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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, PaO2/FiO2 <150 mmHg, or cardiac index less than 2.2 L/min/m². (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., FIO2, 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

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 Patient Safety Net (PSN) 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 into 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

<table>
<thead>
<tr>
<th>Timing</th>
<th>Within 1 week of known clinical insult or new or worsening respiratory symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest imaging</td>
<td>Bilateral opacities – not fully explained by effusions, lobar/lung collapse, or nodules</td>
</tr>
<tr>
<td>Origin of edema</td>
<td>Respiratory failure not fully explained by cardiac failure or fluid overload</td>
</tr>
<tr>
<td>Oxygenation</td>
<td>Mild: (200 \text{ mmHg} &lt; \text{PaO}_2/\text{FiO}_2 \leq 300 \text{ mmHg} ) with PEEP or CPAP ( \geq 5 \text{ cm H}_2\text{O} )</td>
</tr>
<tr>
<td></td>
<td>Moderate: (100 \text{ mmHg} &lt; \text{PaO}_2/\text{FiO}_2 \leq 200 \text{ mmHg} ) with PEEP ( \geq 5 \text{ cm H}_2\text{O} )</td>
</tr>
<tr>
<td></td>
<td>Severe: (\text{PaO}_2/\text{FiO}_2 \leq 100 \text{ mmHg} ) with PEEP ( \geq 5 \text{ cm H}_2\text{O} )</td>
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</tbody>
</table>

CPAP – continuous positive airway pressure; \(\text{FiO}_2\) – fraction of inspired oxygen; \(\text{PaO}_2\) – 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. The pathophysiology of ARDS includes vasoconstriction and direct administration of vasodilators via the airway to improve pulmonary gas exchange is an accepted treatment. Nitric oxide (NO) has been the most studied inhaled vasodilator, but the small trials conducted have not demonstrated a decrease in mortality. 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. 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. Prostacyclins have been studied in mechanically ventilated patients and in patients on biphasic positive airway pressure (BiPAP) therapy. 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.

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. 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.
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, PaO2/FiO2 <150 mmHg, or cardiac index less than 2.2 L/min/m2. (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, 36 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., FiO2, 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
PaO₂/FiO₂ ≤300 mmHg after conventional therapies have been maximized.\textsuperscript{30, 34, 41} (Class IIb, Level B)

4.2.1. Consider initiating doses at 0.03 mcg/kg/min via continuous nebulization.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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\textsubscript{i}O\textsubscript{2}, PEEP, hemodynamics) before initiating inhaled epoprostenol therapy.\textsuperscript{37} (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.\textsuperscript{41} (Class IIb, Level C)

5.2.1. Consider initiating dose at 0.03 mcg/kg/min via continuous nebulization.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 patient’s 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 CPG 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 neonatal 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
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
49. Flolan (intravenous epoprostenol) [Package Insert]. GSK. March 2011.
Appendix A
American Heart Association Grades of Recommendation

SIZE 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

LEVEL A
Multiple populations evaluated*
Data derived from multiple randomized clinical trials or meta-analyses

LEVEL B
Limited populations evaluated*
Data derived from a single randomized trial or nonrandomized studies

LEVEL C
Very limited populations evaluated*
Only consensus opinion of experts, case studies, or standard of care

Suggested phrases for writing recommendations
should
is recommended
is indicated
is useful/effective/beneficial

Comparative effectiveness/oriases
- 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

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