Background:
Inhaled pulmonary vasodilators have been used in acute respiratory distress syndrome (ARDS) associated with refractory hypoxemia in patients with COVID-19. Pulmonary vasodilators have not been associated with improvement in clinical outcomes, but can be used as a salvage maneuver in patients with refractory hypoxemia refractory in addition to standard ARDS treatments.[1-9]

Guideline:
Indications:
- Mechanically ventilated patient with ARDS secondary to COVID-19 meeting any of the following criteria:
    - Patients transferred from an outside facility receiving inhaled epoprostenol or inhaled nitric oxide
    - Patients who are candidates for ECMO who are under the care of the ECMO Care Team with a PaO2:FiO2 ratio < 150 despite aggressive ARDS management (i.e. ventilator optimization, prone ventilation, neuromuscular blockade)

Absolute Contraindications:
1. Known allergy or sensitivity to epoprostenol or glycine diluent
2. Active Pulmonary hemorrhage

Relative Contraindications:
1. Patient less than 16 years of age
2. Thrombocytopenia (platelets less than 50,000/ul)
3. Pregnancy
4. Patients with ARDS that have history of left ventricular dysfunction, signs of left atrial hypertension, or those with elevated pulmonary capillary wedge pressure > 18 mmHg

Procedures:
Initiating inhaled epoprostenol (iEPO) in a patient with ARDS secondary to COVID-19 or continuing therapy pulmonary vasodilator therapy for a patient transferred from an outside hospital
1. For patients transferred to Henry Ford Hospital who are on a pulmonary vasodilator (inhaled nitric oxide or inhaled epoprostenol) on arrival, the provider will place an order to continue inhaled epoprostenol and consult the ECMO Care Team. After approval by the consulting ECMO Care Team, inhaled epoprostenol can be initiated for patients with ARDS who are deemed candidates for ECMO. The ordering provider must indicate the name of the ECMO Care Team physician approving the order.
2. Inhaled epoprostenol will be managed by a respiratory therapist (RT).
3. Personal protective equipment:
    - Hospital personnel and visitors or other non-healthcare personnel must wear an appropriate mask during treatment and for at least 60 minutes after the completion of treatment:
        i. Hospital personnel: N95 mask that has been fit tested and appropriately sized.
        ii. Visitors or non-healthcare personnel: surgical mask.
4. An inhaled epoprostenol syringe will immediately be prepared by central pharmacy. If the patient is continuing therapy from an outside hospital the inhaled epoprostenol syringe prepared by central pharmacy will replace the product from the outside hospital.

- Pharmacy will prepare and deliver a 24-hour supply of inhaled epoprostenol (three syringes) to the medical ICU pod 4 or P4 pod 2 Pyxis refrigerator based on patient location

5. Based on the patient location, RT will remove an epoprostenol syringe from the medical ICU pod 4 or P4 pod 2 Pyxis refrigerator.
6. Inhaled epoprostenol will be administered by a RT.
7. Inhaled epoprostenol will be started at 0.05 mcg/kg/min based on ideal body weight.
    - For patients continuing therapy from an outside hospital, this dose adjustment will occur only after the new inhaled epoprostenol syringe prepared at Henry Ford Hospital has replaced that used by the outside hospital.
    - If the patient is on inhaled nitric oxide, once inhaled epoprostenol has been started wean nitric oxide therapy in half every 30 minutes till 5 ppm, then to 2 ppm, then 1 ppm, then to off
        i. A methemoglobin level should be ordered daily while a patient is receiving inhaled nitric oxide
8. Due to lack of compatibility data with other aerosolized medications, all other scheduled and PRN nebulized medications should be discontinued by the provider.
9. When RT removes the last syringe from the MICU pod 4 or P4 pod 2 Pyxis refrigerator, RT will notify pharmacy to dispense another 24 hours' worth of iEPO syringes for <u>each patient</u> on iEPO. Pharmacy can be reached by calling 16-3324 or 16-5469.
10. A positive response to treatment is defined as a 10-20% improvement in PaO2 or a 10% increase in the PaO2:FiO2 (P:F) ratio from baseline (prior to initiation of inhaled epoprostenol) to 4 hours after therapy initiation.
    - If there is no clinical response at 0.05 mcg/kg/min, notify the providers for orders to wean therapy.

<u>iEPO Initial Dosing:</u>

1. Epoprostenol will be initiated at **0.05 mcg/kg/min** based on the dosing weight via continuous nebulization via Aeronebs device. The dosing weight will be ideal body weight. If the patient's actual body weight is less than the ideal body weight, then actual body weight will be used for dosing.

2. Obtain patient's ideal body weight (IBW)
    Body Weight Calculation:
    IBW kg(male) = 50 + 2.3 (ht. in inches – 60)
    IBW kg(female) = 45 +2.3 (ht. in inches – 60)

3. Using the appropriate dosing weight, determine the inhaled epoprostenol infusion rate (ml/hr) using the formula below (usual dosage range: 0.005-0.05 mcg/kg/min, Maximum dose = 0.05 mcg/kg/min)
4. If hypotension (decrease in mean arterial pressure by 10-20 mmHg or increase in vasopressor use by 50%) should occur when inhaled epoprostenol is initiated, immediately decrease dose by 0.01 mcg/kg/min and notify the provider.
5. A positive response to treatment is defined as a 10-20% improvement in PaO2 or a 10% increase in the PaO2:FiO2 ratio from baseline (prior to initiation of inhaled epoprostenol) to 4 hours after therapy initiation.
    a. If there is no clinical response at 0.05 mcg/kg/min, notify the providers for orders to wean therapy.

Infusion Rate Formula:

Infusion rate (mL/hr) = $\frac{\text{dosing weight (kg) x epoprostenol dose (mcg/kg/min) x 60}}{\text{30 mcg/mL}}$

Weaning protocol:

To prevent rebound pulmonary vasoconstriction and hypoxemia, weaning should be performed per protocol (see protocol below).

Once the patient is ready to be weaned off inhaled epoprostenol, the primary team will enter the order in EPIC to initiate weaning protocol.

1. Do not decrease dose by more than 0.01 mcg/kg/min.
2. Repeat assessment of PaO2, SpO2, and/or PaO2:FiO2 ratio every **30 minutes to 2 hours** and reduce dose as tolerated until drug is discontinued.
    a. Decrease dose by 0.01 mcg/kg/min from tolerated dose until 0.01 mcg/kg/min, then reduce by 50% and off
        i. Example: 0.03 mcg/kg/min → 0.02 mcg/kg/min → 0.01 mcg/kg/min → 0.005 mcg/kg/min → OFF
    b. The respiratory therapist taking care of the patient will document dose weaning in the patient's MAR.
    c. If patient PaO2 decreases by 20% or PaO2/FiO2 by 10% since the last dose titration, consider resuming previous dose.
3. It may be necessary to increase the FiO2 and support hemodynamics during discontinuation. If rebound hypotension, tachycardia or increasing vasopressor needs occur, contact the providers. It may be helpful to wean the dose slowly before discontinuation.
4. Epoprostenol can be discontinued after contacting provider once the rate has been at 0.005 mcg/kg/min for 30 minutes to an hour and no negative response (PaO2 decreases by 20% or PaO2/FiO2 by 10% since the last dose titration) has occurred unless otherwise specified by provider

Administration by Respiratory Therapist

1. If RT received a provider order to start inhaled epoprostenol in the medical ICU, RT will notify central pharmacy that iEPO is to be started in the MICU and request that pharmacy prepare 3 iEPO syringes for the patient and request enough iEPO syringes for any other active patient(s) receiving iEPO on MICU for the next 24 hours.
2. Prepare ventilator circuit and proprietary nebulizer set with syringe pump
3. Once patient is started on inhaled epoprostenol, additional syringes may be obtained from MICU pod 4 or P4 pod 2 Pyxis refrigerator.
4. When RT removes the last syringe from the MICU pod 4 or P4 pod 2 Pyxis refrigerator, RT will notify pharmacy to dispense another 24 hours' worth of iEPO syringes for each patient on iEPO. Pharmacy can be reached by calling 16-3324 or 16-5469.
5. Inhaled epoprostenol will be the only medication attached to the Alaris syringe pump. No other Alaris IV or syringe modules are to be used on the Alaris pump being utilized for administration of inhaled epoprostenol.
6. Label pump and distal end of tubing "Epoprostenol for Inhalation"
7. Set-up Alaris Pump using provided 60-ml syringe. NOTE: total volume for drug is 50 ml.
8. Double-check and document the epoprostenol route, calculations, and pump settings:
    - Epoprostenol rate in mcg/kg/min x Dosing weight_{kg} = Epoprostenol rate in mcg/minute
    - Epoprostenol rate in mcg/minute ÷ epoprostenol concentration in mcg/mL = Epoprostenol infusion rate in mL/minute.
    - Epoprostenol infusion rate in mL/min x 60 = Epoprostenol infusion rate in mL/hr.

- RT must verify and document the dose and infusion rate calculations and pump settings with double check and documentation in EPIC by a second RT. If iEPO is initiated in the OR, another provider (eg, physicians, CNP, OR nurse) will need to double check dose, infusion rate calculation, and pump settings.

9. EPIC will request a co-sign as double check prior to administration in the OR and if administered on MICU
10. Initiate therapy and assess for desired clinical response.
    - If there is no clinical response at maximum dose after 4 hours, notify the providers to wean off therapy
    - Treatment may be continued if the desired clinical response is observed after 4 hours of treatment
11. Aerosol delivery into the ventilator circuit must be confirmed visually.
    - Verify that the epoprostenol is running, a drip may be visualized approximately every 30 seconds. Due to the precise nature of the Aerogen medication nebulizer, it is not unusual for the nebulizer to *appear* as though it has run dry between drops of medication. This does not affect the dosing.
12. Wean therapy as described in the "Weaning protocol" section above
13. Inhaled epoprostenol should not be interrupted even during transport.

Monitoring and Documentation:
****EMR documentation of initiation and decrease of dose MUST be noted in the patient's MAR and a comment should be added upon initiation of medication and change in the dose afterwards and in the adult respiratory flowsheet.

Ventilator parameters (peak airway pressure, plateau pressure, autopeep) will be monitored and documented by RT upon set-up of epoprostenol. The RT will monitor the administration of inhaled epoprostenol and document on the inhaled epoprostenol flowsheet initially and at 30 minutes post-initiation, 2 hours post-initiation then every 4 hours.

Once weaning has begun, monitoring and documentation will be every 30 minutes until weaned off medication.

At high doses, there is a potential for "spillover" into the systemic circulation which worsens shunt fraction and results in systemic hypotension. If "spillover" is suspected, contact the provider and the dose should be lowered.

<u>Nursing Monitoring and Documentation</u>

Heart rate, blood pressure, oxygen saturation, and respiratory rate will be monitored and documented per ICU standards. If advanced hemodynamic monitoring is present, assess and document hemodynamic parameters per ICU standards. Notify the provider for hypotension 10-20 mmHg or 50% increase in vasopressor requirements.

Once weaning has begun, monitor and document vital signs every 30 minutes until weaned off the therapy. The nurse will continue to monitor and document vital signs 30 minutes and 60 minutes after discontinuation of therapy. Notify the provider of any changes in the patient condition.

Although the Respiratory Therapist is responsible for set up and administration of the medication, the nurse can assist with monitoring the remaining amount of the medication in the syringe. If the syringe volume is low, notify the RT to obtain a new syringe. Do not abruptly stop

inhaled medication. If needed, the nurse can assist the Respiratory Therapist with troubleshooting the Alaris pump.

A dedicated Alaris syringe pump will be used for the inhaled medication. Ensure the Alaris syringe pump is independent from all other medication infusions. All other medications will be on a separate Alaris pump.

Ensure there are no interruptions in receiving the inhaled medication, including during transport. Patients will remain connected to the ventilator, with the inhaled Flolan administered during transportation.

If there is an emergent situation such as a code; the patient will remain on the ventilator. Do not take patient off vent or use an ambu bag. The patient must be ventilated using the “manual breath” button on the ventilator. Be aware the high - pressure alarm will sound when doing this.

Respiratory Therapy Responsibilities:

Be careful not to waste the solution. It takes 3 to 5 mL to prime the tubing.

Due to lack of compatibility data with other aerosolized medications, ensure all other scheduled and PRN nebulized medications are discontinued by the primary team.

Only administer Epoprostenol during invasive ventilation with a heated circuit and HEPA filter or 2 expiratory filters if HEPA filter not available.

Alert pharmacy (16-5469 or 16-5087) as soon as the last syringe is removed from the MICU pod 4 or P4 pod 2 Pyxis refrigerator when a patient is actively receiving therapy.

Perform ventilator /patient assessment as per normal policy with peak and plateau pressures along with auto-peep will be monitored and documented as stated in the above section.

Ensure two expiratory filters are used and changed every 4 hours or prn as indicated with auto-peep increase or if condensation present.

Monitor vital signs for a 20% improvement in oxygenation to consider continued therapy after 4 hour.

Wear gloves while priming the IV tubing used to administer the inhalation. IV tubing for epoprostenol solution needs to be changed every 24 hours.

**A second respiratory therapist will double check the infusion set-up and document in the electronic medical record before starting and with subsequent syringe exchanges.

Verify patient IBW in kg before setting up pump.

Epoprostenol solution is dispensed by pharmacy with an Amber overwrap; DO NOT REMOVE THE AMBER OVERWRAP.

Both the epoprostenol solution and drip feeding tubing need to be changed at least every 24 hours.

Alert pharmacy (16-5469 or 16-5087) as soon as the **last syringe** is removed from the MICU pod 4 or P4 pod 2 Pyxis refrigerator.

Epoprostenol solution is dispensed by pharmacy with an Amber overwrap; DO NOT REMOVE THE AMBER OVERWRAP.

AEROGEN AERONEB Vibrating Mesh Nebulizer to be used:
(Infusion pump device still to be determined at this time)

1. Assemble the vibrating mesh nebulizer for continuous use:
    a. Insert nebulizer into dry side of humidifier on ventilator circuit.
    b. Connect feed set to inlet of nebulizer.
    c. Select Continuous Mode before connecting medication tubing by holding blue button for 3 seconds.

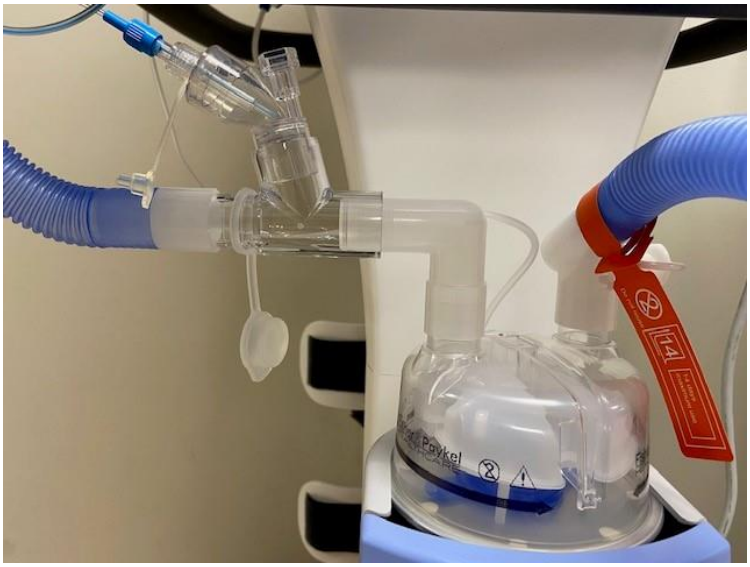
    Note: The silicon plug tethered to nebulizer should not be removed. Plug functions as a cap for nebulizer when not in use.

    Nebulization should be visible with regular intermittent pauses.

    Note: No aerosol output may be caused by:

    - Pressure build up in the reservoir
    - Reservoir cup over filling
    - If this occurs, draw out and discard medication.
    - During Transport the device operates using a rechargeable battery and when unplugged will change to the 30 Minute Interval Mode ONCE at destination and plugged in the respiratory therapist must change back to continuous mode.

AEROGEN AERONEB Set-up:



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