Supplemental Digital Content

Summary of Institutional Guidelines for the use of Aerosolized Epoprostenol (Prostacyclin, Flolan®) and Aerosolized Iloprost (Ventavis®) in Adult Patients

	Epoprostenol	Iloprost
Emergent Indications	A. Acute RHF with shock and/or a low Cardiac Index (CI) (<2.5 l/min/m^2) refractory to standard therapy. (Administration of Epoprostenol is **not** a substitute for conventional treatments) Supportive strategies include: 1. Ventilator strategies: a. Increase fraction of inspired oxygen (FIO_2) to 100%. b. Decrease positive end-expiratory pressure (PEEP) and reduce auto PEEP. c. Hyperventilate to pCO_2 of approximately 30 mm Hg to induce a respiratory alkalosis. 2. Circulatory management: a. Optimize intravascular volume b. If mean arterial pressure (MAP) is increased, consider a balanced pulmonary/systemic vasodilator (e.g. nitroprusside) c. If MAP is decreased, consider vasopressors (e.g. norepinephrine) d. Inotropes for cardiogenic shock. B. Life threatening hypoxemia (PO_2 < 55) refractory to conventional therapies (defined below). Since this indication is as a "salvage" treatment for temporary stabilization of a patient with ARDS who is dying of hypoxemia, epoprostenol should only be administered if the patient fails to respond to, or cannot receive, the conventional treatments listed below (#1). Furthermore, other treatments such as those described below (#2) should be considered as alternatives to inhaled epoprostenol for treatment of life-threatening	A. Same Supportive strategies include: 1. Ventilator strategies a. Same 2. Circulatory management a. Same b. Same c. If MAP is decreased, consider vasopressors (e.g., norepinephrine and/or vasopressin). d. Same

	hypoxemia. The decision to initiate inhaled epoprostenol over one of the other alternatives depends on the side effect profile of the modality and the individual clinical circumstances.	
Elective Indications	**To decrease pulmonary artery pressure (PAP) in patients with PHTN (mPAP > 25) in the following two settings:** A. As a diagnostic test for pulmonary vascular responsiveness (i.e. during right heart catheterization) B. Treatment of peri-operative PHTN to avoid morbidity e.g. RHF, or more invasive treatment modalities e.g. right ventricular assist device (RVAD), for the operative procedures listed below: 1. Heart and lung transplantation 2. Left ventricular assist device implantation 3. Mitral valve surgery (and rarely other valves) 4. Pulmonary thromboendarterectomy 5. Cardiac surgery complicated by right ventricular myocardial dysfunction.	**To decrease pulmonary artery pressure (PAP) in patients with PHTN (mean PAP > 30 mm Hg) in the following settings:** A. Same B. Treatment of peri-operative PHTN to avoid morbidity (e.g., acute RHF) or more invasive treatment modalities [e.g., right ventricular assist device (RVAD)] for the operative procedures listed below: 1-5. Same 6. Patients with pulmonary hypertension (mPAP > 30 mm Hg)
Contraindications and Exclusions	**Relative Contraindications:** A. Active and significant bleeding B. Thrombocytopenia (<50 K) C. Patients with cardiac failure secondary to left ventricular dysfunction **Exclusion Criteria:** A. Pregnant Women B. Patients <17 years of age	**Relative Contraindications:** Same **Exclusion Criteria:** Same
Treatment Goals	A. PHTN: Testing of pulmonary vascular responsiveness 1. Treatment goal: Decrease PVR by > 15% B. PHTN: Peri-operative management (see Elective Indications 2.B on previous page) a. Treatment goal: Decrease PVR by > 15 % Additional Details: 1. Positive response: A positive response is defined as a decrease in pulmonary artery pressure by 15% or an improvement in cardiac index by 10% or PaO2/FiO2 ratio by 10%. 2. Negative response: A negative response is defined as an increase in pulmonary	A. Same B. Same Additional Details: 1. Positive Response: A positive response is defined as a decrease in pulmonary artery pressure and/or pulmonary vascular resistance by 15% or an improvement in cardiac index by 15%. 2. Negative Response: A negative response is defined as an increase in pulmonary artery pressure by 15%, if cardiac index decreases to less than 2.2 L/min/m2.

	artery pressure by 15%, if cardiac index decreases to less than 2.2 L/min/m2 or if the PaO2/FiO2 ratio is less than 150.	
Administration	**Starting Dose Recommendation:** For patients weighing > 80 kg, the starting dose is 20,000 ng/mL; for all other patients start at 10,000 ng/mL.	**Starting Dose Recommendation:** 1. Starting dose is 10 mcg iloprost inhaled over 15 minutes. 2. Starting drug dose: 10 mcg inhaled iloprost over 15 minutes in 3 mL volume 3. Repeat 10 mcg inhaled iloprost dose every 90-120 minutes 4. Hold dose if mPAP < 30 mmHg
Weaning	**The weaning of epoprostenol should be started in the ICU and as soon as the patient's hemodynamics are stable.** A trial of epoprostenol weaning should be attempted within the first two hours after the patient arrives on the unit. During this trial close hemodynamic monitoring is required. Chart patient vitals before and 10 minutes after changing epoprostenol dose -- pulmonary artery pressures, pulmonary vascular resistance, cardiac index, arterial blood pressure, oxygen saturation, FiO2, etc. If the patient's pulmonary artery pressures and/or PVRI increase by more than 15% after changing epoprostenol doses, continue the previous dose and resume weaning as soon as possible. If PAP does not significantly increase after changing the epoprostenol dose, continue at that new and lower dose for up to 3 hours prior to weaning again. **Contraindications for Weaning Epoprostenol:** 1. FiO2 > 0.6 2. Mean BP < 60 mmHg 3. CI < 2.0 l/min/m2 4. Hemodynamic instability or high dose pressors (i.e. epinephrine > 4 mcg/min) **Inhaled Epoprostenol Discontinuation Procedure:** A. At the start of the ICU weaning trial an attempt to discontinue the epoprostenol should be tried. B. Resume the epoprostenol if the patient has a 20% increase in the PVR or PASP.	**The weaning of iloprost should be started in the ICU and as soon as the patient's hemodynamics are stable.** A. To wean inhaled iloprost increase inhalation intervals to 3-4 hours and set threshold hold parameter for mean PAP and/or CI (set by prescribing physician - recommended mean PAP < 30- 35 mm Hg and/or CI > 2.2 l/min/m2). 1. Consider reducing the dose by half, to 10 mcg inhaled over 15 minutes. 2. If patient doesn't receive iloprost for > 12 hours treatment should be discontinued. 3. Document hemodynamic variables every 30 minutes for the first 4 hours of therapy. Record results on the Adult Critical Care Flowsheet (NU-2101). The default setting should be the patient receives iloprost unless defined parameters trigger a hold order.

	1. Record baseline hemodynamic parameters and ABG 2. Stop oxygen flow to nebulizer, stop delivery of epoprostenol from syringe pump. 3. Record hemodynamic parameters every 10 minutes for 30 minutes 4. At the 20 –30 min mark a decision should be made if the epoprostenol should be discontinued or restarted. 5. If the epoprostenol is to be restarted, resume at previous dose. (see above) 6. Record discontinuation or restart time. **Inhaled Epoprostenol Weaning Procedure:** 1. Contact the Pharmacy at least 30 minutes prior to weaning attempt. 2. The pharmacy will prepare a syringe of epoprostenol at ½ the current dose (i.e. for the patient receiving 20,000 ng/mL, a 10, 000 ng/mL syringe will be prepared). Contents of the current dose syringe should be saved and not discarded by RN or RT, in the event the patient fails the weaning attempt the previous dose needs to be resumed. Contact the Pharmacy for a spare syringe if less than 20mL remains of the previous dose. 3. The inhaled epoprostenol syringes are prepared by Pharmacy in standard concentrations. As a patient is weaned from inhaled epoprostenol the concentration is halved with subsequent doses [20,000 ng/mL → 10,000 ng/mL → 5000 ng/mL → 2500 ng/mL → 1250 ng/mL (optional last weaning dose) → then discontinue]. 3. Record baseline hemodynamic parameters and ABG 4. Stop oxygen flow to nebulizer, stop delivery of epoprostenol from syringe pump. DO NOT discard the contents of the current dose syringe (for use again in the event the patient fails the weaning process). 5. Replace the syringe with the new (lower concentration) syringe and fill the nebulizer to the 15 mL mark. 6. Restart the epoprostenol nebulizer at 2-3	

	lpm and pump at 8 mL/hr 7. Record hemodynamic parameters every 10 minutes for 30 minutes 8. At the 20 –30 minute mark, decide if the epoprostenol should be continued at the lower dose or restarted at the previous dose. 9. If > 15% increase in pulmonary artery pressures occurs after a dose reduction return to administration of previous concentration (from saved syringe). 10. If a significant increase in pulmonary artery pressures does not occur, consider decreasing the dose again. 11. Contact the pharmacy; notify them of success in weaning and the continuation of therapy or plan to reduce the dose again. 12. Once the lowest effective dose of epoprostenol is determined, continue at that dose for up to 3 hours before restarting the weaning process. 13. Record results on Critical Care flowsheet (NU-2101) each time a syringe is replaced regardless of dosage. 14. If the Mini-HEART nebulizer appears to have excessive amounts of rainout, consider discarding the contents of the nebulizer and mixing a new concentration from the syringe itself. **Procedure to return to previous concentration:** 1. If the patient demonstrates a negative response to the new concentration of epoprostenol then the nursing staff or anesthesiologist, if the patient is in the OR, should restart the infusion at the previous dose; use the available drug on hand or call Pharmacy and reorder a STAT syringe of the previous (higher dose) concentration. If the need is urgent and there is no immediate access to the higher concentration then nitric oxide can be considered.	**Procedure to return to previous iloprost dose:** 1. If the patient demonstrates a negative response to the new dose of iloprost, the respiratory therapist or anesthesiologist (if the patient is in the OR), should restart the nebulization at the previous dose. 2. If hypoxemia is the main concern, consider nitric oxide inhalation.
Monitoring	A. Consider placing an arterial line B. Verify patient's weight C. Document baseline vital signs/hemodynamics D. Starting drug dose: For patients	A. Place an arterial line and pulmonary artery catheter to monitor effect and side effects (systemic hypotension) of therapy. B. Obtain ABG at the following times:

	weighing > 80 kg, initiate therapy 20,000 ng/mL; all other patients start at 10,000 ng/mL. E. Obtain ABG at the following times: 1. Prior to initiation of epoprostenol (if no recent ABG available) 2. 30 minutes after the initiation of the drug 3. 30 minutes after each concentration change 4. At hours 2, 4, 6, 12 and every 6 hours after the initiation of epoprostenol (while the patient is on the inhaled drug) F. The following vitals signs should be documented: HR, BP, PAP, CVP, CO, CI, wedge, SV, PVR, SVR, SvO2, SpO2, Temp, and pain scale. (See attached Adult Critical Care Flowsheet, NU-2101 example) G. Current ventilator settings (Mode, Rate, Tidal volume, PEEP, Peak Inspiratory Pressure and Minute Ventilation) should be documented. H. Arterial blood gases should also be recorded.	1. Prior to initiation of inhaled iloprost (if no recent ABG available) 2. Repeat ABG when clinically necessary. C. The Aerogen Nebulizer can be used for ventilated and non-ventilated patients. Inhaled iloprost can be given after extubation and continued need for therapy should not be a reason to defer extubation. D. Chart vital signs (HR, BP, PAP, mPAP) just prior to the initiation of the inhaled drug cycle. E. Once the inhaled drug cycle is complete, chart vital signs (HR, BP, PAP, mPAP) every 15 minutes times one hour for the first two inhalation cycles. F. Chart vital signs (HR, BP, PAP, mPAP) every 30 minutes times one hour for the third and any subsequent inhalation cycles. G. Current ventilator settings (mode, rate, tidal volume, PEEP, peak inspiratory pressure and minute ventilation) should be documented on RT flowsheet per RT protocol and on nursing graphic q 1 hour and prn. RT will document treatments on non-ventilated patients in the computerized charting system. H. Arterial blood gases should also be recorded in the lab values section of the graphic.
Equipment	1. Two disposable filters will be placed on the expiratory limb of the ventilator circuit proximal to the water trap and one on the inspiratory limb of the ventilator circuit. A heated humidification system must be used on the ventilator. Both expiratory limb filters will be changed every 2 hours. 2. A MiniHEART nebulizer and charging volume tubing will be assembled and placed on the inspiratory side of the ventilator circuit proximal to the patient "wye". The nebulizer must be kept upright at all times. (See diagram below) 3. Attach oxygen-connecting tubing from the nebulizer to oxygen flow meter. The	TREATMENT MUST BE GIVEN THROUGH A HEATED WIRE VENTILATOR CIRCUIT. 1. Assembly all parts of the Aerogen Nebulizer. Place the filler cap into the opening of the nebulizer unit and connect the nebulizer unit to the adult T-adaptor by pushing the nebulizer unit firmly onto the T-adaptor. 2. Place the T-adaptor/nebulizer into the ventilator circuit, on the inspiratory limb, just before the patient wye. 3. Connect the Control Module and Nebulizer unit with the control module cable. 4. Plug in the AC adaptor and place the control module in the bracket. 5. Place the ordered dose of Iloprost in the

	flow rate should be set at a minimum of 2 LPM to a maximum of 3 LPM. 4. Prior to starting the nebulizer check to make sure that nursing has filled the nebulizer chamber to the 15 mL mark when they primed the IV tubing. 5. Maintain 15 mL of the solution in the reservoir of the MiniHEART at all times. Adjustments of flow to the nebulizer may need to occur hourly to maintain this volume in the nebulizer reservoir. Increasing or decreasing flow will also change nebulizer output. 6. Measured tidal volumes on the ventilator will increase slightly due to the addition of nebulizer flow into the circuit. Additional flow into the ventilator circuit through continuous nebulization can affect the flow triggering capabilities of the ventilator. The respiratory therapist must pay attention to the patient's ability to trigger the ventilator and make adjustments in sensitivity as needed. 7. PEEP must be monitored and expiratory filters must be changed every two hours to prevent inadvertent PEEP due to clogging filters. 8. When the epoprostenol concentration is changed, respiratory therapy is responsible for emptying the nebulizer chamber according to Infection Control guidelines for liquid waste material. Changing the concentration involves refilling the nebulizer chamber directly from the new syringe or by nursing priming the IV tubing into the sink or trash and this process will need to be coordinated with nursing. 9. The inhaled epoprostenol syringes are prepared by Pharmacy in standard concentrations. As a patient is weaned from inhaled epoprostenol the concentration is halved with subsequent doses [20,000 ng/mL → 10,000 ng/mL → 5000 ng/mL → 2500 ng/mL → 1250	nebulizer chamber and start the Aerogen Nebulizer, running it for the appropriate time period for the volume of fluid, i.e. 15 minutes for < 3 mL, and 30 minutes for > 3 mLs. 6. Always maintain the nebulizer in a vertical orientation (with the filler cap uppermost) while in the patient circuit. This orientation prevents condensate from blocking the nebulizer and ensures proper function. 7. Remove the nebulizer unit between treatments. When removing the nebulizer unit from the patient circuit always replace the T-adaptor plug to maintain circuit pressure. 8. Clean the nebulizer unit between treatments. Remove the filler cap from the nebulizer unit and rinse the parts with sterile water. Shake excess water from the parts and allow parts to air dry. Note: Respiratory care is responsible to have nebulizer sterilized by steam autoclave between patients.

	ng/mL (optional last weaning dose) → then discontinue]. 10. Document the initiation of therapy on the ventilator flow sheet and document the dosage and patient's tolerance every four hours or when the dosage changes until the drug is discontinued. 11. A spring-loaded T and flex tube setup should be added to the Ambu bag for episodes when the patient needs to be manually ventilated. **Epoprostenol must be continued when the patient is manually ventilated.**	