Providence HEALTH CARE	**RESPIRATORY SERVICES**	DATE CREATED: February 2011 DATE REVIEWED/REVISED: **May 2018**
PROTOCOL	TITLE: CRITICAL CARE – Flolan Administraion Via AERONED and Medfusion 3500 Syringe Pump (Respiratory Therapy) NUMBER: B-00-12-12073	RELATED DOCUMENTS:

SITE APPLICABILITY:

ST. PAUL'S HOSPITAL

POLICY STATEMENT:

Inhaled nebulized Epoprostenol Sodium (Flolan) is to be administered by a Respiratory Therapist upon receipt of a physician order. Inhaled Flolan is restricted to intubated patients in critical care areas only.

GENERAL INFORMATION:

Flolan is a naturally occurring prostaglandin known as prostacyclin PGI_2, with a pharmacologic action of direct vasodilation of the pulmonary and systemic arterial vascular beds, as well as inhibition of platelet aggregation. Due to its short half-life (3-7 minutes) Flolan requires continuous nebulization.

Flolan that is administered via inhalation exerts localized selective pulmonary vasodilator effects, rendering it a desirable agent for the management of pulmonary arterial hypertension without compromising systemic arterial blood pressure. It has also been proposed that the anti-thrombotic property of Flolan aids in maintaining pulmonary blood flow in hypoxemia secondary to ARDS.

EXHIBITS:

A. Nebulized Flolan – Standard Dosing Protocol (AERONEB)

INDICATIONS:

1. **Acute Pulmonary Arterial Hypertension:**
   - Post-cardiopulmonary bypass (including post-heart transplant)
   - Right ventricular heart failure/ severe pulmonary hypertension

2. **Refractory Hypoxemia:**

- PaO_2/FiO_2 less than 100 mmHg

CAUTIONS:

- Systemic hypotension is uncommon but may occur with doses higher than those found in this protocol
- Side effects normally associated with *systemic* administration of Flolan (facial flushing, headache, jaw pain, diarrhea) have *not* been observed in trials studying *inhaled* Flolan
- Platelet inhibition with Flolan has been observed *in vitro*, but not clinically
- Rebound PAH has been observed after discontinuation of Flolan; continue to monitor hemodynamic parameters for at least 4 hours after Flolan has been discontinued

SPECIAL CONSIDERATIONS:

1. The syringe pump rate should not be set higher than 8 mL/hour. As the rate is decreased the nebulizer reservoir may run dry between drips – this is to be expected and does not affect the overall dose being delivered at that particular rate.

2. Due to the sticky nature of reconstituted Flolan, ventilator filters may become congested or clogged. Routinely change bacteria/viral filter every 4 hours or sooner if any signs of expiratory resistance occur:
    - Increase in peak inspiratory pressure
    - Increase in expiratory flow resistance on ventilator flow waveform
    - Increase in inadvertent PEEP

3. Reconstituted Flolan is photosensitive. Use the dark packaging that Pharmacy sends with the syringe to cover the syringe once it has been loaded into the pump. Be sure that the covering will not interfere with the operation of the pump, and that the syringe markings are easily accessible to monitor remaining volume. (i.e. “tent” the plastic covering over the syringe).

4. In order for the vibrating mesh properties of the AERONEB to function properly, the nebulizer must remain upright. Care should be taken during patient care activities to ensure that it remains in the proper position.

5. The control module internal battery life is 30 – 45 minutes. Continuous mode is not possible while using the internal battery. In the event the AERONEB is not connected to power, it must be operated using the *intermittent* setting until the module can be plugged in to a power source. During intermittent mode the nebulizer automatically stops after 30 minutes.

6. Avoid direct inhalation when handling the nebulizer system.

7. The nebulizer chamber and t-piece should be changed every 7 days. The infusion tubing should be changed every 96 hours.

8. Discard the Flolan syringe when:
    a. It is empty
    b. It has been at room temperature for more than 3 days
    c. The labeled expiry date/time has been met

    NOTE: The drug remaining in the tubing does not need to be discarded or changed.

9. Response should be observed within minutes of starting nebulization. If patient shows no improvement in PaO_2/FiO_2 after one hour, consult with the physician to reassess and consider alternative therapies.

10. If the patient responds to therapy titrate Flolan infusion rate as per Nebulized Flolan – Standard Dosing Protocol (AERONEB).

11. Nebulized Flolan via the AERONEB system may not be used in the following cases:
    a. Ventilator circuits with a heat-moisture exchanger in use
    b. Diagnostic nitric challenge
    c. MRI
    d. T1 transport ventilator

RECOMMENDED DOSAGE:

Literature suggests a Flolan dose of 5 – 50 ng/kg/min for the management of acute PAH and hypoxemia. The initial dose is nebulized for 2 – 4 hours, titrated to effect, and then weaned off as tolerated.

Refer to ***Nebulized Flolan – Standard Dosing Protocol (AERONEB)***

DRUG SUPPLIED AND STORAGE:

- Flolan is supplied as a sodium salt of Epoprostenol and is reconstituted by the pharmacist or the bedside nurse in 50 mL of sterile diluent to a final concentration of 20 000 ng/mL
- Total volume of drug supplied is 50 mL in a 60 mL syringe
- The reconstituted solution is stable for 7 days when refrigerated and for 3 days at room temperature
- A backup syringe with reconstituted Flolan will be maintained in Pharmacy whenever Flolan is in use

REQUIRED SUPPLIES & EQUIPMENT:

- AERONEB Solo Pro-X controller with AC/DC power cable and control module cable
- Disposable nebulizer unit, T-adapter
- MEDFUSION 3500 syringe pump
- AEROGEN infusion tubing with luer lock* **infusion tubing will be kept in the ICU vent room*
- AEROGEN 60 mL syringe with cap* **Syringes will be kept in Pharmacy; a backup supply is in Katmandu*
- Reconstituted PGI_2 (Flolan) from Pharmacy (50 mL)
- Expiratory filters BACT TRAP HEPA BASIC bacterial/viral (non-HME)

Aeroneb System

OBTAINING DRUG FROM PHARMACY – INITIAL ORDERS AND REORDERS:

NOTE: Pharmacy is not able to prepare the drug between the hours of 2400 - 0600. If the initial order was placed during this time, Pharmacy will send the non-reconstituted drug to the unit, and the bedside RN will be responsible for reconstituting the drug as per the supplied directions.

1. For **INITIAL ORDERS** the Physician must write an order on the **Prescribers Order Sheet.** Ensure Flolan order forwarded to Pharmacy via fax. Telephone Pharmacy directly to confirm they have received the order.

    a) Delivery of the reconstituted drug to the unit will occur within 2 hours. If the drug is required urgently, telephone Pharmacy and request the drug be prepared as soon as possible.

    NOTE: In CSICU the drug will be delivered to the ADC/Omnicell fridge. Use the ADC/Omnicell procedure to access and remove the drug.

    b) The drug and dosage must be transcribed onto the **Medication Administration Record**.

2. **TO REORDER,** print off a **Medication Order Memo** via Softmed, fill in the relevant information and fax to Pharmacy.

    a) Pharmacy must receive the reorder request *at least 2 hours prior* to:
        i. Expiration of reconstituted drug – Pharmacy will indicate the date on the syringe.
        ii. Estimated time at which the syringe will be empty - determined by dividing the volume in the syringe (mL) by the set Flolan infusion rate (mL/hr).
        iii. 2200 if it's expected that the syringe will be empty before 0600.

3. Connect the Aerogen infusion tubing to the Aerogen syringe containing the Flolan

4. Document Flolan expiry time and Flolan reorder status on the **Inhaled Pulmonary Vasodilator Flowsheet.**

PROCEDURE FOR OPERATING THE MEDFUSION 3500 SYRINGE PUMP:

LOAD SYRINGE:

1. Lift the syringe barrel clamp and swivel it away to rest on the handle.
2. Squeeze the syringe plunger release lever on the syringe plunger driver and pull it out gently to extend it all the way outward.
3. Load the syringe onto the pump. Make sure the flange on the syringe barrel is secure in the syringe barrel flange clip.
4. Squeeze the syringe plunger release lever on the end of the syringe plunger driver and gently advance the plunger driver toward the syringe plunger.
5. Once it is flush with the syringe plunger, release the lever so that both syringe holders close around it.
6. Turn and lower the barrel clamp onto the barrel of the syringe and thread the infusion tubing through the tubing holders.

POWER ON:

1. Connect pump to a power source.
2. Press **POWER** to switch on the pump. Observe the self-test. Do not move the syringe plunger driver or manipulate the pump until the profile selection screen appears.

PROGRAM AN INFUSION:

1. Press **#1 (mL/Hr).** *Aerosolized Flolan* option should be displayed on the screen. Press **#1** again. *Aerosolized Flolan* is now displayed in large font in the centre of the screen. Press soft key for **YES**.
2. Press **#1 (B-D).** Verify that the display indicates a *B-D 60 mL* syringe has been detected. Press **ENTER.**
3. Enter the desired pump **RATE** (*1-8 mL/hr*). Press **ENTER.**
4. Press and hold the **BOLUS/<<** key to prime the pump. Press **EXIT** once complete. Note that the volume of the infusion tubing is 3.65 mL.
5. Press **START/<** to begin the infusion**.**

SYRINGE LOADING/TROUBLESHOOTING:

1. If syringe is incorrectly loaded, the pump displays arrows to identify the problem:
    a. **UP** = check flange clip
    b. **LEFT** = check plunger driver
    c. **DOWN** = check barrel clamp

FLOWSENTRY PRESSURE MONITOR AND OCCLUSION DETECTION:

1. When pressure increases to the FlowSentry monitor sensitivity setting, the pump may trigger a **pressure increasing** or an **occlusion alarm**.
2. To override occlusion settings, select **OPTIONS**, and then select **OVERIDE OCCL LIMIT.** The current setting will be highlighted. Choices include **VERY LOW** (most sensitive), **LOW, NORMAL** and **HIGH** (least sensitive). Adjust as appropriate.

TOTAL VOLUME DELIVERED:

1. **TVD** (Total Volume Delivered) appears on the display screen while an infusion is running. It is an accumulation of the amount of fluid that has been delivered during the time the pump has been powered on, and is useful for documentation of total fluid delivery to a patient.

PROCEDURE for DELIVERY via AERONEB Pro-X Solo VIBRATING MESH NEBULIZER:

1. Connect the remaining end of the AEROGEN infusion tubing to the nebulizer unit.

2. Place the t-adaptor in the ventilator circuit on the dry side of the humidifier chamber. Insert the nebulizer unit into the opening of the t-adapter. Ensure the nebulizer is positioned upright.

    NOTE: The silicone plugs tethered to the nebulizer and t-adapter should not be removed. The plugs function as caps for the nebulizer and t-piece when not in use.

T-adaptor

Vibrating Mesh Nebulizer

3. Connect the control module cable to the nebulizer unit. Ensure the module is plugged in to a power source.

4. Place a bacterial/viral expiratory filter into the expiratory limb before the existing ventilator expiratory filter.

5. Activate the AERONEB controller module. For continuous mode, press and hold the blue on/off button for 3 seconds – the green continuous LED indicator should be lit.

6. Confirm medication is nebulizing by observing the t-piece; mist should be visible with regular intermittent pauses. The nebulizer may run dry between drops, which will not affect overall dose. If there is no output, the cause may be due to pressure build up in the reservoir or an overfilled reservoir cup; draining the cup may correct this.

Aerosol Mist

7. Clearly label the syringe pump as **Nebulized Inhaled Flolan** and move the Flolan syringe pump away from any other pumps used to administer intravenous medications.

DOCUMENTATION, COMMUNICATION, EDUCATION:

Document rate changes on the **Medication Administration Record**, **Respiratory Services Flowsheet**, and **Inhaled Pulmonary Vasodilator Flowsheet**. Documentation of relevant hemodynamic parameters and ABG results should occur in each of the following situations:

a. Prior to initiation of Flolan
b. 1 hour post initiation of Flolan
c. Immediately prior to any drug rate/concentration change
d. 1 hour post drug rate/concentration change
e. 1 hour *and* 4 hours post discontinuation of therapy
f. With routine ventilator monitoring

NEBULIZED FLOLAN – STANDARD DOSING PROTOCOL (AERONEB):

1. Initiate Flolan nebulization at 20 000 ng/mL (160 000 ng/hr), which is a rate of 8 mL/hour.

2. Wean the delivered dosage of Flolan according to protocol, providing the patient does not exhibit a decrease in PaO_2/FiO_2 by 10% or more. If a negative weaning response is observed, return to the previous delivered dose.

3. When weaning, the concentration of Flolan delivered to the nebulizer is constant at 20 000 ng/mL. A decrease in the infusion rate will alter the overall delivered dose the patient receives over time.

4. Continue weaning until the delivered dose of Flolan is 2500 ng/mL (20 000 ng/hr) and the patient is not exhibiting a negative response. Continue to monitor P/F ratio for 4 hours after therapy discontinued.

REFERENCES:

1. Ari, A., Areabi, H., & Fink, J.B. (2010). Evaluation of aerosol generator devices at 3 locations in humidified and non-humidified circuits during adult mechanical ventilation. *Respiratory Care*, 55(7), 837-844.
2. Fattouch, K., Sbraga, F., Sampognaro, R., Bianco, G., Gucciardo, M., et al. (2006). Treatment of pulmonary hypertension in patients undergoing cardiac surgery with cardiopulmonary bypass: A randomised, prospective, double blind study. *Journal of Cardiovascular Medicine*, 7(2), 119-123
3. Fattouch, K., Sbraga, F., Bianco, G., Spieziale, G., Gucciardo, M., et al. (2005). Inhaled prostacyclin, nitric oxide, and nitroprusside in pulmonary hypertension after mitral valve replacement. *Journal of Cardiac Surgery,* 20, 171-176.
4. Khan, T. A., Schnickel, G., Ross, D., Bastani, S., Laks, H., et al (2009). Prospective, randomised, crossover pilot study of inhaled nitric oxide versus inhaled prostacyclin in heart transplant and lung transplant recipients. *The Journal of Thoracic and Cardiovascular Surgery*, 138(6), 1417-1424.
5. Poston J., Lieure K., Lat I., & Morgan S. (2010). Inhaled vasodilators as salvage therapy in ARDS caused by H1N1 infection. *American Thoracic Society.*
6. Leistiko, T., Schelde, C., & Park, D. (2008). An alternative method for titratable aerosolized prostacyclin administration during mechanical ventilation (abstract). *Respiratory Care*, 53.
7. Leistiko, T., Ray, J., & Park, D. R. (2004). Nebulized prostacyclin clogs expiratory HEPA filters and causes Auto-PEEP (abstract). *Respiratory Care,* 49(11).
8. Siobal, M. S., Kallet, R. H., Pittet, J. F., Warnecke, E. L., Kraemer, R. W, et al. (2003). Description and evaluation of a delivery system for aerosolized prostacyclin. *Respiratory Care,* 43(8), 742-753.
9. Medfusion 3500 Syringe Pump Quick Reference Card. Smiths Medical. 2011.

DEVELOPED BY:

PHC Respiratory Services
Pharmacy

REVIEWED BY:

1. Professional Practice Leader, Respiratory Therapy
2. RT Site Leader, Respiratory Services
3. ICU Core Therapist, Respiratory Services
4. Supervisor, Parenteral Services, SPH Pharmacy
5. Pharmacist, SPH ICU
6. Practice Consultant, Professional Practice

RESPIRATORY SERVICES

Nebulized Flolan – Standard Dosing Protocol (AERONEB)

The concentration of Flolan delivered to the nebulizer at any given time is constant at 20 000 ng/mL. A change in the rate of the infusion pump will alter the overall delivered dose the patient receives over time. *Therefore, weaning occurs by decreasing the infusion rate of the syringe pump, which in turn decreases the overall delivered hourly dose.*

Hour	Flolan® Dose Delivered (ng/hr) Concentration of 20 000 ng/mL	Syringe Pump Infusion Rate (mL/hr)
2	160,000 ng/hr	**8**
4	120,000 ng/hr	**6**
6	90,000 ng/hr	**4.5**
8	60,000 ng/hr	**3**
10	50,000 ng/hr	**2.5**
12	30,000 ng/hr	**1.5**
14	20,000 ng/hr	**1**

Wean FiO_2 to less than 0.5 ***before*** **weaning Flolan**

EXHIBIT A. *Nebulized Flolan – Standard Dosing Protocol (AERONEB)*