Disclosure Statement

• The speaker has no actual or potential conflicts of interest in relation to this presentation.
Objectives

• Describe the most commonly targeted therapies utilized in the management of pulmonary hypertension (PH) in pediatric patients
  - Risk evaluation and mitigation strategies (REMS)

• Identify potential causes of PH medication-related safety pitfalls in the inpatient and outpatient settings and discuss strategies to enhance safety around these agents
Texas Children’s Hospital (TCH)

• 684-bed, tertiary-care teaching hospital
  - Baylor College of Medicine

• Texas Medical Center

  - Pulmonary #1
  - Cardiology #2

• PHA-accredited Center of Comprehensive Care
General Measures

- Early treatment of fever
- Early and aggressive treatment of respiratory illnesses
- Immunizations
  - Influenza vaccine
  - Pneumococcal
- Treatment of anemia
- Restriction of physical activity

Nonspecific Supportive Therapies

• Diuretics – Use cautiously as patients with PH are often preload dependent to maintain adequate cardiac output
  - Furosemide, chlorothiazide, spironolactone

• Digoxin – Limited data especially with chronic use

• Anticoagulation – Limited data (potential benefit of long-term use has not been studied in pediatric PH)
  - Recommended in children with idiopathic or heritable PH, low cardiac output, hypercoagulable states, and long-term indwelling IV catheter → consider risks vs. benefits
  - Warfarin (target INR 1.5–2), enoxaparin (target anti-Xa level 0.2-0.4 units/mL), heparin, aspirin

## Pharmacologic Therapies

<table>
<thead>
<tr>
<th>Class</th>
<th>Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium channel blockers</td>
<td>Nifedipine, Diltiazem, Amlodipine</td>
</tr>
<tr>
<td>Nitric oxide</td>
<td></td>
</tr>
<tr>
<td>Phosphodiesterase-5 inhibitors (PDE-I)</td>
<td>Sildenafil, Tadalafil</td>
</tr>
<tr>
<td>Endothelin receptor antagonists (ERA)</td>
<td>Bosentan, Ambrisentan, Macitentan</td>
</tr>
<tr>
<td>Prostacyclin and analogues</td>
<td>Epoprostenol, Treprostinil, Iloprost</td>
</tr>
<tr>
<td>Other agents</td>
<td>Riociguat, Selexipag</td>
</tr>
</tbody>
</table>
Calcium Channel Blockers

• Mechanism of action (MOA): Inhibition of Ca^{++} flux across calcium channels \(\rightarrow\) inhibition of contractile process of smooth muscle (relaxation of vascular smooth muscle)

• Historically used primarily for the management of PH due to absence of alternative therapies
  - Rarely used due to other targeted options

• Only for those reactive to acute vasodilator testing (AVT) and >1 year of age

• Beneficial in \(\sim\)20% of positive responders

Calcium Channel Blockers

<table>
<thead>
<tr>
<th>Agent</th>
<th>Initial Dose</th>
<th>Maintenance Dose</th>
<th>Max Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nifedipine</td>
<td>0.1 - 0.2 mg/kg PO TID</td>
<td>2-3 mg/kg/day PO divided TID</td>
<td>180 mg/DAY</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>0.5 mg/kg PO TID</td>
<td>3-5 mg/kg/day PO divided TID</td>
<td>360 mg/DAY</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>0.1-0.3 mg/kg PO daily</td>
<td>2.5-10 mg PO daily</td>
<td>10 mg/DAY</td>
</tr>
</tbody>
</table>

- Adverse effects: Hypotension, peripheral edema, headache, dizziness, bradycardia, constipation

- May be difficult to tolerate long-term due to the need for higher doses and adverse effects
  - Must monitor closely as patients may deteriorate over time on monotherapy

Nitric Oxide (iNO)

- MOA: Increase cGMP → decreases intracellular Ca → pulmonary vasodilation
  - Selective effect on pulmonary vasculature

- Shown to be safe and efficacious in the treatment of PPHN

- Used in critically ill children with PH
  - Often used intra- and post-operatively
  - Dosage range: 1-20 ppm as continuous inhalation

http://www.reading.ac.uk/nitricoxide/intro/no/cgmp.htm
## Nitric Oxide (iNO)

<table>
<thead>
<tr>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Requires delivery via continuous inhalation due to short half-life (inpatient therapy)</td>
</tr>
<tr>
<td>Different delivery modes (via endotracheal tube, nasal canula (NC), high flow NC, nasal continuous positive airway pressure, etc.)</td>
</tr>
<tr>
<td>- Differences in actual delivery of medication</td>
</tr>
<tr>
<td>Costly</td>
</tr>
</tbody>
</table>

- **Adverse effects:** Hypotension, hypoxemia, methemoglobinemia, pulmonary edema

- **Risk of rebound PH**
  - Avoid abrupt discontinuation
  - One dose of sildenafil may be used to help wean off iNO

Phosphodiesterase-5 Inhibitors

• Sildenafil

  - MOA: Selective inhibitor of PDE type 5 → increase cGMP → vascular smooth muscle relaxation
  
  - Most widely used PH-targeted therapy in children

  • Shown to attenuate rebound PH associated with withdrawal of inhaled nitric oxide

  • Shown to improve exercise capacity and hemodynamics in children with PPHN, idiopathic PH, and PH associated with congenital heart disease (small studies)

Sildenafil

• Pharmacokinetics (adults)
  - Rapid oral absorption; oral bioavailability 40%
  - Protein binding ~96%
  - Half-life 4 hours
  - Metabolism via CYP450 enzyme system
    • CYP3A4 (major); CYP2C9 (minor)
    • Drug interactions (e.g., bosentan)
  - Excretion: Feces (80%); urine (13%)
  - Decreased clearance with moderate to severe renal or hepatic function

Sildenafil

<table>
<thead>
<tr>
<th>Dosage Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infants</strong></td>
</tr>
<tr>
<td>0.5-1 mg/kg PO three times daily</td>
</tr>
<tr>
<td><strong>Children ≥1 year and &lt;20 kg</strong></td>
</tr>
<tr>
<td>10 mg PO three times daily</td>
</tr>
<tr>
<td><strong>Children ≥1 year and ≥20 kg</strong></td>
</tr>
<tr>
<td>20 mg PO three times daily</td>
</tr>
</tbody>
</table>

- **Adverse effects:** Systemic hypotension, headache, diarrhea, vomiting, flushing

- Long-term vision or hearing problems?

FDA Drug Safety Communication: FDA recommends against use of Revatio (sildenafil) in children with pulmonary hypertension

• August 30, 2012

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Low</th>
<th>Med</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥8 – 20</td>
<td>N/A</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>&gt;20 – 45</td>
<td>10</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>&gt;45</td>
<td>10</td>
<td>40</td>
<td>80</td>
</tr>
</tbody>
</table>

FDA Warning

• Pharmacies refused to dispense sildenafil to children

• School nurses refused to administer sildenafil to children

• Parents/caregivers very concerned about safety

FDA Clarification (March 31, 2014)

The purpose of the recommendation was to raise awareness of clinical trial results showing a higher risk of mortality in pediatric patients taking a high dose of Revatio when compared to pediatric patients taking a low dose. This recommendation was not intended to suggest that Revatio should never be used in children; however, some health care professionals have interpreted this information as a contraindication, and have refused to prescribe or administer the drug. We recognize there may be situations in which the benefit-risk profile of Revatio may be acceptable in individual children, for example, when other treatment options are limited and Revatio can be used with close monitoring.

https://www.fda.gov/Drugs/DrugSafety/ucm390876.htm
## Sildenafil (TCH Practice)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Initial Dose</th>
<th>Maintenance Dose</th>
<th>Max Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td>0.25 mg/kg PO Q6h, titrate up by 0.25 mg/kg/dose every 24 hours as tolerated to maintenance dose</td>
<td>1 mg/kg PO Q6h</td>
<td>1 mg/kg/dose</td>
</tr>
<tr>
<td>Children ≥1 year</td>
<td>0.25 mg/kg PO Q8h, titrate up by 0.25 mg/kg/dose every 24 hours as tolerated to maintenance dose</td>
<td>1 mg/kg PO Q8h (or 3 times daily)</td>
<td>1 mg/kg/dose, not to exceed 20 mg/dose</td>
</tr>
</tbody>
</table>
## Sildenafil

### Formulations

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablet</td>
<td>20 mg (Revatio®, generic)</td>
</tr>
<tr>
<td></td>
<td>25 mg, 50 mg, 100 mg (Viagra®)</td>
</tr>
<tr>
<td>Oral suspension</td>
<td>10 mg/mL (Revatio®)</td>
</tr>
<tr>
<td>IV solution</td>
<td>10 mg/12.5 mL (Revatio®, generic)</td>
</tr>
</tbody>
</table>

Sildenafil

• IV dose
  - In adults, IV dose is ~50% of enteral dose
  • Limited data in pediatrics (continuous infusion vs. intermittent infusions)
  • TCH practice

<table>
<thead>
<tr>
<th>IV Sildenafil</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>For sildenafil-naïve or hemodynamically unstable patients</td>
<td>Step 1</td>
</tr>
<tr>
<td></td>
<td>Step 2</td>
</tr>
<tr>
<td></td>
<td>Step 3</td>
</tr>
<tr>
<td></td>
<td>Step 4</td>
</tr>
<tr>
<td>For patients who are hemodynamically stable and previously on enteral sildenafil therapy: Administer 50% of previous enteral dose</td>
<td></td>
</tr>
</tbody>
</table>

Sildenafil

• Medication safety point – oral suspension
  - Commercially-available formulation (10 mg/mL) vs. compounded formulation (2.5 mg/mL)
    • Some pharmacies continuing to compound oral suspension instead of dispensing commercially-available one
      - Clearly specify the concentration on prescription
      - Ensure the patient/parent(s)/caregiver(s) are aware of the concentration ordered
  
• Per the FDA:

  5. What are the risks associated with compounded drugs?

  There can be health risks associated with compounded drugs that do not meet federal quality standards. Compounded drugs made using poor quality practices may be sub- or super-potent, contaminated, or otherwise adulterated. Additional health risks include the possibility that patients will use ineffective compounded drugs instead of FDA-approved drugs that have been shown to be safe and effective.

  [Link to FDA guidance](https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm339764.htm#risks)
Phosphodiesterase-5 Inhibitors

• Tadalafil
  - Longer half-life of 15-17.5 hours; 35 hours (if not receiving bosentan) → once daily dosing
  - Limited data in infants and children
    • Transition from sildenafil maintenance dose: 1 mg/kg PO daily (max: 40 mg/dose)

Formulations

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablet</td>
<td>20 mg (Adcirca®)</td>
</tr>
<tr>
<td></td>
<td>2.5 mg, 5 mg, 10 mg, 20 mg (Cialis®)</td>
</tr>
<tr>
<td>Oral suspension (compounded)</td>
<td>5 mg/mL</td>
</tr>
</tbody>
</table>
Tadalafil

• Medication safety point – *compounded* oral suspension
  - Tablets crushed and mixed with various ingredients
  - Settling of active ingredient may occur when sitting on the shelf → must shake vigorously prior to each dose

Tadalafil

• Medication safety point – *compounded* oral suspension
  
  - Electronic medical record (EPIC) order entry of nonformulary compounded medication

  • Use of “custom medication” option

```sql
custom medication 1 mg/kg (Dosing Weight) [154563210]
Ordered Dose: 1 mg/kg × 9.5 kg (Dosing Weight)
Administration Dose: --
Start: 08/11/16 0900

Admin Instructions:
* Non-Formulary UNIT DOSE Medication *
Tadalafil 5 mg/mL suspension
Dose = 9.5 mg = 1.9 mL
```
Endothelin Receptor Antagonists

• Bosentan (Tracleer®)
  - Dual antagonist (ET_A and ET_B)
  - Substrate and inducer of CYP 2C8/9, 3A4
  - Adverse effects: ↑ LFTs (~3% in children), anemia, edema, headache, flushing

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Oral/Enteral Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10 kg</td>
<td>1 mg/kg BID x 4 weeks then increase to 2 mg/kg BID</td>
</tr>
<tr>
<td>10-20 kg</td>
<td>31.25 mg daily x 4 weeks then increased to 31.25 mg BID</td>
</tr>
<tr>
<td>&gt;20-40 kg</td>
<td>31.25 mg BID x 4 weeks then increase to 62.5 mg BID</td>
</tr>
<tr>
<td>&gt;40 kg</td>
<td>62.5 mg BID x 4 weeks then increase to 125 mg BID</td>
</tr>
</tbody>
</table>

- Dose adjustment needed for hepatic injury

Bosentan

• Oral formulations
  - Tablet 62.5 mg, 125 mg

• Crushing of tablets not recommended; tablets will disintegrate rapidly (within 5 minutes) in 5-25 mL of water → appropriate aliquot of the suspension can be used to deliver the prescribed dose. Any remaining suspension should be discarded.
  - Should not be mixed or dissolved in liquids with a low (acidic) pH (e.g., fruit juices) due to poor solubility
Bosentan

• Medication safety point
  - Unscored tablets (TCH practice)
    • Using a pill cutter, split no more than once
    • For doses <62.5 mg

  Step 1: Split 62.5 mg tablet in half using pill cutter
  Step 2: Dissolve ½ tablet in 10 mL of water (concentration 3.125 mg/mL)
  Step 3: Withdraw appropriate volume as instructed to obtain prescribed dose and administer immediately
  Step 4: Discard remaining solution
Endothelin Receptor Antagonists

- **Ambrisentan (Letairis®)**
  - Type-A selective antagonist
  - Dose
    
    | Oral/enteral dose |
    |-------------------|
    | Adults            |
    | 5 mg daily; can increase to 10 mg daily |

- Limited data in pediatrics

  - Retrospective cohort study in 2 pediatric centers

<table>
<thead>
<tr>
<th>Patient body weight (kg)</th>
<th>Initial dose (patients number)</th>
<th>Current dose (patients number)</th>
<th>Discontinue patients (patients number)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>2.5 mg (3)</td>
<td>5 mg (3)</td>
<td>(0)</td>
</tr>
<tr>
<td>20–40</td>
<td>2.5 mg (8), 5 mg (12)</td>
<td>5 mg (13), 10 mg (4)</td>
<td>2.5 mg (1), 5 mg (2)</td>
</tr>
<tr>
<td>&gt;40</td>
<td>5 mg (15)</td>
<td>5 mg (7), 10 mg (6)</td>
<td>5 mg (2)</td>
</tr>
</tbody>
</table>

Ambrisentan (Letairis®)

• Oral formulations: Tablet 5 mg, 10 mg

• Administration
  - Swallow tablet whole; do not split, crush, or chew tablet

• Advantages
  - Once daily dosing
  - No drug interaction with PDE-5 inhibitors observed
  - Similar AE profile as bosentan but with ↓ risk of hepatotoxicity (check liver function every 3 months)

Newer Agent – Macitentan (Opsumit®)

• Dual antagonist ($\text{ET}_A$ and $\text{ET}_B$)

<table>
<thead>
<tr>
<th>Oral/enteral dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
</tr>
<tr>
<td>10 mg daily</td>
</tr>
</tbody>
</table>

• Administration
  - Swallow tablet whole; do not split, crush, or chew tablet

• Very limited data in pediatrics
  - Phase III trial (TOMORROW): Multicenter, controlled, randomized, open-label event-driven study to assess efficacy, safety, and pharmacokinetics of macitentan vs. standard of care in children

Risk Evaluation and Mitigation Strategies (REMS)

• Food and Drug Administration Amendments Act of 2007 gave FDA authority to require REMS from manufacturers to ensure benefits outweigh its risks

• Factors considered when determining need for REMS

• >100 drugs with required REMS

http://www.ashp.org/REMS
### REMS Requirements

| Bosentan | Prescribers and patients must enroll in REMS program  
Prescriber must:  
- Determine reproductive status of female patients  
- Educate and counsel patients/caregivers about risks  
- Monitor liver function **monthly** for all patients  
- Monitor pregnancy status **monthly** for applicable patients  
- Report any adverse effects and pregnancies  
- Inpatient pharmacy must obtain certification to stock and dispense bosentan |

| Ambrisentan Macitentan | Prescribers and female patients must enroll in REMS program  
Prescriber must:  
- Determine reproductive status of female patients  
- Educate and counsel female patients/caregivers about risks  
- Monitor pregnancy status **monthly** for applicable patients  
- Report any adverse effects and pregnancies  
- Inpatient pharmacy must obtain certification to stock and dispense macitentan |

*NOTE: ERAs only available through a limited # of certified pharmacies*
Online Resources

• www.tracleerrems.com

• www.letairisrems.com

• www.opsumitrems.com
Inpatient Pharmacy Certification for Bosentan

- Complete training in the Tracleer REMS Program by reading the Prescribing Information, Medication Guide and the Prescriber and Pharmacy Guide for the Tracleer REMS Program
- Train all dispensing staff on the Tracleer REMS Program requirements and Tracleer REMS materials before they dispense Tracleer
- Put processes and procedures in place to ensure the REMS requirements are met
- Dispense only to those patients under the supervision and care of a healthcare provider who is enrolled in the Tracleer REMS Program
- Dispense to a patient only after he/she has been enrolled in the Tracleer REMS Program or if he/she will be enrolled prior to discharge from the healthcare facility. A patient who has not been enrolled by the certified prescriber will not have access to Tracleer in the outpatient setting until registration has been completed
- Dispense no more than a fifteen (15) day temporary supply of Tracleer upon discharge of any patient
- Notify Actelion or FDA of any adverse events, including hepatotoxicity, and report any pregnancy during Tracleer treatment
- Not transfer Tracleer to any pharmacy, practitioner or any healthcare setting not certified by Actelion Pathways
- Develop a process to track compliance with the conditions above and provide information about its compliance to Actelion
TCH Practice

<table>
<thead>
<tr>
<th>DISPLAY_NAME</th>
<th>DOSE</th>
<th>UNITS</th>
<th>FREQ_NAME</th>
<th>PROV_NAME</th>
<th>PHYSICIAN</th>
<th>LIVER</th>
<th>PREG</th>
</tr>
</thead>
<tbody>
<tr>
<td>bosentan PO SOLN (TCH) 7 mg</td>
<td>7</td>
<td>MG</td>
<td>2 TIMES DAILY</td>
<td>NEPTUNE, ELIZABETH J</td>
<td>Dr. N. Varghese</td>
<td>Yes</td>
<td>N/A</td>
</tr>
<tr>
<td>bosentan PO SOLN (TCH) 7 mg</td>
<td>7</td>
<td>MG</td>
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<td>MG</td>
<td>2 TIMES DAILY</td>
<td>NEPTUNE, ELIZABETH J</td>
<td>Dr. N. Varghese</td>
<td>Yes</td>
<td>N/A</td>
</tr>
<tr>
<td>bosentan PO SOLN (TCH) 31.25 mg</td>
<td>31.25</td>
<td>MG</td>
<td>2 TIMES DAILY</td>
<td>VARGHESE, NIDHY PAULOSE</td>
<td>Dr. N. Varghese</td>
<td>Yes</td>
<td>N/A</td>
</tr>
<tr>
<td>bosentan PO SOLN (TCH) 31.25 mg</td>
<td>31.25</td>
<td>MG</td>
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<td>Dr. N. Varghese</td>
<td>Yes</td>
<td>N/A</td>
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<td>bosentan PO SOLN (TCH) 31.25 mg</td>
<td>31.25</td>
<td>MG</td>
<td>2 TIMES DAILY</td>
<td>VARGHESE, NIDHY PAULOSE</td>
<td>Dr. N. Varghese</td>
<td>Yes</td>
<td>N/A</td>
</tr>
<tr>
<td>bosentan PO SOLN (TCH) 48 mg</td>
<td>48</td>
<td>MG</td>
<td>EVERY 12 HOURS</td>
<td>BRYANT, TASHA D</td>
<td>Liz Neptune (PA-C)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>bosentan PO SOLN (TCH) 12.5 mg</td>
<td>12.5</td>
<td>MG</td>
<td>2 TIMES DAILY</td>
<td>DIKE, PEACE</td>
<td>Dr. F. Ruiz</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>bosentan PO SOLN (TCH) 12.5 mg</td>
<td>12.5</td>
<td>MG</td>
<td>2 TIMES DAILY</td>
<td>DIKE, PEACE</td>
<td>Dr. F. Ruiz</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>bosentan PO SOLN (TCH) 10.5 mg</td>
<td>10.5</td>
<td>MG</td>
<td>2 TIMES DAILY</td>
<td>NEPTUNE, ELIZABETH J</td>
<td>Dr. N. Varghese</td>
<td>Yes</td>
<td>N/A</td>
</tr>
<tr>
<td>bosentan PO SOLN (TCH) 10.5 mg</td>
<td>10.5</td>
<td>MG</td>
<td>2 TIMES DAILY</td>
<td>NEPTUNE, ELIZABETH J</td>
<td>Dr. N. Varghese</td>
<td>Yes</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Prostacyclin

- Epoprostenol
  - MOA: Stimulation of adenylyl cyclase $\rightarrow$ increased cAMP $\rightarrow$ vasodilation of all vascular beds
  - Administration
    - Continuous IV infusion
      - Initiate at 1-2 ng/kg/min and up-titrate by 1-2 ng/kg/min at intervals of $\geq$15 minutes to clinical effect or until dose-limiting adverse effects (no maximum dose)
      - TCH practice: Titrate every 6-12 hours as tolerated

Epoprostenol

• Administration

  - Continuous inhalation (limited data in pediatrics)

    • Dosage range 6.25-50 ng/kg/min
    • Requires constant rate via nebulizer (e.g., 8 mL/hr, 16 mL/hr)

    • Some institutions use inhaled epoprostenol as an alternative to iNO

Epoprostenol

• Disadvantages
  - Very short half-life of 3-5 MINUTES (continuous IV infusion)
    • Need for back-up medication, pump, supplies
  - Risk for central line infection
  - Flolan®
    • Limited stability (8 hours at room temperature)
    • Only compatible with Flolan®-specific diluent

• Adverse effects
  - Hypotension (dose-limiting), headache, dizziness, nausea, chest pain, flushing, jaw pain

Epoprostenol

<table>
<thead>
<tr>
<th>Formulations</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>IV, powder for reconstitution</td>
<td>0.5 mg, 1.5 mg (Flolan®, Veletri®, generic)</td>
</tr>
</tbody>
</table>

• Advantages of Veletri®
  - Longer stability (24-72 hours at room temperature dependent on concentration and preparation/storage)
  - Compatible with NS and sterile water
Epoprostenol – Nursing Implications (TCH Practice)

• Must have dedicated IV access with dedicated patent back-up access site
  - Patient may have CVC and back up PIV, double-lumen CVC, or 2 PIVs

• Do NOT flush line or stop infusion abruptly; do NOT turn off in a coding patient

• Dosing adjustments made according to patient-specific dosing sheet

• Monitor closely for adverse effects
Prostacyclin Analogue

• Treprostinil (Remodulin®)
  - Continuous IV or subcutaneous (SQ) administration
  - Half-life about 4 hours
  - Stable at room temperature and neutral pH
  - Similar adverse effect profile as epoprostenol
    • Pain, erythema, inflammation at SQ injection site
Treprostinil (Remodulin®)

• Dosage titration

- Required dose typically higher than epoprostenol

<table>
<thead>
<tr>
<th>Prostacyclin-naïve</th>
<th>Dosage Titration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiate at 1-2 ng/kg/min and uptitrate by 1-2 ng/kg/min every 6-12 hours (inpatient) or more slowly as outpatient</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Transition from epoprostenol</th>
<th>Table</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step</td>
<td>Epoprostenol Dose</td>
</tr>
<tr>
<td>1</td>
<td>Maintain current dose</td>
</tr>
<tr>
<td>2</td>
<td>Decrease to 80% initial dose</td>
</tr>
<tr>
<td>3</td>
<td>Decrease to 60% initial dose</td>
</tr>
<tr>
<td>4</td>
<td>Decrease to 40% initial dose</td>
</tr>
<tr>
<td>5</td>
<td>Decrease to 20% initial dose</td>
</tr>
<tr>
<td>6</td>
<td>Decrease to 5% initial dose</td>
</tr>
<tr>
<td>7</td>
<td>Discontinue epoprostenol</td>
</tr>
</tbody>
</table>
Treprostinil (Remodulin®)

• Preferred parenteral prostacyclin for chronic use due to longer half-life compared to epoprostenol (4 hours vs. 3-5 minutes)

• Can be administered IV; however, subcutaneous infusion often preferred for long-term use
Transition from Epoprostenol to IV Treprostinil (TCH Practice)

Transition from IV epoprostenol (Veletri®) to IV treprostinil (Remodulin®)

- Titrate every 6 hours as tolerated per Pulmonary Hypertension Service recommendations
- Compatibility
  - Epoprostenol (Veletri®) and treprostinil (Remodulin®) NOT compatible with other medications; NS may be used as a carrier fluid as needed for epoprostenol and treprostinil rates < 1 mL/hr
  - NOTE: If NS used as carrier fluid, rate should be 1 mL/hr.
- Access
  - Epoprostenol (Veletri®) and treprostinil (Remodulin®) each need a dedicated line; back-up line needed
  - Do NOT flush, interrupt or stop the infusions
- Back-up
  - Epoprostenol (Veletri®) must have a back-up syringe and pump readily available; back-up dose kept in medication refrigerator
- During transition, increases in PH symptoms (e.g., decrease in oxygen saturation, trouble breathing), should be first treated with an increase in treprostinil (Remodulin®) dose. Occurrence of prostacyclin-associated side effects (e.g., hypotension, headache, nausea/vomiting, refusal to eat, diarrhea, flushing, irritability) should be treated by decreasing the dose of epoprostenol (Veletri®).
- Do NOT adjust the dose based on changes in weight without first discussing with the Pulmonary Hypertension Service

<table>
<thead>
<tr>
<th>Expected Date/Time</th>
<th>Actual Date/Time</th>
<th>VELETRI® Continuous IV</th>
<th>REMODULIN® Continuous IV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Dose (ng/kg/min)</td>
<td>Conc. (ng/mL)</td>
</tr>
<tr>
<td>68</td>
<td></td>
<td>10.09</td>
<td>30,000</td>
</tr>
<tr>
<td>54</td>
<td></td>
<td>1.73</td>
<td>15,000</td>
</tr>
<tr>
<td>41</td>
<td></td>
<td>1.31</td>
<td>15,000</td>
</tr>
<tr>
<td>27</td>
<td></td>
<td>2.59</td>
<td>5,000</td>
</tr>
<tr>
<td>14</td>
<td></td>
<td>1.34</td>
<td>5,000</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>1.44</td>
<td>1,000</td>
</tr>
<tr>
<td>Discontinue</td>
<td></td>
<td>82</td>
<td>30,000</td>
</tr>
</tbody>
</table>

Any questions or issues, contact the PH Team:
- During business hours: PH pager 2024
- After hours/weekends: Pulmonary Fellow On-Call via page operator
Treprostinil (Remodulin®)

• Subcutaneous pump may not be available from the hospital; provided by a Specialty Pharmacy like Accredo Therapeutics or CVS Caremark
  - CADD-MS3 pump often used for subcutaneous infusion
    • Minimum rate 0.002 mL/hr with increases only in increments of 0.002 mL/hr
  - Treprostinil (straight drug) in 3-mL subcutaneous syringe good for 72 hours

IV Treprostinil – Nursing Implications (TCH Practice)

• Must have dedicated IV access with patent back-up access site

• Do NOT flush line or stop infusion abruptly

• No need for back-up syringe and pump due to half-life of about 4 hours

• Dosing adjustments made according to patient-specific dosing sheet

• Monitor closely for adverse effects
SQ Treprostinil – Nursing Implications (TCH Practice)

• Parent(s)/caregiver(s) manages SQ pump including catheter and syringe changes
  - Collaborate with parent(s)/caregiver(s) to ensure proper functioning of pump
  - Rate/dose verify on eMAR

• Assess site/catheter *hourly* with each shift assessment

• Ensure patent IV access
  - For patients on a stable dose of SQ continuous infusion, a dosing sheet for SQ to IV rate conversion available at the bedside
**SQ to IV Transition Sheet (TCH Practice)**

**Subcutaneous Treprostinil (Remodulin®)**

- Patient to use home subcutaneous pump and supplies provided by Accredro Specialty Pharmacy. Parent to manage the pump and supplies.
  - TCH Pharmacy to provide the treprostinil in 3-mL subcutaneous syringe along with tubing
    - Remodulin 1 mg/mL in subcutaneous syringe along with tubing are good for up to 72 hours
  - The subcutaneous pump can only be adjusted in increments of 0.002 mL/hr

- For questions or concerns regarding the subcutaneous pump, Accredro Specialty Pharmacy has a PH support line available 24 hours a day. The number is 1-866-344-4874.

- **Do NOT adjust the dose based on changes in weight without first discussing with the Pulmonary Hypertension Service**

**If SQ Remodulin® infusion malfunctions, and patient must transition to IV Remodulin®**

<table>
<thead>
<tr>
<th>Order-Specific Weight</th>
<th>REMODULIN® Continuous SQ</th>
<th>REMODULIN® Continuous IV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dose (ng/kg/min)</td>
<td>Conc. (mg/mL)</td>
</tr>
<tr>
<td>7.4 kg</td>
<td>54</td>
<td>1</td>
</tr>
</tbody>
</table>

Any questions or issues, contact the PH Team:
- During business hours: PH pager 2024
- After hours/weekends: Pulmonary Fellow On-Call via page operator
## EPIC Nursing Documentation (TCH Practice)

<table>
<thead>
<tr>
<th>Necessity</th>
<th>1100</th>
<th>1200</th>
<th>1300</th>
<th>1400</th>
<th>1430</th>
<th>1500</th>
<th>1600</th>
<th>1700</th>
<th>1800</th>
<th>1900</th>
<th>2000</th>
<th>2100</th>
<th>2200</th>
</tr>
</thead>
<tbody>
<tr>
<td>All lines reviewed for necessity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Y</td>
</tr>
</tbody>
</table>

### Subcutaneous Line - 01/22/15

<table>
<thead>
<tr>
<th>Site Assessment</th>
<th>Placement</th>
<th>Placement/Admission date/Time: 01/22/15 1500</th>
<th>Orientation: Left</th>
<th>Percutaneous Location: Upper arm</th>
<th>Inserted by: David, RN</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDI</td>
<td>CDI</td>
<td>CDI</td>
<td>Infusing</td>
<td>Infusing</td>
<td>CDI</td>
</tr>
<tr>
<td>CDI</td>
<td>CDI</td>
<td>CDI</td>
<td>CDI</td>
<td>CDI</td>
<td>CDI</td>
</tr>
<tr>
<td>CDI</td>
<td>CDI</td>
<td>CDI</td>
<td>CDI</td>
<td>CDI</td>
<td>CDI</td>
</tr>
<tr>
<td>CDI</td>
<td>CDI</td>
<td>CDI</td>
<td>CDI</td>
<td>CDI</td>
<td>CDI</td>
</tr>
</tbody>
</table>

### Dressing Quality

| Dressing/Site Care | CDI       | CDI                                         | CDI               | CDI                             | CDI                    |

---

**Saturday January 24, 2015**

**Treprostinil Sodium SOLN**: Dose 20 ng/kg/min × 15.5 kg (Dosing Weight) : Admin Dose 330 ng/min : 0.02 mL/hr : Subcutaneous Infusion : CONTINUOUS

This medication is a non-formulary medication.
To be used with patient’s home subcutaneous pump.
Treprostinil (1 mg/mL) 3-mL syringe
Please dispense in a 3-mL subcutaneous syringe along with the tubing provided by the manufacturer.

**0700 Rate/Dose Verif**: 20 ng/kg/min
SQ Treprostinil – Nursing Implications (TCH Practice)

• Parent(s)/caregiver(s) are able to leave the bedside
  - Ensure reliable form of communication with parent(s)/caregiver(s)
  - Ensure parent(s)/caregiver(s) able to return to bedside within ~2 hours if SQ pump malfunctions
SQ Treprostinil Infusion Site Pain

• Potent vasodilator and pro-inflammatory in soft tissues

• Pain management options

<table>
<thead>
<tr>
<th>Ice packs or warm compresses</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLO gel (compounded topical product provided by Specialty Pharmacy)</td>
</tr>
<tr>
<td>H1 and H2 blockers (e.g., ranitidine, cetirizine)</td>
</tr>
<tr>
<td>Triamcinolone cream 0.1%</td>
</tr>
<tr>
<td>NSAIDs (e.g., ibuprofen)</td>
</tr>
<tr>
<td>Opioids (e.g., hydrocodone/acetaminophen)</td>
</tr>
<tr>
<td>Gabapentin (for older children/adolescents)</td>
</tr>
<tr>
<td>Topical lidocaine or 5% patch (for older children/adolescents)</td>
</tr>
</tbody>
</table>

• Involve Child Life

Photo courtesy of Patricia Lawrence, Children’s Healthcare of Atlanta
Prostacyclin Analogue

• Treprostinil (Tyvaso®)
  - Inhalation therapy (3-9 inhalations/dose)
  - Half life about 4 hours → Administrations 4 times a day
  - Adverse effects
    • Cough, Flushing, throat irritation, hypotension, headache, epitaxis, wheezing
  - Must be used with Tyvaso Inhalation System

• TCH practice: Patient must bring in home device during hospitalizations

Oral Treprostinil (Orenitram®)

• May be used in prostacyclin-naïve patients with titration of dosing every 3 to 4 days or in transition of patients receiving prostacyclin in other forms with simultaneous up- and down-titrations

• BID dosing leads to moderate variation in peak and trough level whereas TID or Q8h dosing results in smoother blood levels

• Extended release tablets must be swallowed whole with food

https://www.orenitram.com/Content/hcp/images/orenitram-dosage-strengths.jpg
Oral Treprostinil (Orenitram®)

• If dose is missed, patient should take as soon as possible.
  - If ≥2 doses missed, restart at a lower dose and re-titrate

• Common adverse effects include diarrhea, nausea/vomiting and headache

• In the event of severe acute gastroenteritis, patients on oral treprostinil may need to be hospitalized to be given IV treprostinil until able to resume oral administration

# Inhaled to Oral Treprostinil – Example
## (TCH Experience)

<table>
<thead>
<tr>
<th>DAY</th>
<th>Dose of Tyvaso®</th>
<th>Dose of Orenitram™</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>12 puffs four times a day</td>
<td>0.125 mg every 8 hours (with food)</td>
</tr>
<tr>
<td>Day 5</td>
<td>11 puffs four times a day</td>
<td>0.25 mg every 8 hours (with food)</td>
</tr>
<tr>
<td>Day 9</td>
<td>10 puffs four times a day</td>
<td>0.375 mg every 8 hours (with food)</td>
</tr>
<tr>
<td>Day 13</td>
<td>9 puffs four times a day</td>
<td>0.5 mg every 8 hours (with food)</td>
</tr>
<tr>
<td>Day 17</td>
<td>8 puffs four times a day</td>
<td>0.625 mg every 8 hours (with food)</td>
</tr>
<tr>
<td>Day 21</td>
<td>7 puffs four times a day</td>
<td>0.75 mg every 8 hours (with food)</td>
</tr>
<tr>
<td>Day 25</td>
<td>6 puffs four times a day</td>
<td>0.875 mg every 8 hours (with food)</td>
</tr>
<tr>
<td>Day 29</td>
<td>5 puffs four times a day</td>
<td>1 mg every 8 hours (with food)</td>
</tr>
<tr>
<td>Day 33</td>
<td>4 puffs four times a day</td>
<td>1.125 mg every 8 hours (with food)</td>
</tr>
<tr>
<td>Day 37</td>
<td>3 puffs four times a day</td>
<td>1.25 mg every 8 hours (with food)</td>
</tr>
<tr>
<td>Day 41</td>
<td>2 puff four times a day</td>
<td>1.375 mg every 8 hours (with food)</td>
</tr>
<tr>
<td>Day 45</td>
<td>1 puff four times a day</td>
<td>1.5 mg every 8 hours (with food)</td>
</tr>
<tr>
<td>Day 49</td>
<td>1 puff twice a day</td>
<td>1.625 mg every 8 hours (with food)</td>
</tr>
<tr>
<td>Day 53</td>
<td>Discontinue</td>
<td>1.75 mg every 8 hours (with food)</td>
</tr>
<tr>
<td>Day 57</td>
<td>---</td>
<td>1.875 mg every 8 hours (with food)</td>
</tr>
<tr>
<td>Day 61</td>
<td>---</td>
<td>2 mg every 8 hours (with food)</td>
</tr>
</tbody>
</table>
Transition from IV to Oral Treprostinil (TCH Experience, n=1)

**Transition from IV treprostinil (Remodulin®) to oral treprostinil (Orenitram™)**
- Orenitram™ dose to be titrated up and Remodulin® dose to be titrated down as tolerated by the patient
- Orenitram™ doses must be administered WITH FOOD
- If patient experiences prostacyclin adverse effects (e.g., hypotension, flushing, headache, nausea, vomiting), contact PH physician

<table>
<thead>
<tr>
<th>IV REMODULIN®</th>
<th>Dose</th>
<th>Order-Specific Weight</th>
<th>Concentration</th>
<th>Rate</th>
<th>ORAL ORENITRAM™</th>
<th>NOTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date/Time</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Date/Time</td>
<td></td>
</tr>
<tr>
<td>Monday, 11/23</td>
<td>60 ng/kg/min (continuation of home dose)</td>
<td>46 kg</td>
<td>60,000 ng/mL</td>
<td>2.76 mL/hr</td>
<td>Monday, 11/23 at 12:00</td>
<td>0.5 mg</td>
</tr>
<tr>
<td>at 11:00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monday, 11/23</td>
<td>48 ng/kg/min</td>
<td>46 kg</td>
<td>60,000 ng/mL</td>
<td>2.21 mL/hr</td>
<td>Monday, 11/23 at 20:00</td>
<td>1 mg</td>
</tr>
<tr>
<td>at 20:00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tuesday, 11/24</td>
<td>36 ng/kg/min</td>
<td>46 kg</td>
<td>60,000 ng/mL</td>
<td>1.66 mL/hr</td>
<td>Tuesday, 11/24 at 04:00</td>
<td>1.5 mg</td>
</tr>
<tr>
<td>at 20:00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Tuesday, 11/24 at 12:00</td>
<td>2 mg</td>
</tr>
<tr>
<td>Tuesday, 11/24</td>
<td>24 ng/kg/min</td>
<td>46 kg</td>
<td>60,000 ng/mL</td>
<td>1.1 mL/hr</td>
<td>Tuesday, 11/24 at 20:00</td>
<td>2.5 mg</td>
</tr>
<tr>
<td>Wednesday, 11/25 at 20:00</td>
<td>24 ng/kg/min</td>
<td>46 kg</td>
<td>60,000 ng/mL</td>
<td>1.1 mL/hr</td>
<td>Wednesday, 11/25 at 05:00</td>
<td>3 mg</td>
</tr>
<tr>
<td>at 20:00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Wednesday, 11/25 at 12:00</td>
<td>3.5 mg</td>
</tr>
<tr>
<td>Thursday, 11/26 at 20:00</td>
<td>12 ng/kg/min</td>
<td>46 kg</td>
<td>30,000 ng/mL</td>
<td>1.1 mL/hr</td>
<td>Thursday, 11/26 at 06:00</td>
<td>4.5 mg</td>
</tr>
<tr>
<td>Thursday, 11/26</td>
<td>DISCONTINUE</td>
<td>46 kg</td>
<td>30,000 ng/mL</td>
<td>1.1 mL/hr</td>
<td>Thursday, 11/26 at 14:00</td>
<td>5 mg</td>
</tr>
<tr>
<td>Friday, 11/27</td>
<td>DISCONTINUE</td>
<td>46 kg</td>
<td>30,000 ng/mL</td>
<td>1.1 mL/hr</td>
<td>Thursday, 11/26 at 22:00</td>
<td>5.5 mg</td>
</tr>
<tr>
<td>at 20:00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Friday, 11/27 at 06:00</td>
<td>6 mg</td>
</tr>
<tr>
<td>Friday, 11/27</td>
<td>DISCONTINUE</td>
<td>46 kg</td>
<td>30,000 ng/mL</td>
<td>1.1 mL/hr</td>
<td>Friday, 11/27 at 14:00</td>
<td>6.5 mg</td>
</tr>
<tr>
<td>Saturday, 11/28</td>
<td>Off IV Remodulin</td>
<td>46 kg</td>
<td>30,000 ng/mL</td>
<td>1.1 mL/hr</td>
<td>Friday, 11/27 at 22:00</td>
<td>7 mg</td>
</tr>
</tbody>
</table>

**Concentration Changing – Change Tubing and Syringe**
- Concentration Changing – Change Tubing and Syringe

**NOTE**: Concentration changing – change tubing and syringe.
Prostacyclin Analogue

• Iloprost (Ventavis®)
  - Inhalation therapy (2.5-5 mcg/dose; max: 45 mcg/DAY)
  - Half life 20-30 minutes → frequent administrations (6-9 times/day)
  - Adverse effects
    • Cough, throat irritation, flushing, hypotension, headache, nausea
  - Must be used with I-neb AAD System
    • TCH practice: Patient must bring in home device during hospitalizations

Iloprost (Ventavis®)

• TCH practice (inpatient)
  - Via ultrasonic nebulizer
  - Dosage titration
    • Step 1: 0.25 mcg/kg Q3h (max: 5 mcg/dose)
    • Step 2: 0.5 mcg/kg Q3h (max: 10 mcg/dose)
    • Step 3: 0.75 mcg/kg Q3h (max: 15 mcg/dose)
    • Step 4: 1 mcg/kg Q3h (max: 20 mcg/dose)

• May be administered as often as every hour based on clinical status of patient
## Prostacyclins

<table>
<thead>
<tr>
<th>Agent</th>
<th>Administration</th>
<th>Half-life</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epoprostenol (Veletri® or Flolan®)</td>
<td>• Continuous IV</td>
<td>• 3-5 MINUTES</td>
<td>• Hypotension, headache, nausea/vomiting, flushing</td>
</tr>
<tr>
<td></td>
<td>• Continuous SQ</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Intermittent inhalation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Oral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treprostinil (Remodulin®, Tyvaso® or Orenitram®)</td>
<td>• Continuous IV</td>
<td>• 2-4 hours</td>
<td>• Similar to epoprostenol plus pain at injection site for SQ infusion</td>
</tr>
<tr>
<td></td>
<td>• Continuous SQ</td>
<td></td>
<td>• Oral formulation difficult to tolerate due to headache and GI adverse effects</td>
</tr>
<tr>
<td></td>
<td>• Intermittent inhalation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Oral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iloprost (Ventavis®)</td>
<td>• Intermittent inhalation</td>
<td>• 20-25 MINUTES</td>
<td>• Similar to epoprostenol plus bronchospasm</td>
</tr>
</tbody>
</table>
Parenteral Epoprostenol and Treprostinil

• Medication safety point
  - Should only be managed by the PH Service
  - TCH practice (safety parameters)
    • Order sets include:
      - Monitoring parameters (vital signs, cardiac monitoring with pulse oximetry)
      - IV access orders; line never to be flushed
      - **ORDER-SPECIFIC** weight must be used
Parenteral Epoprostenol and Treprostinil

• TCH practice (safety parameters)
  - Patient-specific (colored) PH dosing sheet at the bedside provided by the PH Service
  - Patient-specific (colored) back-up access plan at the bedside provided by the PH Service
Patient-Specific Dosing Sheet (TCH-Practice)

**CONTINUOUS IV EPROPROSTENOL (VELETRI®) DOSAGE TITRATION**

- Titrate dose every 6 hours as tolerated per Pulmonary Hypertension Service Recommendations

- Veletri® must be infused via a dedicated line
  - Veletri® NOT compatible with other medications; NS may be used as a carrier fluid, if needed
    - If NS carrier fluid is used, rate should be 1 mL/hr.
    - Y-site should be at the most proximal site to the cap

- Veletri® stable for 24 hours at room temperature

- Do NOT flush, interrupt, or stop the infusion

- Must have back-up syringe and pump readily available; back-up dose kept in medication refrigerator

- Do NOT adjust the dose based on changes in weight without first discussing with the Pulmonary Hypertension Service

<table>
<thead>
<tr>
<th>Expected Date/Time</th>
<th>Actual Date/Time</th>
<th>Dosage (ng/kg/min)</th>
<th>Concentration (ng/mL)</th>
<th>Order-Specific Weight</th>
<th>Rate (mL/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td></td>
<td>1,000</td>
<td>8 kg</td>
<td>1,000</td>
<td>0.96</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>1,000</td>
<td>8 kg</td>
<td>1,000</td>
<td>1.92</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>1,000</td>
<td>8 kg</td>
<td>1,000</td>
<td>2.88</td>
</tr>
</tbody>
</table>

**CONCENTRATION CHANGE – Change syringe and tubing**

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td></td>
<td>5,000</td>
<td>8 kg</td>
<td>0.77</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>5,000</td>
<td>8 kg</td>
<td>0.96</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>5,000</td>
<td>8 kg</td>
<td>1.15</td>
</tr>
<tr>
<td>14</td>
<td></td>
<td>5,000</td>
<td>8 kg</td>
<td>1.34</td>
</tr>
<tr>
<td>16</td>
<td></td>
<td>5,000</td>
<td>8 kg</td>
<td>1.54</td>
</tr>
<tr>
<td>18</td>
<td></td>
<td>5,000</td>
<td>8 kg</td>
<td>1.73</td>
</tr>
<tr>
<td>20</td>
<td></td>
<td>5,000</td>
<td>8 kg</td>
<td>1.92</td>
</tr>
</tbody>
</table>

PH Attending: Dr. Varghese (pager 2287)
PH Pharmacist: Shelly Kim (pager 5443)
Epoprostenol Back-Up Access Plan (TCH-Practice)

CRITICAL INFUSION

CONTINUOUS IV EPOPROSTENOL (VELETRI®)

- Infusing through: Line Type: **CVC (double lumen)**  Site: **Right IJ**  Lumen: **WHITE**

**NOTE:** Bedside nurse must assess back-up access plan at least daily and whenever there is a change in access, notify the PH Service so an updated back-up access plan can be provided.

In case of occlusion or leakage, the infusion must be IMMEDIATELY moved.

- **Step 1:** Identify the backup line. For this patient, it is:
  - Line Type: **PIV (22 gauge)**  Site: **Left lower leg**

- **Step 2:** Prime all tubing with Veletri®

- **Step 3:** In order to account for the deadspace in the new line, infuse **0.5 mL** of Veletri® over **2 minutes** via pump [includes deadspace of the T-connector extension and cap]

- **Step 4:** Draw back at least **1 mL** from the original Veletri® line; in this patient, CVC (right IJ) – **WHITE** lumen, and waste it prior to flushing the line.

Notify Pulmonary Hypertension Service immediately for any interruption.

- PH Attending: Dr. Ruiz (pager 6524)
- PH Fellow: Dr. Tillman (pager 5166)
- PH Pharmacist: Shelly Kim (pager 5443)
Order-Specific Weight (Case Study)

• 14 month old male (actual weight 11.5 kg; dosing weight 9 kg) currently on epoprost enol at a target dose of 40 ng/kg/min using an order-specific weight of 9 kg

• Dosing weight is updated today to 11 kg and you see that the order has been changed with a new rate of 1.76 mL/hr.
Order-Specific Weight (Case Study)

• Medication safety point
  - Increase in rate from 1.44 mL/hr to 1.76 mL/hr is a significant increase in dose → increase in ~9 ng/kg/min using order-specific weight of 9 kg
  - Since parenteral prostacyclins are dosed based on clinical effect and drug tolerance, dose should not be weight-adjusted unless discussed with the PH Service first.
Newer Agent – Riociguat (Adempas®)

- MOA: Soluble guanylate cyclase stimulator (acts synergistically with endogenous NO)

- Indicated for the treatment of adults with chronic thromboembolic PH (CTEPH) after surgical treatment or inoperable disease
  - Do not use with PDE-5 inhibitor
  - Common adverse effects: Headache, abdominal discomfort
  - REMS requirement (pregnancy)

- Very limited pediatric data/experience: Open-label, individual dose titration study underway (children ≥6 to <18 years)

http://www.adempas-us.com/hcp/dosing-and-titration/
Newer Agent – Selexipag (Uptravi®)

• MOA: Novel oral prostacyclin receptor agonist → increased production of cAMP → vascular smooth muscle relaxation

• Common adverse effects: Headache, diarrhea, nausea, vomiting, jaw pain

• Very limited pediatric data/experience

https://www.uptravi.com/hcp/uptravi-titration-and-maintenance/
Other Medication Safety Points

• Frequency
  - Example: every 8 hours not the same as three times daily

• Simplify regimens and improve adherence
  - # of pills/doses
  - Administration times

<table>
<thead>
<tr>
<th>Medication</th>
<th>Sig</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spacer/Aero-Holding Chambers</td>
<td>Use as directed with inhaler</td>
</tr>
<tr>
<td>(AEROCHAMBER Z-STAT PLUS/LARGE)</td>
<td></td>
</tr>
<tr>
<td>MISC</td>
<td></td>
</tr>
<tr>
<td>ADCIRCA 20 MG TABS</td>
<td>TAKE TWO TABLETS BY MOUTH DAILY</td>
</tr>
<tr>
<td>albuterol (PROAIR HFA) INH HFA MDI</td>
<td>Inhal 2 Puffs by mouth as instructed.</td>
</tr>
<tr>
<td>90 mcg/puff</td>
<td></td>
</tr>
<tr>
<td>Treprostinil 0.6 MG/ML SOLN</td>
<td>Inhal 10 inhalation by mouth 4 times daily. Indications: Increased Pressure of Pulmonary Circulation</td>
</tr>
<tr>
<td>mometasone NASAL SPRY 50 mcg/spray</td>
<td>Give 2 Sprays in each nostril 2 times daily.</td>
</tr>
<tr>
<td>Ambrisentan 5 MG TABS</td>
<td>Give 10 mg by mouth daily. Indications: Pulmonary Arterial Hypertension</td>
</tr>
<tr>
<td>aspirin PO CHEW TAB 81 mg</td>
<td>Give 1 Tab by mouth daily.</td>
</tr>
</tbody>
</table>
Other Medication Safety Points

• Inquire about adverse effects (ask open-ended questions)

• Ask about bowel movements
  - Frequency
  - Consistency

• Assess for any barriers to adherence
  - # of pharmacies
  - Insurance/costs

Patient-Specific PH Action Plan (TCH Practice)

### Today's instructions:
**6 Minute Walk Test:** At the next visit, come prepared in comfortable walking shoes and remove nail polish. The test will be done from the PH Clinic.

**Medication changes made today:** none

---

<table>
<thead>
<tr>
<th>My list of medicines I take to treat my Pulmonary Hypertension:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Tadalafil 40 mg once daily</td>
</tr>
<tr>
<td>2. Ambrisentan 10 mg once daily</td>
</tr>
<tr>
<td>3. Warfarin 6.5 mg daily</td>
</tr>
<tr>
<td>4. Remodulin continuous subcutaneous infusion 155 ng/kg/min.</td>
</tr>
<tr>
<td>5. Zantac 150 mg twice daily as needed for site pain.</td>
</tr>
<tr>
<td>6. Cetirizine (Zyrtec) 10 mg daily for site pain.</td>
</tr>
<tr>
<td>7. Tylenol for pain.</td>
</tr>
<tr>
<td>8. Ibuprofen for pain.</td>
</tr>
<tr>
<td>9. Norco (hydrocodone/acetaminophen) 1 tablet by mouth every 4 hours as needed for severe pain.</td>
</tr>
<tr>
<td>10. Zofran 4 mg as needed.</td>
</tr>
</tbody>
</table>

**Respiratory medications:**
- Prazosin 4 puffs every 4 hours as needed with spacer for cough, wheezing or trouble breathing. Use with a spacer.
- Proair 4 puffs every 4 hours as needed with spacer for cough, wheezing or trouble breathing. Use with a spacer.

---

**Oxygen Therapy - NC 1/2 LPM at night.**

**Plans from today:**
1. Continue Remodulin 155 ng/kg/min on weight of 40 kg. Continue Tadalafil 40 mg once daily. Continue Letairis 10 mg once daily.
2. Norco script written for pain control to be used PRN for severe pain. Family counseled on narcotic use.
3. Coumadin 6.5 mg daily. INR monthly. Continue iron pills.
4. Monitor weight gain and continue to be active.
5. Next echo in 6 months.
7. Continue monthly labs at Labcorp: INR, serum pregnancy test. LFTs every 3 months, BNP every 6 months.
8. RTC in 3 months.

---

Also includes PH Team phone numbers, exercise precautions, and when to call 911
AHA/ATS Consensus Pediatric PAH Treatment Algorithm

Consider: Diuretics, Oxygen, Anticoagulation, Digoxin

Acute Vasoreactivity Testing

Positive

Oral CCB

Improved

Lower Risk

ERA or PDE-5i (oral)
Iloprost (inhaled)
Treprostinil (inhaled)

Reassess: consider combo-therapy

Ambrisentan (Class IIa; Level B), Bosentan (Class 1; Level B), CCB (Class 1; Level B), Epoprostenol (Class 1; Level B), Iloprost (Class IIa; Level B), Sildenafil (Class 1; Level B), Tadalafil (Class IIa; Level B), Treprostinil IV/SQ (Class 1; Level B), Treprostinil Inhaled (Class IIa; Level B)

Yes

Continue CCB

Negative

Higher Risk

Epoprostenol IV or Treprostinil (IV/SQ)
Consider Early Combination ERA or PDE-5i (oral)

Atrial septostomy
Lung transplant

Optimization of Pharmacotherapy

• Goals of therapy
  - Prolonged survival
  - Improvement in quality of life

Sequential combination

Evolving Paradigm

Upfront combination

2 or 3 drugs (especially in patients who present with high risk features)

? impact on outcomes

Conclusion

• With the availability of targeted PH therapies, survival of children with PH has improved.

• Management of pediatric PH remains challenging.
  - More pediatric clinical studies are needed to help guide optimal approaches with disease-specific strategies.

• With the specialized use of PH medications, it is important for healthcare professionals to be aware of potential safety pitfalls and to implement processes to ensure safe and effective use of these agents.
Pharmacologic Therapies

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