



Aerosolized Epoprostenol Sodium (Flolan®) Administration Guideline for Patients with Acute Respiratory Distress Syndrome (ARDS)

BACKGROUND:

Epoprostenol, a synthetic analog of prostacyclin, activates the prostaglandin receptor leading to an increase in the intracellular cyclic adenosine monophosphate (cAMP) through activation of adenylate cyclase within smooth muscle cells. The increase in cAMP results in relaxation of the smooth muscle cells. When administered in aerosolized form it produces selective pulmonary vasodilation leading to improvements in ventilation perfusion-mismatch and oxygenation without systemic hemodynamic effects. Pulmonary vasodilation also may decrease pulmonary vascular resistance, reduce right ventricular afterload and increase right ventricular stroke volume.

Aerosolized epoprostenol (aEPO) can be considered in patients with ARDS as per the Berlin definition with worsening oxygenation despite therapy and lung-protective ventilation strategies. Patients with ARDS are defined as those that have an acute presentation of hypoxemia in association with bilateral pulmonary infiltrates/opacities seen on chest radiograph/computed tomography that is not associated with clinical signs of volume overload or cardiac failure. ARDS can be classified into mild ($\text{PaO}_2/\text{FiO}_2$ 300 - >200), moderate ($\text{PaO}_2/\text{FiO}_2$ 200- >100) or severe ($\text{PaO}_2/\text{FiO}_2$ < 100). Aerosolized epoprostenol can be considered as a bridge while other definitive therapies are established/attempted (i.e. prone position ventilation, high frequency oscillation ventilation, lung transplant). This therapy can also be considered in patients with pulmonary hypertension (PHTN) in which other therapies have not been effective or tolerated.

General use:

- Pulmonary hypertension
- Acute right heart dysfunction
- Hypoxemia related to pulmonary vasoconstriction

Epoprostenol pharmacology:

Absolute contraindications:

- Known allergy or sensitivity to epoprostenol or glycine diluent
- Active pulmonary hemorrhage
- Secondary pulmonary artery hypertension (PAH) due to left ventricular systolic dysfunction

Relative contraindications:

- Patient less than 16 years of age
- Thrombocytopenia (platelets less than 50,000/uL)
- Pregnancy

Precautions:

- Abrupt withdrawal of epoprostenol can result in rebound pulmonary hypertension
- Weaning of therapy is recommended

Pharmacokinetics:

- Onset: 1-2 minutes
- Duration: 3-5 minutes
- Metabolism: spontaneous hydrolysis to inactive metabolite

Drug interactions: minimal since aerosolized

Adverse reactions:

- Inhibition of platelet aggregation
- Bronchodilation
- Systemic hypotension
- More common: flushing, headache, nausea & vomiting, hypotension, anxiety, chest pain

RESTRICTIONS: Restricted to critical care, anesthesia and/or pulmonary services. Aerosolized epoprostenol must be ordered by or on behalf of the attending physician

SCOPE OF PRACTICE:

- Attending physicians are responsible for ordering aEPO per restriction criteria
- Pharmacy is responsible for verifying, compounding, and delivering the medication STAT
- Respiratory therapists are responsible for the administration of aEPO and documentation of administration
- Nursing is responsible for monitoring per guidelines according to physician orders

INDICATIONS:

Patients with ARDS ($\text{PaO}_2/\text{FiO}_2 < 300$) with worsening hypoxemia and clinical deterioration despite the use of ventilator strategies recommended by the ARDS network. Aerosolized epoprostenol should be considered when the ventilator strategies provide inadequate support despite an FiO_2 supplementation of 80% or more and a PEEP of 12 or more

DOSING:

- Initiate aEPO at 50 ng/kg/min (based on ideal body weight – IBW, rounded to nearest 10kg) via continuous nebulization with nebulizer connected to the ventilator
- aEPO should be titrated downward every 30 minutes as tolerated to 10 ng/kg/min based on PaO_2 improvement. Do NOT decrease aEPO by more than 10 ng/kg/min every 30 minutes (see **WEANING** section)

IBW (male) = $50 + 2.3 (\text{Height in inches} - 60)$

IBW (female) = $45 + 2.3 (\text{Height in inches} - 60)$

Epoprostenol 1.5 mg/50mL (final concentration 30,000 ng/mL) infusion rate chart*						
Patient's IBW (kg)	aEPO	50 ng/kg/min	40 ng/kg/min	30 ng/kg/min	20 ng/kg/min	10 ng/kg/min
40	mL/hr	4	3.2	2.4	1.6	0.8
50	mL/hr	5	4	3	2	1
60	mL/hr	6	4.8	3.6	2.4	1.2
70	mL/hr	7	5.6	4.2	2.8	1.4
80	mL/hr	8	6.4	4.8	3.2	1.6
90	mL/hr	9	7.2	5.4	3.6	1.8
≥100	mL/hr	10	8	6	4	2

*Doses are based on IBW and should be rounded to nearest 10 kg before using this chart

RESPONSE TO THERAPY

Response to therapy should be apparent within 10 minutes of initiation of treatment

- Positive response:
 - Patient that show $\geq 20\%$ increase in PaO₂
 - ≥ 20 reduction in pulmonary artery pressure (PA)
 - Clinical or diagnostic signs of a reduction in pulmonary artery pressure
- Negative response:
 - If a negative response occurs, resume previously tolerated dose and contact provider
 - Decline in P:F ratio by $> 25\%$ reflects negative response
- Duration of therapy is depended upon clinical response. If no clinical response is noted in 2 hours, the inhaled epoprostenol should be weaned off
- Doses higher than 50 ng/kg/min have not been shown to improve patient response

WEANING

- Do not decrease dose by more than 10 ng/kg/min
- Titration should be reconsidered and attending physician contacted if a patient demonstrates an increase of PA pressures or decrease in oxygenation within 30 minutes of titration or discontinuation
- The dose of epoprostenol can be decreased by 10 ng/kg/min every 30 minutes if there is not a decrease in the PaO₂/FiO₂ by 10%
- If there is a positive response to the initial dose of epoprostenol it is important to establish the minimal effective dose while ensuring patient safety
- Epoprostenol can be discontinued after contacting attending physician once the rate has been at 10 ng/kg/min for 2 hours and no negative response has occurred unless otherwise specified by provider

MONITORING:

- Patient should be continuously monitored as per ICU protocol with continuous telemetry
- Heart rate, blood pressure, oxygen saturation, respiratory rate should monitored continuously
If the patient has a pulmonary catheter (i.e. swan ganz catheter), the mean pulmonary pressures should be recorded at the start of the therapy

- Drug therapy should NOT be interrupted, even during transport
- Patient should remain closely monitored for rebound pulmonary hypertension per ICU protocol with continuous telemetry as described above at least 30 minutes following termination of aEPO

The following parameters will be continuously evaluated to monitor efficacy and safety:

- PA pressure and SaO₂
- Arterial blood gasses (PaO₂)
- Oxygen saturation
- PaO₂/FiO₂
- PEEP requirements
- Patient should be assessed for signs and symptoms of bleeding. Hemoglobin should be checked on a daily basis as per the ICU protocol, or sooner if there are signs and symptoms of active bleeding
- If there is a decrease in mean systolic arterial pressure BP > 10% immediately notify provider and discontinue aEPO. When mean systemic arterial pressure recovers, the medication can be restarted at half (50%) of the starting drip rate

PROCEDURE:

Respiratory therapy implications:

aEPO will be delivered via Aerogen Solo Nebulizer

- 1) Confirm physician order and medication received from pharmacy
- 2) Mechanical ventilator will be assembled with a heated/humidified ventilator circuit (no Heat Moisture Exchanger)
- 3) Insert Aerogen Nebulizer t-piece adaptor and Aerogen Solo nebulizer just proximal to the humidification chamber (dry side)
- 4) Assemble syringe pump, Aerogen controller, and Aerogen Continuous Nebulization Tube Set
- 5) Connect Aerogen Continuous Nebulization Tube Set to syringe pump and prime the tubing
- 6) Activate Aerogen Controller and medfusion pump selecting desired dose in mL/hr
- 7) Ensure 2 filters are located on the expiratory limb at the exhalation valve
- 8) Change filters every 2 hours or if Peak Airway Pressures reflect unexpected increase
- 9) If aEPO syringe needs to be changed more often than q6 hrs based on patient's IBW and dose, RT may send a "Comment to Pharmacy" at least 2 hours prior to when new syringe needed
- 10) RT will verify each new syringe using KBMA to document on the work list manager in Sunrise
- 11) RT will document dose adjustments and epoprostenol syringe exchanges in the mechanical ventilation flowsheet in Sunrise
- 12) With provider approval RT will assure that the order for nebulized epoprostenol is discontinued in Sunrise as soon the medication has been completely weaned off

Pharmacy implications:

Process for aseptic preparation of aerosolized Epoprostenol in the Pharmacy IV Lab

Supplies: 1 x Epoprostenol 1.5 mg vial
1 x 50 mL Epoprostenol sterile diluents
1 x Aerogen 60 mL nebulization syringe and cap
1 x 60 mL monoject syringe
1 x 18 gage needle
1 x Amber light protection bag
Auxiliary stickers: For inhalation only, Refrigerate

- 1) Using proper aseptic technique, withdraw 5 mL of epoprostenol diluent into the 60 mL monoject syringe
- 2) Inject the 5 mL epoprostenol diluent into the 1.5 mg epoprostenol dry powder vial and mix content gently
- 3) Withdraw the 5 mL diluted epoprostenol back into the monoject syringe and transfer the content to the 60 mL Aerogen nebulization syringe
- 4) The Aerogen nebulization syringe contains 1.5 mg of epoprostenol in 5 mL of the diluent
- 5) Add the remaining 45 mL of sterile diluent to the syringe and mix gently
- 6) Seal the aerogen syringe with the nebulization cap
- 7) Final concentration of solution: $1.5 \text{ mg}/50\text{mL} = 30,000 \text{ ng/mL}$ (nanograms/mL)
- 8) Adhere patient's sunrise label to the syringe
- 9) Adhere auxiliary labels: REFRIGERATE and FOR INHALATION ONLY
- 10) Dispense each syringe in brown bag protected from light
- 11) Document all ingredients used in the compounding log sheet to include medication manufacture, lot number, and expiration date. Initial the compounding log sheet with date, time and name of technician preparing the medication and pharmacist checking the final product
- 12) Reconstituted epoprostenol must be stored in the refrigerator prior to the administration
- 13) Epoprostenol is stable for *only 8 hours at room temperature* and 48 hours in refrigerator
- 14) Due to the short room temperature stability of epoprostenol, the dosing interval in Sunrise will default to Q6H scheduled
- 15) At the *initiation* of the therapy **two** epoprostenol syringes will be compounded and delivered **STAT** to the unit. The back up epoprostenol syringe will be stored in the refrigerator until it is administered.
- 16) Epoprostenol syringe will be changed by respiratory therapy *every 6 hours*. One syringe of epoprostenol will be compounded by pharmacy every 6 hours and delivered to the unit until "discontinue" Sunrise order is generated

Nursing implications:

Nursing staff will monitor patients per the guidelines listed above in the **MONITORING** section

References:

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- 4) Ferguson ND, Fan E, Camporota L, Antonelli M, Anzueto A, Beale R, Brochard L, Brower R, Esteban A, Gattinoni L, Rhodes A, Slutsky AS, Vincent JL, Rubenfeld GD, Thompson BT, Ranieri VM. The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. *Intensive Care Med*. 2012 Oct;38(10):1573-82.
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- 6) Afshari A, Brok J, Møller AM, Wetterslev J. Aerosolized prostacyclin for acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). *Cochrane Database Syst Rev*. 2010 Aug 4;(8):CD007733.

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