrantz M et al. J Clin Epidemiol. 2017;87:4-13.):

Quality ratings are *downgraded* if studies:
- Have serious limitations
- Have inconsistent results
- If evidence does not directly address clinical questions
- If estimates are imprecise OR
- If it is felt that there is substantial publication bias

Quality ratings are *upgraded* if it is felt that:
- The effect size is large
- If studies are designed in a way that confounding would likely underreport the magnitude of the effect OR
- If a dose-response gradient is evident

**Certainty of Evidence**
- ☄️ ★★★ High: The authors have a lot of confidence that the true effect is similar to the estimated effect
- ☄️ ★★★ Moderate: The authors believe that the true effect is probably close to the estimated effect
- ☄️ ★★★ Low: The true effect might be markedly different from the estimated effect
- ☄️ ★★★ Very low: The true effect is probably markedly different from the estimated effect

Guideline: Recommendation is from a published guideline that used methodology deemed acceptable by the team
Expert Opinion: Based on available evidence that does not meet GRADE criteria (for example, case-control studies)
Literature Search Methods
A literature search was conducted in January 2019. The search targeted synthesized literature on nitric oxide for 2009 to current and limited to English and humans. The search was executed in Ovid Medline, Embase, Cochrane Database of Systematic Reviews (CDSR) and Turning Research into Practice (TRIP) databases. Two reviewers independently screened abstracts and included guidelines and systematic reviews that addressed optimal diagnosis, treatment, and prognosis of patients who meet pathway inclusion/exclusion criteria. One reviewer extracted data and a second reviewer quality checked the results. Differences were resolved by consensus.

Literature Search Results
The search retrieved 672 records. Once duplicates had been removed, we had a total of 621 records. We excluded 600 records based on titles and abstracts. We obtained the full text of the remaining 21 records and excluded 18. We included 3 studies. The flow diagram summarizes the study selection process.

Flow diagram adapted from Moher D et al. BMJ 2009;339:bmj.b2535
Included Studies
Medical Disclaimer

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required.

The authors have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication.

However, in view of the possibility of human error or changes in medical sciences, neither the authors nor Seattle Children’s Healthcare System nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they are not responsible for any errors or omissions or for the results obtained from the use of such information.

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