

Continuous Intravenous Infusion of Treprostinil (Remodulin)

Guideline for use of Remodulin in PICU, NICU and PCICU

I. BACKGROUND

A. Pulmonary arterial hypertension (PAH) is an abnormal reaction between the endothelial cells and smooth muscle cells in the small blood vessels of the lungs, causing vessel constriction and resultant increase in pulmonary arterial pressure. Prolonged increased pressure can lead to new smooth muscle cell growth and elaboration of extracellular matrix, which worsens narrowing of the pulmonary blood vessels, causing further increases to pulmonary vascular resistance (PVR) and pulmonary artery pressure.

These changes lead to right heart strain and ultimately right heart failure. Symptoms of PAH include dyspnea, fatigue, syncope, cough, dizziness, peripheral edema, cyanosis and chest pain. Clinical signs of PAH, particularly in a neonate, are increased oxygen requirement, increased difference between the pre- and post-ductal saturations, low cardiac output, echo evidence of increased right ventricular pressures (evidenced by interventricular septal position (objectively eccentricity index), tricuspid valve regurgitant jet velocity, pulmonary valve insufficiency jet velocity, direction of intra and extracardiac shunt, and shortened pulmonary artery acceleration time), elevated brain natriuretic peptide and a pattern of extreme oxygen saturation sensitivity to bedside interventions (i.e. suctioning, changing linens/diapers, repositioning).

B. Prostacyclin analogs, including treprostinil (herein use of term treprostinil also refers to trademarked Remodulin in its intravenous formulation) are the physiologic equivalent of the endogenous vasodilator prostacyclin. They cause direct vasodilation of pulmonary and systemic arterial vascular beds, inhibit platelet aggregation, and mediate vascular remodeling. Treprostinil is indicated to treat pediatric PAH. The goals of prostanoid therapies are to reduce pulmonary vascular resistance, reduce vascular remodeling, decrease pulmonary artery pressure, increase cardiac output, improve right ventricular function, decrease right ventricular hypertrophy, reduce symptoms and ultimately prolong life.

C. Symptoms/signs that patients may exhibit during treprostinil dose escalation may include, but are not limited to flushing, diarrhea, hypotension, hypoxemia, nausea, vomiting, and jaw pain.

II. INDICATIONS:

Pediatric patients including newborns >30 weeks gestation who have clinical or echo evidence of PH with a suboptimal response to inhaled nitric oxide, sildenafil, milrinone and/or bosentan. It is not necessary to fail all therapies prior to initiation of treprostinil. Among the disease processes associated with PH where the addition of a prostacyclin analog may be beneficial include but are not limited to:

1. Bronchopulmonary dysplasia (BPD)
2. Congenital diaphragmatic hernia (CDH)
3. Persistent pulmonary hypertension of the newborn (PPHN)
4. Meconium aspiration syndrome (MAS)
5. Congenital heart disease with perioperative PH or delayed closure of intracardiac shunts

III. RELATIVE CONTRAINDICATIONS:

1. Left-sided cardiac obstructive lesions (pulmonary vein stenosis, mitral stenosis, moderate to severe LV dysfunction or failure)
2. Congenital heart disease with ductal dependent systemic blood flow
3. Thrombocytopenia below 50,000/CE^oL
4. Active bleeding

III: DOSING FOR CONTINUOUS TREPROSTINIL IV INFUSION

Goal of treatment: to establish a dose at which PAH symptoms are improved, while minimizing excessive pharmacologic effects of treprostinil (hypotension, flushing, headache, nausea, emesis, restlessness, anxiety, and infusion site pain or reaction).

1. **Start dose:** Initial dose is 1-2 ng/kg/minute.
2. **Increase in dose:** Dose may be increased by 1 ng/kg/min up to every 60 minutes until there is:
 - a. A decrease in blood pressure below lower limit of normal for age refractory to intervention or other significant side effects (severe flushing, headache, nausea, diarrhea, worsening hypoxemia).
 - b. Objective evidence of decrease in pulmonary hypertension and satisfactory clinical improvement.
 - c. Once dose of 20 ng/kg/min is reached, titration should not exceed 2-3 ng/kg/min every 12-24 hours.
3. There is no maximum theoretical dose, but the target therapeutic dose is 50-80 ng/kg/min in infants and children, particularly when patient has been exposed to drug long term (e.g. chronic PAH).

IV: PRECAUTIONS

1. Treprostinil infusion requires a dedicated central line. In an emergency it can be administered temporarily through a PIV, while further central access is actively being obtained.
2. Only normal saline may be used as a trailer for the infusion. However, to avoid the inadvertent bolus administration of treprostinil, the trailer's rate cannot be increased once initiated unless directed by PH attending. Trailer rate should run at 2 ml/hr unless otherwise authorized by PH team.
3. A 0.2 micron filter should be used when infusing treprostinil.
4. **Avoid infusion interruptions.**
 - a. Although the half-life of treprostinil is 4 hours, symptoms of rebound PH can occur within 2 hours. In the event of drug disruption, all efforts should be made to restart infusion **as soon as possible but at most within 2 hours**. PH team must be alerted to disruptions beyond 2 hours, as it may be necessary to initiate inhaled prostacyclins.
 - b. If stopped, restarting the treprostinil infusion within 2 hours after an interruption can be done using the same dose rate. Interruptions for longer periods may require the dose of to be re-titrated.
5. **Avoid accidental bolusing.** A bolus of treprostinil may cause extreme hypotension and hypoperfusion.
 - a. DO NOT FLUSH treprostinil line.
 - b. No maintenance fluids, intermittent fluid boluses, or medications can be infused or piggybacked with treprostinil
6. No routine blood draws from dedicated treprostinil line to minimize infusion interruptions and decrease risk of line infections.

V. PROCEDURE - Inpatient Treprostinil Continuous IV Initiation

A. PRESCRIBING: Patients are to be admitted to the NICU, PICU or PCICU service; however, the infusion is to be managed by the Pulmonary Hypertension Attending Physician and Pulmonary Hypertension Nurse Practitioner. Titrations may be made by service attendings or fellows, but this should be done with PH team guidance. Contact the PH Service Attending or NP on-call with questions related to problems with the infusion.

B. DISPENSING (Pharmacy)

1. The pharmacist will verify the order in EMR

- a. Verify the order was entered by the Pediatric PH Attending Physician (On call physician to be found in on call directory).
 - b. Ordered concentration is appropriate base on patient's weight.
- 2. Pharmacist will direct the pharmacy technician to compound the medication using a 3-check system before dispensing the final products:
 - a. Check concentration and number of treprostinil vials, number of glycine diluents and appropriate IV syringe/viaflex bag to be used for mixing (first check)
 - b. Check the volume of each additive/diluent prepared in the hood before mixing. (second check)
 - c. Check the final mixture. (third check)
- 3. Pediatric pharmacist will:
 - a. Run daily EMR reports
 - b. Communicate with bedside RN daily to coordinate medication care plan for the next 24 hours.
 - c. Coordinate with the Central pharmacy the dispensing of medication for the next 24 hours.

C. ADMINISTRATION (Nursing)

- 1. IV treprostinil syringes are changed every 24 hours.
- 2. IV treprostinil tubing is changed per unit standard and with concentration
- 3. Follow the High Alert IV Infusion Medication Administration workflow located by clicking on the BCMA (Barcode Medication Administration) Workflows within the hyperspace EMR.
- 4. Each new syringe/bag, rate change, and dosage calculation must be independently checked by two RNs. This verification must be documented in the EMR.
- 5. Verify pump function and rate every 1 hour. This verification must be documented in the EMR as assumed care.
- 6. Patient will have routine unit monitoring (cardio-respiratory monitor, pulse oximetry).
- 7. Assess and document vital signs every 15 minutes x 4 after any rate change, then if stable, every hour x 4, and then every 2 hours at a minimum.
- 8. Evaluation and management of side effects and adverse reactions include and will be reported:
 - a. Site pain/erythema
 - b. Rash
 - c. Flushing
 - d. Hypotension
 - e. Dizziness
 - f. Jaw pain
 - g. Headache

- h. Bradycardia
- i. Nausea/vomiting
- j. Chest pain
- k. Diarrhea/abdominal pain
- l. Other adverse events include catheter-related skin infections, catheter-related bloodstream infection or sepsis, malfunctions in the delivery system (catheter fracture or pump malfunction), inadvertent bolus of or reduction in dosing, and thrombocytopenia.

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