Flagler Health+	***Inter-Professional Policy and Procedure***

Policy: I - PHARM - GEN -Inhaled Epoprostenol (Flolan) for Continuous Nebulization

Policy Number: I-PHARM-GEN-

Applicable to the following locations/departments:	**Flagler Hospital**
Responsible Department:	**Pharmacy**
Coordinating Departments:	**Critical Care** **Respiratory Therapy**
Original Issue Date:	**9/1/2018**
Medical Director/Staff Approval: (if applicable)	
Legal and Regulatory References:	**N/A**
Other References/Corresponding Policies:	1. Ventetuolo CE, Klinger JR. Management of Acute Right Ventricular Failure in the Intensive Care Unit. Annals of the American Thoracic Society. 2014; 11(5):811-822. doi:10.1513/AnnalsATS.201312-446FR. 2. Buckley MS, Feldman JP. Inhaled epoprostenol for the treatment of pulmonary arterial hypertension in critically ill adults. Pharmacotherapy. 2010; 30(7):728-40. 3. Ammar MA, Bauer SR, Bass SN, et al. Noninferiority of inhaled epoprostenol to inhaled nitric oxide for the treatment of ARDS. Ann Pharmacoher. 2015; 49(10):1105-12. 4. Bhatt AM, Stein EJ. Clinical complications with the delivery of inhaled epoprostenol in the operating room. Anesth. 2017; 127(383). 5. Tabrizi MB, Schinco MA, Tepas JJ, et al. Inhaled epoprostenol improves oxygenation in severe hypoxemia. J Trauma and Acute Care Surgery. 2012; 73(2):503-506. 6. Preston IR, Kristen DS, Roberts KE, et al. Comparison of acute hemodynamic effects of inhaled nitric oxide and inhaled epoprostenol in patients with pulmonary hypertension. Pulm Circ. 2013; 3(1): 68-73. 7. Dzierba, Amy L. et al. "A review of inhaled nitric oxide and aerosolized epoprostenol in acute lung injury or acute respiratory distress syndrome." *Pharmacotherapy* 34 3 (2014): 279-90. 8. Searcy RJ, Morales JR, Ferreira JA. The role of inhaled prostacyclin in treating acute respiratory distress syndrome. Ther Adv Respir Dis. 2015; 9(6): 302-312. 9. Vanderbilt University Medical Center Multidisciplinary Surgical Critical Care Service Inhaled epoprostenol guidelines 10. University Hospital aerosolized epoprostenol sodium administration guideline for patients with acute respiratory distress syndrome (ARDS). 11. WellSpan Health York Hospital. Pulmonary Services Policy and Procedure. Inhaled Flolan/epoprostenol via nebulization during mechanical ventilation. Attachments: APPENDIX A: Epoprostenol Inhalation Dosing Chart APPENDIX B: Pharmacy Procedure for Preparation of Inhaled Epoprostenol

I. Objective

To clearly define the process of ordering, dispensing, administering and monitoring inhaled epoprostenol (Flolan) as continuous nebulization resulting from collaboration between the Pulmonary Intensivist Team, Pharmacy, Respiratory Therapy and Nursing.

II. Scope

Flagler Health+ Pharmacy Services

III. Definitions

N/A

IV. Policy

a. Inhaled epoprostenol (Flolan) continuous nebulization can ONLY be prescribed by Intensivists

b. Inhaled epoprostenol (Flolan) can only be made by pharmacy in the IV room and dispensed to a respiratory therapist

c. Inhaled epoprostenol (Flolan) is administered and monitored by respiratory therapists in collaboration with registered nurses

d. Inhaled epoprostenol (Flolan) is to be initiated for mechanically ventilated intensive care unit (MICU/SICU/OHR) patients ONLY

V. Procedure

a. CRITERIA FOR USE INDICATION:

   i. Salvage therapy for patients with severe acute respiratory distress syndrome (ARDS) and refractory hypoxemia
   ii. Patients with ARDS ($PaO_2/FiO_2 < 100$) with worsening hypoxemia and clinical deterioration despite the use of ventilator strategies recommended by the ARDS network
   iii. Additional criteria required:

      1. Mechanically ventilated Intensive Care Unit (MICU/SICU/OHR) patients
      2. Trials of recruitment maneuver and prone positioning, if not contraindicated, have failed
      3. Acute RV failure with moderate to severe pulmonary hypertension. Additional criteria required:

(a) Mechanically ventilated Intensive Care Unit (MICU/SICU/OHR) patients with pulmonary artery catheter in place
(b) Documented RV dilatation and or decreased RV function by echocardiogram
(c) Mean pulmonary artery pressure (mPAP) > 30 mmHg
(d) Hypotension (mean artery pressure (MAP) < 65 mmHg or systolic blood pressure (SBP) < 90 mmHg refractory to combination of norepinephrine and vasopressin along with dobutamine or milrinone IV infusions

b. Absolute Contraindications:

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

c. Relative Contraindications:

i. Patients with significant active bleeding
ii. Thrombocytopenia (i.e. platelets less than 50,000/uL
iii. Pregnancy

d. PRECAUTIONS:

i. Abrupt withdrawal of epoprostenol can result in rebound hypertension. Weaning of therapy is recommended
ii. Adverse reactions:

1. Inhibition of platelet aggregation
2. Bronchodilation
3. Systemic hypotension

iii. Common side effects:

1. Flushing, headache, nausea and vomiting, hypotension, anxiety, chest pain

e. GOAL(S) OF THERAPY:

i. ARDS OR Refractory Hypoxemia
PaO2:FiO_2 > 200, FiO_2 is ≤ 60% and PEEP is ≤ 10 cm H_2O
ii. Acute RV failure with moderate to severe pulmonary hypertension
mPAP < 25 mmHg, MAP > 65 mmHg, and SBP > 100 mmHg
iii. Limit therapy for all indications for duration to less than 48 hours

f. MONITORING RESPONSE TO THERAPY:

i. Response to inhaled epoprostenol will be determined based on the following criteria:
ii. **ARDS OR Refractory Hypoxemia**

1. No Response: Less than 10% increase in PaO_2 OR less than 5% increase in SaO_2.

2. Partial Response: 10 - 20% Increase in PaO_2 by 10-20% OR Increase in SaO_2 by 5-10%
3. Full Response: Increase in PaO_2 greater than or equal to 20% OR Increase in SaO_2 by greater than 10%.

iii. **Acute RV failure with moderate to severe pulmonary hypertension**

1. No Response: mPAP greater than 30 mmHg
2. Partial Response: mPAP greater than 25 mmHg but less than 30 mmHg with MAP greater than 65 mmHg or SBP greater than 100 mmHg
3. Full Response: mPAP less than or equal to 25 mmHg

iv. The Respiratory Therapist will assess and monitor patient for 15 minutes after initiation and with any dose change, then every 2 hours
v. Response to therapy should be evident within 10 minutes of initiation of treatment. If no response in 2 hours, the inhaled epoprostenol should be weaned off
vi. Any new events including changes in vital signs should be reported to the Intensivist
vii. The Respiratory Therapist must remain at the patient's bedside for at least the first 15 minutes after any dosage change to monitor for adverse effects and report any adverse effects immediately
viii. The Respiratory therapist will calculate and document the PaO_2:FiO_2 Ratio on the Respiratory Flow Sheet every 2 hours
ix. Nebulizer volume will be monitored every two hours to prevent over or under filling. The Respiratory Therapist will call pharmacy at least two hours ahead for nebulizer refills

g. INITIAL DOSE:

i. Epoprostenol will be administered by Respiratory Therapy per protocol via continuous nebulization ONLY
ii. Starting Dose:

1. 50 ng/kg/min (Ideal Body Weight, IBW) administered as a continuous nebulization via Aerogen nebulizer
2. Male IBW: 50 + 2.3 (height in inches – 60)
3. Female IBW: 45 + 2.3 (height in inches – 60)
4. Doses should be weaned as tolerated to the lowest effective dose based on monitoring of patient response to therapy
5. Doses higher than 50 ng/kg/min have not been shown to improve patient response

h. ADMINISTRATION

i. Respiratory therapy service will administer epoprostenol solution through Aerogen Nebulizer
ii. Epoprostenol is incompatible with other nebulized medications. All other nebulizer treatments should be discontinued while the patient is on epoprostenol continuous infusion
iii. The dose will be programmed into a Med-Infusion Syringe pump that will deliver epoprostenol to the Aerogen nebulizer

iv. Refer to APPENDIX A: EPOPROSTENOL INHALATION DOSING CHART for conversion of ng/kg/min to infusion rate in ml/hr
v. A standardized concentration of epoprostenol will be used

1. 1.5 mg/50 ml = 30,000 ng/ml

i. EPOPROSTENOL ADJUSTMENT PROTOCOL:

i. The Respiratory therapist may adjust or discontinue epoprostenol continuous nebulization based on the criteria stated below:

1. Within 2 hours of initiation:

(a) If No Response to therapy is observed, discontinue inhaled epoprostenol and notify the Pulmonary Intensivist and Pharmacy (x4755 or x 4320)
(b) If a Full or Partial Response to therapy is observed, Continue inhaled epoprostenol at 50 ng/kg/min, then reassess every 2 hours

2. When PaO2/FiO_2 Ratio is > 200, FiO_2 is ≤ 60% and PEEP is ≤ 10 cm H_2O for ARDS or Refractory Hypoxemia OR when hemodynamic stabilization with mPAP < 25 mmHg, MAP > 65 mmHg, and SBP > 100 mmHg for 12 hours for Acute RV failure with moderate to severe pulmonary hypertension

(a) Begin Weaning process

(i) Decrease the initial dose by 50% to 25 ng/kg/min (IBW)
(ii) Oxygen saturations, mPAP, heart rate, and respiratory rate should be monitored to assess the patients' response

(1) If the patient tolerates the decreased dose with no significant changes in the parameters, maintain at 25 ng/kg/min for 2 hours, then reduce to 10 ng/kg/min. Maintain dose at 10 ng/kg/min for 2 hours, then discontinue
(2) If patient does not tolerate the decreased dose, a slower weaning process maybe used
(3) Decrease dose by 10 ng/kg/min every 2 hours until less than 10 ng/kg/min, then discontinue

(b) Titration should be reconsidered and attending physician contacted if patient demonstrates an increase of PA pressures or decrease in oxygenation within 30 minutes of titration or discontinuation

ii. If at any time during therapy with inhaled epoprostenol an adverse effect occurs or decline in PaO2/FiO_2 Ratio or increase in mPAP by 25% (i.e. nausea/vomiting, hypotension, chest pain, dyspnea, bradycardia, tachycardia, headache, anxiety, or dizziness):

1. Reduce the dose by 50% and notify the Pulmonary Intensivist MMEDIATELY
2. Notify Pharmacy (x4755 or x 4320)
3. Document in EMR

4. If no further adverse effects observed after dose reduction, continue current dose and monitoring per protocol
5. If patient continues to have adverse effects, continue to wean epoprostenol off by 50%. Once at 10 ng/kg/min for at least 30 minutes, notify physician, and discontinue

iii. Do not decrease dose by more than 10 ng/kg/min every 30 minutes

j. DOCUMENTATION:

i. The initial epoprostenol dose and any subsequent dose change will be documented by the Respiratory Therapist in electronic medical record using the KBC Adult Assessment Intervention flow sheet
ii. Initiation of first syringe, all syringe changes, and all dose changes must be co-signed in EMR by 2 respiratory therapists or RT and RN
iii. All pertinent information including: PA pressure and SaO2, PaO2, PaO2:FiO2 ratio, PEEP requirements, and hemodynamic parameters will be documented at baseline and every 2 hours

k. PHARMACY PREPARATION AND DISPENSING:

i. Storage:

1. Epoprostenol vials are stored in the “Helmer”
2. After mixing, epoprostenol Aerogen syringes are stored in the refrigerator

ii. Preparation:

1. **USE ONLY FLOLAN DILUENT TO DILUTE**
2. To avoid waste, pharmacy should not mix more than 50 mL at a time
3. Beyond Use Dating:

(a) 48 hours (refrigerated)
(b) 24 hours (out of refrigerator with cold pack)
(c) 8 hours (out of refrigerator, without cold pack)
(d) Expiration: 48 hours (refrigerated)

4. See APPENDIX B: PHARMACY PREPARATION OF INHALED EPOPROSTENOL

iii. Dispensing:

1. Place Aerogen syringe in light protective bag
2. Label Protect from Light and Refrigerate
3. Provide one Aerogen syringe containing 50 mL to Respiratory Therapist
4. Store the second Aerogen syringe containing 50 mL in the pharmacy refrigerator

l. RESPIRATORY THERAPY EQUIPEMENT SET-UP:

i. RT will contact pharmacy when an order for inhaled epoprostenol is received to coordinate pickup of the initial dose of reconstituted epoprostenol in 60 ml Aerogen syringe
ii. RT will pick up first syringe, then back up syringe when needed from pharmacy
iii. Confirm physician order, proper medication/strength received from pharmacy
iv. The mechanical ventilator will be assembled with a heated circuit and humidification device
v. Insert Aerogen nebulizer on the inspiratory limb, just proximal (before) the humidifier reservoir
vi. Assemble Medfusion pump, Aerogen controller and tubing
vii. Insert Aerogen respiratory syringe
viii. Connect tubing to Aerogen nebulizer
ix. Ensure that two hepa filters are located on the expiratory limb of the circuit
x. Activate Aerogen controller and Medfusion pump at starting dose in mL/hr (see APPENDIX A: EPOPROSTENOL INHALATION DOSING CHART
xi. Visually verify aerosol production
xii. Ensure epoprostenol syringe is covered with photosensitive protective bag provided by pharmacy
xiii. Place a sign on the infusion pump that states: RESPIRATORY THERAPY USE ONLY. FLOLAN BEING ADMINISTERED
xiv. Place a sign on the ventilator stating, INHALED FLOLAN IN USE. DO NOT ADMINISTER ANY OTHER AEROSOLIZED MEDICATIONS
xv. Expiratory filters must be changed every 2 hours to prevent sticking of expiratory valve and auto PEEP. Change the IV tubing every 24 hours. Nebulizer cups can be changed when necessary
xvi. The syringe must be changed every 8 hours or sooner to maintain stability. Any remaining epoprostenol should be discarded per the medication disposal policy
xvii. If the patient responds to treatment, pharmacy will must call pharmacy 2 hours before the syringe infusion is complete or 6 hours after the syringe infusion is started, whichever is sooner, to allow adequate time for preparation and pickup of a replacement syringe if therapy will continue for greater than 8 hours
xviii. Pharmacy will reconstitute additional syringes. A back-up syringe must always be in the refrigerator for emergencies for patients receiving epoprostenol nebulization
xix. The need to continue treatment should be reassessed every 2 hours. RT will notify pharmacy when patient has been successfully weaned off therapy.

m. ADVERSE REACTIONS AND SPECIAL CONSIDERATIONS:

i. Epoprostenol delivered as a continuous intravenous infusion is a potent vasodilator of all vascular beds. Although systemic side effects are rate at doses less than or equal to 50 ng/kg/min, the following side effects are possible:

1. Hypotension
2. Flushing
3. Headache
4. Nausea/vomiting
5. Anxiety
6. Chest pain

7. Dizziness
8. Bleeding

ii. Continuous nebulization should never be interrupted unless the patient develops serious side effects (i.e. significant hypotension) at which point the Intensivist should be notified immediately. Abrupt discontinuation could result in rebound pulmonary hypertension, right ventricular heart failure, hypoxemia, etc.
iii. If any adverse effects occur (i.e. nausea/vomiting, hypotension, chest pain, dyspnea, bradycardia, tachycardia, headache, anxiety, or dizziness), decrease the epoprostenol dose by 50% and notify Intensivist immediately.
iv. Upon nebulization the glycine buffer diluent has a “sticky” characteristic and has a tendency to accumulate on and impair ventilator valve function, hence the need for frequently changing expiratory filters. Practitioners should monitor for signs of increased peak airway or end-expiratory pressures that may indicate clogged filters.
v. Do NOT transport the patient while epoprostenol continuous nebulization is occurring to avoid complications.