Epoprostenol Inhaled – Neonatal/Pediatric/Adult – Inpatient Clinical Practice Guideline

Table of Contents

Note: Active Table of Contents Click to follow link

CPG Contact for Content:
Name: Cindy Gaston, PharmD, BCPS – Department of Pharmacy
Phone Number: (608) 265-8161
Email Address: cgaston@uwhealth.org

CPG Contact for Changes:
Name: Philip Trapskin, PharmD, BCPS – Drug Policy Program Manager, Department of Pharmacy
Phone Number: (608) 263-1328
Email Address: ptrapskin@uwhealth.org

Guideline Update Author:
Cindy Gaston, PharmD, BCPS

Coordinating Team Members:
Cindy Gaston, PharmD, BCPS

Review Individuals/Bodies:
J. Runo, MD, Department of Medicine – Pulmonary; J. Wells, MD, Department of Medicine – Pulmonary; J. Limjoco, MD, Department of Pediatrics – Neonatology; Paula Breihan, RRT, Respiratory Therapy; Kristine Ostrander, MA, RRT; Katie Willenborg, PharmD, Department of Pharmacy; Department of Pharmacy; Rhonda Yngsdal-Krenz, RRT

Committee Approvals/Dates:
Pharmacy & Therapeutic Committee

Release Date:
July 2015

Next Review Date:
July 2018

Executive Summary

Guideline Overview

Guidance is provided for appropriate indications, dosing, titration, and tapering of inhaled epoprostenol in adult, pediatric and neonatal patients.

Key Practice Recommendations

Adult Patients

1. **Acute Respiratory Distress Syndrome**
   - Initiate at a dose of 0.05 mcg/kg/min via continuous nebulization. Doses higher than 0.05 mcg/kg/min have not been studied in ARDS. (Class IIb, Level C)
   - The duration of therapy is dependent upon the clinical response observed. If no response is noted in 4 hours, wean off the inhaled epoprostenol. (Class IIb, Level C)
   - The dose of epoprostenol should be decreased by 0.01 mcg/kg/min every 2 hours as tolerated by the patient when weaning off therapy. (Class IIb, Level C)

2. **Pulmonary Hypertension, Right Heart Failure Following Pulmonary Embolism, Severe Right Heart Failure**
   - Inhaled epoprostenol therapy may be considered for patients with refractory hypoxemia and mean pulmonary artery pressure >30 mmHg, PaO_2/FiO_2 <150 mmHg, or cardiac index less than 2.2 L/min/m^2. (Class IIb, Level C)
     - Initiate at a dose of 0.01 mcg/kg/min. (Class IIb, Level C)
     - The dose of epoprostenol may be titrated up by 0.01 mcg/kg/min every two hours to a maximum of 0.05 mcg/kg/min. (Class IIb, Level C)
   - The duration of therapy is dependent upon the clinical response observed. If no response is noted in 4 hours, weaning off inhaled epoprostenol is reasonable. (Class IIb, Level C)
     - Consider decreasing the dose of epoprostenol by 0.01 mcg/kg/min every 2 hours as tolerated until weaned off. (Class IIb, Level C)

3. **Post Cardiac Surgery Patients**
   - Administer inhaled epoprostenol to intubated cardiac surgery patients or patients on continuous BiPAP with refractory hypoxemia. For patients on BiPAP weigh the benefit of epoprostenol therapy with the risk of rebound pulmonary hypertension if therapy is interrupted accidentally by removal of the BiPAP mask. (Class IIb, Level C)
   - It is reasonable to initiate dosing at 0.03 mcg/kg/min. Doses higher than 0.03 mcg/kg/min have not been studied in this population. (Class IIb Level C)
   - The dose of epoprostenol may be decreased by 0.01 mcg/kg/min every 2 hours as tolerated by the patient. (Class IIb, Level C)
   - The duration of therapy is dependent upon the clinical response observed. If no response is noted in 4 hours, weaning off inhaled epoprostenol is reasonable. (Class IIb, Level C)

Pediatric Patients

4. **Acute Respiratory Distress Syndrome**
   - Inhaled epoprostenol therapy may be considered for patients with refractory hypoxemia associated with ARDS. (Class IIb, Level B)
     - Consider initiating doses at 0.03 mcg/kg/min via continuous nebulization. (Class IIb, Level B)
     - The dose of epoprostenol can be increased to 0.05 mcg/kg/min if the patient does not respond to the initial dose. (Class IIb, Level B)
     - The dose of epoprostenol can be decreased by 0.01 mcg/kg/min every 2 hours as tolerated by the patient. (Class IIb, Level C)

5. **Primary and Secondary Pulmonary Hypertension**
   - Maximize other therapies to improve oxygenation (i.e., F_iO_2, PEEP, and hemodynamics) before initiating inhaled epoprostenol therapy. (Class I, Level C)

- Inhaled epoprostenol therapy can be considered for patients with refractory hypoxemia. (Class IIb, Level C)
  - Consider initiating dose at 0.03 mcg/kg/min via continuous nebulization. (Class IIb, Level B)
  - The dose of epoprostenol can be increased to 0.05 mcg/kg/min if the patient does not respond to the initial dose. (Class IIb, Level B)
  - The dose of epoprostenol can be decreased by 0.01 mcg/kg/min every 2 hours as tolerated by the patient. (Class IIb, Level C)
- The duration of therapy is dependent upon the clinical response observed. If no response is noted in 4 hours, weaning off inhaled epoprostenol is reasonable. (Class IIb, Level C)

Neonate Patients

6. Inhaled epoprostenol may improve oxygenation in hypoxemia neonates when all other therapies to improve oxygenation have failed. (Class I, Level B)
   - Initial doses of 0.03 mcg/kg/min are recommended and can be titrated up to 0.05 mcg/kg/min if necessary. (Class I, Level C)
   - It is reasonable to discontinue therapy by decreasing the dose 0.01 mcg/kg/min every 2 hours as tolerated. (Class IIa, Level C)

General Recommendations for Treatment

7. Do not administer epoprostenol to patients with:
   - Allergy or sensitivity to epoprostenol or glycine diluent (Class III, Level C)
   - Cardiac failure secondary to left ventricular dysfunction (Class III, Level C)

8. Avoid use or use cautiously in patients with active and significant bleeding (Class IIb, Level C)

9. Epoprostenol is a pregnancy class B drug Inhaled epoprostenol should be used with caution in pregnant women. (Class I, Level C)

10. Wean patients off epoprostenol; abrupt withdrawal can result in rebound pulmonary hypertension. (Class IIa, Level B)

Monitoring Parameters

11. Vital signs including blood pressure, heart rate, and oxygen saturation every 15 minutes for one hour during the first hour of treatment and after each dose change, then every hour thereafter. (Class I, Level C)
    - Hemodynamic monitoring may include the following based on the patients condition and comorbidities: central venous pressure (CVP), echocardiography, ultrasound, cardiac index (CI), peripheral vascular resistance, total pulmonary resistance, mean pulmonary artery pressure, and stroke volume but is not required (Class I, Level C)

12. Monitor for symptoms of epoprostenol toxicity: jaw pain, headache, flushing, nausea, vomiting, diarrhea, abdominal pain, signs of bleeding, bronchoconstriction or hypotension. (Class I, Level C)

Companion Documents

1. Epoprostenol Intravenous – Adult- Inpatient Clinical Practice Guideline
2. Order set – IP- Inhaled Epoprostenol – Procedure [2234]

Pertinent UWHC Policies & Procedures

1. UW Health Respiratory Manual Policy 3.51 Inhaled Epoprostenol

Patient Resources: none

Scope

Disease/Condition(s):

Adults - pulmonary hypertension, acute respiratory distress syndrome (ARDS), right heart failure following pulmonary embolism, and severe right heart dysfunction

Pediatrics/Neonates – pulmonary hypertension, ARDS

Clinical Specialty & Intended Users:

Pulmonary, Critical Care, physicians, mid-level providers, nurses, pharmacists, respiratory therapist

Major Outcomes Considered:

Safe and effective administration of inhaled epoprostenol.

Guideline Metrics:

Evaluate Adverse Drug Events in the Healthcare Event Reporting Online (HERO) reporting system for errors in administration of patient harm with inhaled epoprostenol.

Methodology

Rating Scheme for the Strength of the Recommendations:

A modified Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system developed by the American Heart Association and the American College of Cardiology Foundation has been used to assess the Quality and Strength of the evidence in this Clinical Practice Guideline.[1] (Appendix A).

A PUBMED, Cochrane Library and International Pharmaceutical Abstracts were searched using the terms inhaled or aerosolized, epoprostenol or prostacyclin, acute respiratory distress syndrome.

Cost Analysis:

The UW Health cost for epoprostenol for an 80 kg patient at a dose of 0.05 mcg/kg/min is approximately $450 per 24 hours, whereas cost for inhaled nitric oxide is approximately $3600 per 24 hours.

A small single center trial compared safety and efficacy of inhaled epoprostenol and inhaled nitric oxide for hypoxic respiratory failure in adult intensive care patients (ICU).[2] There was no difference in duration of therapy, mechanical ventilation, length of stay in the ICU, or duration hospitalization. However, the cost of therapy was 4.5 to 17 times higher for inhaled nitric oxide (depending on contract pricing).

Definitions

1. Pulmonary hypertension – is characterized by increased pulmonary arterial pressure and secondary right-sided heart failure and is defined as a mean pulmonary artery pressure ≥25 mmHg with a pulmonary capillary wedge pressure ≤15 mm Hg.[3] Pulmonary hypertension is divided in to five sub-categories:[4]
    - 1.1. Primary pulmonary hypertension
    - 1.2. Pulmonary hypertension due to left-sided heart failure
    - 1.3. Pulmonary hypertension associated with hypoxemia
    - 1.4. Pulmonary hypertension associated with thromboembolic disease
    - 1.5. Pulmonary hypertension associated with disorders affecting the pulmonary vasculature

2. Acute respiratory distress syndrome –
   Berlin definition of acute respiratory distress syndrome in adults[5]

Timing	Within 1 week of known clinical insult or new or worsening respiratory symptoms
Chest imaging	Bilateral opacities – not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload
Oxygenation Mild	 200 mmHg < PaO_2/FIO_2 ≤ 300 mmHg with PEEP or CPAP ≥ 5 cm H_2O
Moderate	100 mmHg < PaO_2/FIO_2 ≤ 200 mmHg with PEEP ≥ 5 cm H_2O
Severe	PaO_2/FIO_2 ≤ 100 mmHg with PEEP ≥ 5 cm H2O
CPAP – continuous positive airway pressure; FIO_2- fraction of inspired oxygen; PaO_2 – partial pressure of oxygen; PEEP – positive end-expiratory pressure	

3. Prostacyclin – an endogenous prostaglandin that inhibits platelet function and is a vasodilator
4. Epoprostenol – a synthetic prostacyclin
5. Microgram to nanogram conversion: 0.01 mcg/kg/min is equal to 10 ng/kg/min

Introduction

The mortality of ARDS is approximately 30 – 40%, but can be reduced by therapeutic interventions.[6-8] The pathophysiology of ARDS includes vasoconstriction and direct administration of vasodilators via the airway to improve pulmonary gas exchange is an accepted treatment.[9, 10] Nitric oxide (NO) has been the most studied inhaled vasodilator, but the small trials conducted have not demonstrated a decrease in mortality .[11-17] Nitric oxide activates guanylyl cyclase to increase cyclic-guanine monophosphate in vascular smooth muscle cells producing relaxation. Nitric oxide is efficacious in improving surrogate markers of oxygenation but, it does not improve survival near term or long term.[18] Alternatives have been explored secondary to nitric oxide's potential side effects and its high cost. Inhaled prostacyclins are the most widely studied alternative in adult and pediatric patients to NO. Inhaled prostacyclin produces similar changes in oxygenation and pulmonary artery pressure as NO.[19] Prostacyclins have been studied in mechanically ventilated patients and in patients on biphasic positive airway pressure (BiPAP) therapy.[20, 21] Prostacyclins cause an increased activity of the adenylate cyclase enzyme that causes a compensatory increase in intracellular cyclic adenosine monophosphate levels. Through a series of reactions including increased potassium conductance, blockage of calcium channels, and a decrease in cytosolic calcium, epoprostenol causes smooth muscles to relax which leads to vasodilation. Vasodilation improves oxygenation by allowing blood to flow into areas of the lung that are better ventilated, thus improving oxygenation of the blood.[22]

Epoprostenol is administered intravenously for the treatment of pulmonary hypertension (UW Health Epoprostenol by Intravenous Infusion Clinical Practice Guideline), but inhaled epoprostenol is an alternative method of treatment. Intravenous epoprostenol is preferred for the longer term management of patients with pulmonary hypertension. Inhaled epoprostenol is for the short term management of pulmonary hypertension. Several studies demonstrate that inhaled epoprostenol is effective in the management of acute pulmonary hypertension and produces similar decreases in pulmonary artery pressure comparable to NO.[21, 23-35] When administered by inhalation, epoprostenol has few systemic effects. This is likely due to the low concentrations of epoprostenol found in the blood after inhalation and the short half-life of 3-6 minutes.[22]

Recommendations

Adult Patients

1. **Acute Respiratory Distress Syndrome**
   - 1.1. Maximize other therapies to improve oxygenation (i.e., FIO2, PEEP, hemodynamics, recruitment) before initiating inhaled epoprostenol therapy. (Class I, Level C)
   - 1.2. Inhaled epoprostenol therapy can be effective for patients with refractory hypoxemia associated with ARDS. Inhaled epoprostenol therapy should be reserved for patients with the inability to maintain adequate oxygenation despite appropriate ventilator management except in special situations.[19, 26-28, 36, 37] (Class IIa, Level C)
     - 1.2.1. Initiate at a dose of 0.05 mcg/kg/min via continuous nebulization.[19, 27] Doses higher than 0.05 mcg/kg/min have not been studied in ARDS. (Class IIb, Level C)
     - 1.2.2. The duration of therapy is dependent upon the clinical response observed. If no response is noted in 4 hours, wean off the inhaled epoprostenol.[21, 38] (Class IIb, Level C)
     - 1.2.3. The dose of epoprostenol should be decreased by 0.01 mcg/kg/min every 2 hours as tolerated by the patient when weaning off therapy. (Class IIb, Level C)

2. **Pulmonary Hypertension, Right Heart Failure Following Pulmonary Embolism, Severe Right Heart Failure**
   - 2.1. Maximize other therapies to improve oxygenation (i.e., FIO2, PEEP, and hemodynamics) before initiating inhaled epoprostenol therapy.[21, 23] (Class I, Level C)
   - 2.2. Inhaled epoprostenol therapy may be considered for patients with refractory hypoxemia and mean pulmonary artery pressure >30 mmHg, PaO_2/FiO_2 <150 mmHg, or cardiac index less than 2.2 L/min/m^2. (Class IIb, Level C)
     - 2.2.1. Initiate at a dose of 0.01 mcg/kg/min.[23] (Class IIb, Level C)
     - 2.2.2. The dose of epoprostenol may be titrated up by 0.01 mcg/kg/min every two hours to a maximum of 0.05 mcg/kg/min.[23] (Class IIb, Level C)
   - 2.3. The duration of therapy is dependent upon the clinical response observed. If no response is noted in 4 hours, weaning off inhaled epoprostenol is reasonable.[21, 39] (Class IIb, Level C)
     - 2.3.1. Consider decreasing the dose of epoprostenol by 0.01 mcg/kg/min every 2 hours as tolerated by the patient until weaned off. (Class IIb, Level C)

3. **Post Cardiac Surgery Patients**
   - 3.1. Maximize other therapies to improve oxygenation (i.e., FIO2, PEEP, and hemodynamics) before initiating inhaled epoprostenol therapy.[21] (Class I, Level C)
   - 3.2. Administer inhaled epoprostenol to intubated cardiac surgery patients or patients on continuous BiPAP with refractory hypoxemia.[21, 30] For patients on BiPAP weigh the benefit of epoprostenol therapy with the risk of rebound pulmonary hypertension if therapy is accidentally interrupted by removal of the BiPAP mask. (Class IIb, Level C)
   - 3.3. It is reasonable to initiate dosing at 0.03 mcg/kg/min.[21] Doses higher than 0.03 mcg/kg/min have not been studied in this population. (Class IIb Level C)
   - 3.4. Inhaled epoprostenol can be useful to decrease mean and systolic pulmonary artery pressures.[40] (Level IIa, Class B)
   - 3.5. The dose of epoprostenol may be decreased by 0.01 mcg/kg/min every 2 hours as tolerated by the patient.[21] (Class IIb, Level C)
   - 3.6. The duration of therapy is dependent upon the clinical response observed. If no response is noted in 4 hours, weaning off inhaled epoprostenol is reasonable.[21, 39] (Class IIb, Level C)

Pediatric Patients

4. **Acute Respiratory Distress Syndrome**
   - 4.1. Maximize other therapies to improve oxygenation (i.e., F_iO_2, PEEP, hemodynamics, recruitment) before initiating inhaled epoprostenol therapy.[34] (Class I, Level B)
   - 4.2. Inhaled epoprostenol therapy may be considered for patients with refractory hypoxemia associated with ARDS. Inhaled epoprostenol therapy should be reserved for patient with a

$PaO_2/FiO_2 \leq 300$ mmHg after conventional therapies have been maximized.[30, 34, 41] (Class IIb, Level B)

4.2.1. Consider initiating doses at 0.03 mcg/kg/min via continuous nebulization.[34] (Class IIb, Level B)

4.2.2. The dose of epoprostenol can be increased to 0.05 mcg/kg/min if the patient does not respond to the initial dose.[34] (Class IIb, Level B)

4.2.3. The dose of epoprostenol can be decreased by 0.01 mcg/kg/min every 2 hours as tolerated by the patient.[34] (Class IIb, Level C)

4.3. The duration of therapy is dependent upon the clinical response observed. If no response is noted in 4 hours, weaning off inhaled epoprostenol is reasonable. (Class IIb, Level C)

5. **Primary and Secondary Pulmonary Hypertension**

5.1. Maximize other therapies to improve oxygenation (i.e., F_iO_2, PEEP, hemodynamics) before initiating inhaled epoprostenol therapy.[41] (Class I, Level C)

5.2. Inhaled epoprostenol therapy can be considered for patients with refractory hypoxemia for primary and secondary pulmonary hypertension in children.[41] (Class IIb, Level C)

5.2.1. Consider initiating dose at 0.03 mcg/kg/min via continuous nebulization.[34] (Class IIb, Level B)

5.2.2. The dose of epoprostenol can be increased to 0.05 mcg/kg/min if the patient does not respond to the initial dose.[34, 35, 42] (Class IIb, Level B)

5.2.3. The dose of epoprostenol can be decreased by 0.01 mcg/kg/min every 2 hours as tolerated by the patient. (Class IIb, Level C)

5.3. The duration of therapy is dependent upon the clinical response observed. If no response is noted in 4 hours, weaning off inhaled epoprostenol is reasonable. (Class IIb, Level C)

Neonate Patients

6. Inhaled epoprostenol may improve oxygenation in hypoxemia neonates when all other therapies to improve oxygenation have failed.[41, 43-47] (Class I, Level B)

6.1. Initial doses of 0.03 mcg/kg/min are recommended and can be titrated up to 0.05 mcg/kg/min if necessary. (Class I, Level C)

6.2. It is reasonable to discontinue therapy by decreasing the dose 0.01 mcg/kg/min every 2 hours as tolerated. (Class IIa, Level C)

General Recommendations for Treatment

7. Do not administer epoprostenol to patients with:

7.1. Allergy or sensitivity to epoprostenol (Class III, Level C)

7.2. Cardiac failure secondary to left ventricular dysfunction (Class III, Level C)

8. Avoid use or use cautiously in patients with active and significant bleeding (Class IIb, Level C)

9. Epoprostenol is a pregnancy class B drug.[48, 49] Use inhaled epoprostenol with caution in pregnant women. (Class I, Level C)

In animal studies epoprostenol has not been shown to cause harm to a fetus. There are no human trials evaluating the safety of inhaled epoprostenol in pregnancy. There are case reports of the use of intravenous epoprostenol in pregnant patients with no harm to the fetus.[50, 51] Epoprostenol is not considered a hazardous medication; pregnant care givers may handle and administer the medication.

10. Wean patients off epoprostenol; abrupt withdrawal can result in rebound pulmonary hypertension. (Class IIa, Level B)

Monitoring Parameters

11. Monitor vital signs including blood pressure, heart rate, and oxygen saturation every 15 minutes for one hour during the first hour of treatment and after each dose change, then every hour thereafter. (Class I, Level C)
    11.1. Hemodynamic monitoring may include the following based on the patients condition and comorbidities: central venous pressure (CVP), echocardiography, ultrasound, cardiac index (CI), peripheral vascular resistance, total pulmonary resistance, mean pulmonary artery pressure, and stroke volume but is not required. (Class I, Level C)
12. Toxicity
    12.1. Monitor for symptoms of epoprostenol toxicity: jaw pain, headache, flushing, nausea, vomiting, diarrhea, abdominal pain, signs of bleeding, bronchoconstriction or hypotension.[23] (Class I, Level C)
    12.2. Monitor for symptoms of bleeding. (Class I, Level C) Inhibition of platelet aggregation is demonstrated in vitro for inhaled epoprostenol, but not in vivo[52]

Companion/Collateral documents (as applies to CPG content)

Epoprostenol Intravenous – Adult- Inpatient Clinical Practice Guideline
UW Health Respiratory Manual Policy 3.51 Inhaled Epoprostenol

UW Health Implementation

Potential Benefits:

Describes the anticipated benefits associated with implementing the Clinical Practice Guideline's recommendations, as stated in the CPG text, to target populations or intended users. Where applicable, the field includes information on the major subgroup(s) of patients within the target population most likely to benefit from the Clinical Practice Guideline recommendations, as identified by the developer.

Potential Harms:

Describes the anticipated harms, potential risks or adverse consequences associated with the CPGs recommendations, as stated in the guideline text, to target populations or intended users. Where identified by the original Clinical Practice Guideline document, the major subgroup(s) of patients with the target population most likely to suffer harm/adverse consequences associated with the guideline recommendations will also be described.

Qualifying Statements

Only small clinical trials and case reports support the use of inhaled epoprostenol for adult, pediatric, and neonate patients. Further large clinical trials may changes the recommendations included in this document.

Implementation Plan/Tools

1. Guideline will be housed on U-Connect in a dedicated folder for CPGs.
2. Release of the guideline will be advertised in the Clinical Knowledge Management Corner within the Best Practice newsletter.
3. Links to this guideline will be updated and/or added in appropriate Health Link or equivalent tools, including: epoprostenol inhaled medication order records
3. Order set – IP- Inhaled Epoprostenol – Procedure [2234] facilitates ordering, monitoring and weaning of inhaled epoprostenol for adult, pediatric, and neonatal patients.

Disclaimer

CPGs are described to assist clinicians by providing a framework for the evaluation and treatment of patients. This Clinical Practice Guideline outlines the preferred approach for most patients. It is not intended to replace a clinician's judgment or to establish a protocol for all patients. It is understood that some patients will not fit the clinical condition contemplated by a guideline and that a guideline will rarely establish the only appropriate approach to a problem.

References

1. Jacobs AK, Kushner FG, Ettinger SM, et al. ACCF/AHA clinical practice guideline methodology summit report: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology* 2013;61:213-265.

2. Torbic H, Szumita PM, Anger KE, Nuccio P, LaGambina S, Weinhouse G. Inhaled epoprostenol vs inhaled nitric oxide for refractory hypoxemia in critically ill patients. *Journal of critical care* 2013;28:844-848.

3. Badesch DB, Abman SH, Simonneau G, Rubin LJ, McLaughlin VV. Medical therapy for pulmonary arterial hypertension: updated ACCP evidence-based clinical practice guidelines. *Chest.* Vol 131. United States2007:1917-1928.

4. Simonneau G, Galie N, Rubin LJ, et al. Clinical classification of pulmonary hypertension. *J Am Coll Cardiol.* Vol 43. United States2004:5S-12S.

5. Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin Definition. *JAMA* 2012;307:2526-2533.

6. Guerin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. *The New England journal of medicine* 2013;368:2159-2168.

7. Papazian L, Forel JM, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. *The New England journal of medicine* 2010;363:1107-1116.

8. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *The New England journal of medicine* 2000;342:1301-1308.

9. Kemming G, Habler O, Kleen M, Kisch-Wedel H, Welte M, Zwissler B. Searching the ideal inhaled vasodilator: from nitric oxide to prostacyclin. *Eur Surg Res* 2002;34:196-202.

10. Pierrakos C, Karanikolas M, Scolletta S, Karamouzos V, Velissaris D. Acute respiratory distress syndrome: pathophysiology and therapeutic options. *J Clin Med Res* 2012;4:7-16.

11. Michael JR, Barton RG, Saffle JR, et al. Inhaled nitric oxide versus conventional therapy: effect on oxygenation in ARDS. *Am J Respir Crit Care Med* 1998;157:1372-1380.

12. Troncy E, Collet JP, Shapiro S, et al. Inhaled nitric oxide in acute respiratory distress syndrome: a pilot randomized controlled study. *Am J Respir Crit Care Med* 1998;157:1483-1488.

13. Dellinger RP, Zimmerman JL, Taylor RW, et al. Effects of inhaled nitric oxide in patients with acute respiratory distress syndrome: results of a randomized phase II trial. Inhaled Nitric Oxide in ARDS Study Group. *Crit Care Med* 1998;26:15-23.

14. Lundin S, Mang H, Smithies M, Stenqvist O, Frostell C. Inhalation of nitric oxide in acute lung injury: results of a European multicentre study. The European Study Group of Inhaled Nitric Oxide. *Intensive Care Med.* Vol 25. United States1999:911-919.

15. Gerlach H, Keh D, Semmerow A, et al. Dose-response characteristics during long-term inhalation of nitric oxide in patients with severe acute respiratory distress syndrome: a prospective, randomized, controlled study. *Am J Respir Crit Care Med.* Vol 167. United States2003:1008-1015.

16. Taylor RW, Zimmerman JL, Dellinger RP, et al. Low-dose inhaled nitric oxide in patients with acute lung injury: a randomized controlled trial. *JAMA.* Vol 291. United States2004:1603-1609.

17. Afshari A, Brok J, Moller AM, Wetterslev J. Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) and acute lung injury in children and adults. *Cochrane Database Syst Rev* 2010:CD002787.

18. Angus DC, Clermont G, Linde-Zwirble WT, et al. Healthcare costs and long-term outcomes after acute respiratory distress syndrome: A phase III trial of inhaled nitric oxide. *Crit Care Med* 2006;34:2883-2890.

19. Van Heerden PV, Blythe D, Webb SA. Inhaled aerosolized prostacyclin and nitric oxide as selective pulmonary vasodilators in ARDS--a pilot study. *Anaesth Intensive Care* 1996;24:564-568.

20. Brown AT, Gillespie JV, Miquel-Verges F, et al. Inhaled epoprostenol therapy for pulmonary hypertension: Improves oxygenation. *Pulm Circ* 2012;2:61-66.

21. De Wet CJ, Affleck DG, Jacobsohn E, et al. Inhaled prostacyclin is safe, effective, and affordable in patients with pulmonary hypertension, right heart dysfunction, and refractory hypoxemia after cardiothoracic surgery. *J Thorac Cardiovasc Surg.* Vol 127. United States2004:1058-1067.

22. Lowson SM. Inhaled alternatives to nitric oxide. *Crit Care Med* 2005;33:S188-195.

23. Mikhail G, Gibbs J, Richardson M, et al. An evaluation of nebulized prostacyclin in patients with primary and secondary. *Eur Heart J* 1997;18:1499-1504.

24. Webb SA, Stott S, van Heerden PV. The use of inhaled aerosolized prostacyclin (IAP) in the treatment of pulmonary. *Intensive Care Med* 1996;22:353-355.
25. Schroeder RA, Rafii AA, Plotkin JS, Johnson LB, Rustgi VK, Kuo PC. Use of aerosolized inhaled epoprostenol in the treatment of portopulmonary. *Transplantation* 2000;70:548-550.
26. Walmrath D, Schneider T, Pilch J, Grimminger F, Seeger W. Aerosolised prostacyclin in adult respiratory distress syndrome. *Lancet* 1993;342:961-962.
27. van Heerden PV, Barden A, Michalopoulos N, Bulsara MK, Roberts BL. Dose-response to inhaled aerosolized prostacyclin for hypoxemia due to ARDS. *Chest* 2000;117:819-827.
28. Zwissler B, Kemming G, Habler O, et al. Inhaled prostacyclin (PGI2) versus inhaled nitric oxide in adult respiratory. *Am J Respir Crit Care Med* 1996;154:1671-1677.
29. Della Rocca G, Coccia C, Costa MG, et al. Inhaled areosolized prostacyclin and pulmonary hypertension during anesthesia for. *Transplant Proc* 2001;33:1634-1636.
30. Fattouch K, Sbraga F, Sampognaro R, et al. Treatment of pulmonary hypertension in patients undergoing cardiac surgery with. *J Cardiovasc Med (Hagerstown)* 2006;7:119-123.
31. Fiser SM, Cope JT, Kron IL, et al. Aerosolized prostacyclin (epoprostenol) as an alternative to inhaled nitric oxide. *J Thorac Cardiovasc Surg* 2001;121:981-982.
32. Lowson SM, Doctor A, Walsh BK, Doorley PA. Inhaled prostacyclin for the treatment of pulmonary hypertension after cardiac. *Crit Care Med* 2002;30:2762-2764.
33. Walmrath D, Schneider T, Schermuly R, Olschewski H, Grimminger F, Seeger W. Direct comparison of inhaled nitric oxide and aerosolized prostacyclin in acute. *Am J Respir Crit Care Med* 1996;153:991-996.
34. Dahlem P, van Aalderen WM, de Neef M, Dijkgraaf MG, Bos AP. Randomized controlled trial of aerosolized prostacyclin therapy in children with. *Crit Care Med* 2004;32:1055-1060.
35. Kelly LK, Porta NF, Goodman DM, Carroll CL, Steinhorn RH. Inhaled prostacyclin for term infants with persistent pulmonary hypertension. *J Pediatr* 2002;141:830-832.
36. Tabrizi MB, Schinco MA, Tepas JJ, 3rd, Hwang J, Spiwak E, Kerwin AJ. Inhaled epoprostenol improves oxygenation in severe hypoxemia. *J Trauma Acute Care Surg* 2012;73:503-506.
37. Domenighetti G, Stricker H, Waldispuehl B. Nebulized prostacyclin (PGI2) in acute respiratory distress syndrome: impact of primary (pulmonary injury) and secondary (extrapulmonary injury) disease on gas exchange response. *Crit Care Med* 2001;29:57-62.
38. McMillen JC, Burke CF, Dhingra A, Dudney TM, Faircloth BE. Use of inhaled epoprostenol in patients with H1N1 influenza-associated acute. *Ann Pharmacother* 2011;45:e26.
39. Camamo JM, McCoy RH, Erstad BL. Retrospective evaluation of inhaled prostaglandins in patients with acute respiratory distress syndrome. *Pharmacotherapy* 2005;25:184-190.
40. Groves DS, Blum FE, Huffmyer JL, et al. Effects of early inhaled epoprostenol therapy on pulmonary artery pressure and blood loss during LVAD placement. *Journal of cardiothoracic and vascular anesthesia* 2014;28:652-660.
41. Kovach J, Ibsen L, Womack M, Steusse D, Law YM. Treatment of refractory pulmonary arterial hypertension with inhaled epoprostenol in an infant with congenital heart disease. *Congenit Heart Dis* 2007;2:194-198.
42. Carroll CL, Backer CL, Mavroudis C, Cook K, Goodman DM. Inhaled prostacyclin following surgical repair of congenital heart disease--a. *J Card Surg* 2005;20:436-439.
43. Gupta M, Guertin S, Martin S, Omar S. Inhaled prostacyclin and high-frequency oscillatory ventilation in a premature infant with respiratory syncytial virus-associated respiratory failure. *Pediatrics* 2012;130:e442-445.
44. Kelly LK, Porta NF, Goodman DM, Carroll CL, Steinhorn RH. Inhaled prostacyclin for term infants with persistent pulmonary hypertension refractory to inhaled nitric oxide. *J Pediatr* 2002;141:830-832.
45. Dhillon R. The management of neonatal pulmonary hypertension. *Arch Dis Child Fetal Neonatal Ed* 2012;97:F223-228.
46. Zwissler B, Rank N, Jaenicke U, et al. Selective pulmonary vasodilation by inhaled prostacyclin in a newborn with congenital heart disease and cardiopulmonary bypass. *Anesthesiology* 1995;82:1512-1516.
47. Bindl L, Fahnenstich H, Peukert U. Aerosolised prostacyclin for pulmonary hypertension in neonates. *Arch Dis Child Fetal Neonatal Ed* 1994;71:F214-216.
48. Veletri [package insert]. San Francisco , CA: Actelion Pharmaceuticals US, Inc; 2012. .
49. Flolan (intavenous epoprostenol) [Package Insert]. GSK. March 2011.
50. Garabedian MJ, Hansen WF, Gianferrari EA, et al. Epoprostenol treatment for idiopathic pulmonary arterial hypertension in pregnancy. *J Perinatol.* Vol 30. United States2010:628-631.
51. Goland S, Tsai F, Habib M, Janmohamed M, Goodwin TM, Elkayam U. Favorable outcome of pregnancy with an elective use of epoprostenol and sildenafil in women with severe pulmonary hypertension. *Cardiology.* Vol 115. Switzerland2010:205-208.
52. Haraldsson A, Kieler-Jensen N, Wadenvik H, Ricksten SE. Inhaled prostacyclin and platelet function after cardiac surgery and. *Intensive Care Med* 2000;26:188-194.

Appendix A

American Heart Association Grades of Recommendation[1]

SIZE OF TREATMENT EFFECT

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT

	CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/ administered	CLASS IIa *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	CLASS IIb *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	CLASS III *No Benefit* or CLASS III *Harm* Procedure/Test / Treatment COR III: No benefit — Not Helpful / No Proven Benefit COR III: Harm — Excess Cost w/o Benefit or Harmful / Harmful to Patients
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit: is not recommended; is not indicated; should not be performed/ administered/ other; is not useful/ beneficial/ effective COR III: Harm: potentially harmful; causes harm; associated with excess morbidity/mortality; should not be performed/ administered/ other
Comparative effectiveness phrases†	treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B		