CONWAY MEDICAL CENTER

PROCEDURE

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TITLE:	Aerosolized Epoprostenol		
ISSUED BY:	Cardiopulmonary Services	REFERENCE #:	CPS-57.52-PRO
APPROVED BY:	Director of Cardio-Pulmonary	EFFECTIVE DATE:	8/19/21

SCOPE: Cardiopulmonary Services, Pharmacists and pharmacy technicians, Attending physicians, Nursing

STATEMENT:

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 (PaO2/FiO2 300 - >200), moderate (PaO2/FiO2 200- >100) or severe (PaO2/FiO2 < 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.

PURPOSE:

To provide evidence-based, practice management guidelines for the use of aerosolized epoprostenol (aEPO) in patients with refractory hypoxemia associated with acute respiratory distress syndrome, right heart dysfunction or pulmonary hypertension in the critical care setting.

PROCEDURE:

I) Indications

A) Severe pulmonary hypertension in adult patients

A) Mean Pulmonary Arterial Pressure (mPAP) > 30 mmHg

B) Acute right heart failure (RHF) with shock and/or a low cardiac index (CI) (< 2.2 L/min/m^2) refractory to standard therapies

C) Acute respiratory distress syndrome with hypoxemia (PaO2:FiO2 ratio < 200) refractory to standard therapies

A) FiO2 > 80%

B) PEEP > 10 cm H_2O

C) Maximal ventilator management per ARDS net protocol

D) Vasodilator testing in PAH

E) PAH related to cardiopulmonary bypass

II) Contraindication

A) Absolute

A) Allergy or sensitivity to epoprostenol or glycine diluent

B) Heart failure secondary to left ventricular dysfunction

C) Active pulmonary hemorrhage

B) Relative

A) Active and significant bleeding

B) Thrombocytopenia (platelets <50,000)

C) Pregnancy

III) Precautions

A) Abrupt withdrawal of therapy may lead to rebound pulmonary hypertension. Weaning of therapy is recommended.

B) Weaning of therapy is recommended

IV) Restrictions

A) Locations: Use is restricted to Intensive care units/areas, cath lab and operating room

B) Ordering: Restricted to Pulmonology, critical care intensivists, anesthesiology, cardiology

V) Dosing

A) Doses will be calculated using ideal body weight (IBW) rounded to the nearest 10kg.

B) Initial dosing will be 50 ng/kg/min unless a lower dose is specified by the ordering provider. Doses higher than 50 ng/kg/min have not been shown to improve patient response.[2]

C) Doses are weaned as tolerated (generally by 10 ng/kg/min every 4 hours) based on positive clinical response. See section G for "response" definitions.

D) Duration of therapy is based on clinical response observed. If no response is noted within 2 hours of initiation, therapy should be weaned off rapidly (decrease rate by 50% every 2 hours until rate is less than 10 ng/kg/min, then stop aEPO therapy) and alternative measures considered.

E) Dosing chart

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 chart**						

VI) Response to Therapy

A) Positive response

A) Increase in SpO2 by 5%
B) Increase in PaO2 by 10 mmHG
C) Improvement in PaO2:FiO2 ratio by 10%
D) Decrease in mPAP by 15%
E) Clinical or diagnostic signs of reduction in pulmonary artery pressure

B) Negative Response

A) Decrease in SpO2 by 5%
B) Decrease in PaO2 by 10 mmHg
C) Increase in mPAP by 15%
D) Decline in cardiac index by 10% (or to less than 2.2 L/min/m2)
E) Decline in Pao2:FiO2 ratio by 10%

VII) Monitoring

A) Continuous telemetry, oxygen saturation and respiratory rate
B) The following will be recorded at baseline, 1 hour after starting therapy, one hour following every dose change and as specified below, if available and applicable
   A) Heart rate, Blood Pressure, Pulmonary artery pressure, central venous pressure (CVP), cardiac output (CO) or cardiac index (CI) Spo2, and temperature, aerogen nebulizer and syringe pump.
C) Every 2 hours
   A) Ventilator settings including measured parameters (RR, TV, PEEP, PIP, pPLAT, VE, FIO2)
D) Daily minimum requirement
   A) ABG (PaO2/FiO2 will be evaluated with every ABG)
   B) CBC

VIII) Pharmacy Preparation of aEPO

A) Supplies
   A) 1 x Epoprostenol (Veletri) 1.5 mg vial
   B) 1 x 50 mL SWI or Normal Saline
   C) 1 x Aerogen 60 mL nebulization syringe and cap (obtain from RT department)
   D) 1 x 60 mL monoject syringe
   E) 1 x 18 gage needle
   F) 1 x Amber light protection bag
   G) Auxiliary stickers: For inhalation only, Refrigerate

B) Admixture
   A) Using proper aseptic technique, withdraw 5 mL SWI or NS into the 60 mL monoject syringe.
   B) Inject the 5 mL SWI or NS into the 1.5 mg epoprostenol dry powder vial and mix content gently.
   C) Withdraw the 5 mL diluted epoprostenol solution into the monoject syringe and transfer the content to the 60 mL Aerogen nebulization syringe.
   D) The Aerogen nebulization syringe now contains 1.5 mg of epoprostenol in 5 mL of SWI or NS.

E) Add the remaining 45 mL of SWI or NS to the Aerogen syringe and mix gently.
F) Seal the Aerogen syringe with the nebulization cap.
G) Final concentration of solution: 1.5 mg/50mL = 30,000 ng/mL (nanograms/mL).
H) Adhere patient's medication label to the syringe.
I) Adhere auxiliary labels to the syringe: REFRIGERATE and FOR INHALATION ONLY.
J) Dispense each syringe in brown bag protected from light.
K) Reconstituted epoprostenol must be stored in the refrigerator prior to the administration
L) Epoprostenol is stable for only 8 hours at room temperature and 48 hours in refrigerator.
M) At the initiation of the therapy two epoprostenol syringes will be compounded. The first dose will be compounded by pharmacy and delivered STAT to the unit. The backup epoprostenol syringe will be stored in the refrigerator until it is administered. (Repeat steps 1-10 for the 2nd dose after completion of 1st dose).

IX) Administration of aEPO

A) Treatment will be initiated using an Aeroneb syringe prepared by pharmacy, containing 1.5 mg epoprostenol per 50 mL of SWI or NS (30,000 ng/mL concentration).
   1) Reconstituted epoprostenol is stable at room temperature for 8 hours and is stable for 48 hours under refrigeration.
   2) Syringes and tubing will be changed at a minimum of every 8 hours due to stability or as infusion pump flow rate dictates.
   3) Syringes should be protected from light during administration using the overwrap provided by pharmacy.
   4) Syringes used will be specifically designed for use with Aeroneb Solo nebulizer, with an offset, unique Luer connector for safety.
      a. Syringe requires specialized tubing which will be dispensed from respiratory therapy.
B) Aerosolized epoprostenol is delivered via a Syringe Pump to the Aeroneb Solo nebulizer.
   1) Dosing is programmed into the pump via ml/hr based on the dosing chart. THIS RATE CANNOT EXCEED 12 mL/hr (0.2 mL/min).
C) Patients should NOT receive other inhaled medications (bronchodilators, etc.) while receiving aEPO. If inhaled medications remain on the patient's eMAR after aEPO started, the RT or RN should clarify with the prescriber if they want to continue these medications.

X) Respiratory Therapy Set up

A) Equipment
   1) Ventilator with humidifier and heated wire circuit (preferred)
   2) 2 bacterial filters – both on expiratory limb
   3) Aeroneb Solo nebulizer
   4) Nebulizer must be changed at a minimum of every 7 days per manufacturer recommendations, but may be changed more frequently or as patient condition dictates.
   5) Aeroneb Solo T adapter
   6) Aeroneb Pro-X controller, AC adapter and nebulizer cable

B) Set-Up
   1) Insert nebulizer unit with the T-piece into the inspiratory limb of the breathing circuit proximal to the ventilator, but distal to the patient
      A) arrow on the T-piece should be positioned by the RT so that it faces in the same
      direction as the flow of the circuit
   2) Place 2 bacterial filters on the expiratory limb
      A) Change the filter(s) every 12 hours and PRN, as epoprostenol is a "sticky" medication and may occlude filters over time.
      B) Monitor PEEP and ventilator PIP for signs of expiratory resistance due to filter occlusion.
   3) Connect the Aeroneb Pro-X controller to the Aeroneb Solo nebulizer using the cable provided.
   4) Connect the Aeroneb Pro-X controller to its AC adapter
      a. The unit should remain plugged into the wall at all times to operate in continuous mode.
      b. Battery power may be used for transport of up to 30 minutes
         - Controller will shut off in 30 minutes without AC power
         - Controller will be in "intermittent" mode when on battery power, as AC power is required for continuous operation.

C) Remove the syringe cap (1) from the medication-filled syringe.
D) Attach the syringe end of the tubing (5) onto the syringe (2).
E) Prime the tubing (6) until the medication reaches the end of the tubing (Point A).
   A) NOTE: The tubing priming volume is a max of 3.65 mL
F) Unplug the tethered cap (7) from the Aeroneb Solo nebulizer (3), but do NOT remove it from the nebulizer. (It functions as a cap for the nebulizer when not in use.)
G) Screw the nebulizer end of the tubing (8) onto the top of the nebulizer.

H) Attach the medication syringe to the syringe Pump while maintaining proper nebulizer positioning.
   A) A "NOT FOR IV USE" sticker should be placed on the syringe tubing near the connector to minimize the risk of accidental IV use

I) Epoprostenol syringes will be delivered to the Pyxis refrigerator by pharmacy. One-hour after new epoprostenol syringe is started, please check refrigerator for the "next dose" syringe. Contact pharmacy if one is not yet available.

XI) Weaning of aEOP

POSITIVE Response

A) Inhaled epoprostenol weaning is recommended every 4 hours if a positive response is documented, unless otherwise ordered by a physician. A standard weaning protocol is described below, but may be altered per physician order.
   A) After 4 hours of initial therapy, if a positive response is documented, decrease aEPO dose by 10 ng/kg/min every 4 hours.
      1) If a negative response to the dose reduction occurs, resume previously tolerated dose and contact physician.
      2) If a positive response to the dose reduction occurs, continue to lower dose by 10 ng/kg/min every 4 hours.
      3) When the dose reaches 10 ng/kg/min, continue this dose and contact provider for further instruction.

NEGATIVE Response

B) Fast weaning
   A) After 2 hours of initial therapy, if a negative response is documented, decrease aEPO dose by 50% every 2 hours until 10 ng/kg/min rate is reached.
   B) When the dose reaches 10 ng/kg/min, continue this dose and contact provider for instruction to discontinue aEPO therapy.

REFERENCE STANDARDS:

I) NIAHO Standards
A) MM.1 SR2, SR.4, SR.5, and SR.6
B) RC.2 SR.1 thru SR.2

II) Siegel, Mark D. Acute respiratory distress syndrome: Novel therapies in adults. In: UpToDate Waltham, MA. (Accessed: July 2014).

III) Dzierba AL, Abel EE, Buckley MS, Lat I. A review of inhaled nitric oxide and aerosolized epoprostenol in acute lung injury or acute respiratory distress syndrome. Pharmacotherapy 2014;34(3):279-290.

3) Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS.Acute respiratory distress syndrome: the Berlin Definition. JAMA. 2012 Jun 20;307(23):2526-33.

IV)) 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.

V)) Pacheco J, Arnold H, Skrupky L, Watts P, Micek ST, Kollef MH.Predictors of Outcome in 216 Subjects With ARDS Treated With Inhaled Epoprostenol. Respir Care. 2013 Nov 19.

VI)) 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.

REVISION/REVIEW HISTORY:

Date	Affected Section(s)	Summary of Changes ('Reviewed' or details of change)
8/19/21	All	New Procedure