Pulmonary Hypertension in Congenital Heart Disease
Neonatal and Pediatric Patients
What the Nurse Caring for a Patient with Pulmonary Hypertension Needs to Know

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Introduction (Pediatric Pulmonary Hypertension Guideline from the American Heart Association and American Thoracic Society, 2015)
Pediatric pulmonary hypertension (PH) is defined as a resting mean pulmonary artery pressure (mPAP) > 25 mmHg at >3months of age at sea level. It is associated with multiple conditions including cardiac, pulmonary, and systemic diseases in neonates, children, and young adults. Pulmonary hypertension contributes to significant morbidity and mortality. The focus of this guideline is PH as it relates to congenital heart disease (CHD) and Primary (idiopathic) PH in neonates and children. (See Adult Care Guidelines for care of Adult CHD Patient with Pulmonary Hypertension)

Key Points

- PH in pediatric patients linked to lung growth and development before and immediately after birth
- Timing of adverse stimuli critical to abnormal growth and function
    - Frequently occurs with changes in the pulmonary circulation during transition from fetal to neonatal life

    - Affects both structural and functional changes
    - Adverse stimuli include hyperoxia, hypoxia, hemodynamic stress, inflammation
- Normal lung maturation depends on:
    - Influence of hemodynamic blood flow on vascular development
    - Normal vascular bed necessary for:
        - Development of lung structure and distal air space
        - Maintenance of lung structure and function
            - Metabolism and gas exchange
            - Response to increased workloads
- Abnormal pulmonary vascular blood flow from CHD influences development of pulmonary vascular bed
- Diagnosis of PH difficult to establish in children
    - Symptoms at presentation often non-specific
        - Symptoms of low cardiac output (LCO) in infants
            - Failure to thrive
            - Tachypnea
        - Symptoms of LCO in older children similar to adults
            - Exercise intolerance
            - Occasionally chest pain
    - Initial presenting symptom in IPAH and PAH-CHD = Dyspnea on exertion
    - Symptoms in severe disease
        - Near syncope or syncope
        - More frequently seen in IPAH and familial PAH patients
    - Symptom of significant lung disease or intra-cardiac shunting = Cyanosis

Classification

- Pulmonary vascular resistance (PVR)
    - Falls after birth
    - Equivalent to adult PVR by two-three month of age
- The World Health Organization Classification of Pulmonary Hypertension as outlined in the 2015 Pediatric Pulmonary Hypertension Guidelines from the American Heart Association and the American Thoracic Society has five main categories:
    1. Pulmonary artery hypertension including: idiopathic, familial, associated with other disease processes such as collagen vascular disease, congenital systemic to pulmonary shunts, HIV infection, toxins or connective tissue disorders, associated with venous or capillary disorders and persistent pulmonary hypertension in the newborn
    2. Pulmonary hypertension with left sided heart disease including: left sided atrial, ventricular or valve disease
    3. Pulmonary hypertension associated with hypoxemia and/or lung disease.
    4. Pulmonary hypertension due to chronic embolic or thrombotic disease.
    5. Other miscellaneous disorders including: compression of the pulmonary vasculature, sarcoidosis and others.

Pulmonary Hypertension and Congenital Heart Disease

PH in CHD results from increased pulmonary blood flow; pulmonary vascular remodeling and dysfunction from a progressive rise in pulmonary vascular resistance (PVR) and right heart pressures; and pulmonary venous hypertension. Long-term outcomes from late intervention or uncorrected congenital defects may result in Eisenmenger syndrome from irreversible injury to the pulmonary vasculature. (See Adult Guidelines on Eisenmenger Syndrome)

Patient Risk Factors:

- Persistent systemic to pulmonary artery shunt
    - At risk for post-operative pulmonary hypertension
    - Defects include:
        - Large patent ductus arteriosus
        - Large ventricular septal defect
        - Aortopulmonary window
        - Complete atrioventricular septal defect
        - Truncus arteriosus
- Patients with CHD who have large left-to-right shunts anatomy without symptoms of congestive heart failure (CHF)
    - May be at higher risk for pulmonary hypertension
    - Usually have elevated PVR
        - Prevents pulmonary overcirculation
        - Prevents symptoms of CHF
- Neonates within 2-6 weeks of life
- Ex-premature infants with bronchopulmonary dysplasia
- Pulmonary venous outflow obstruction
    - Defects include:
        - Obstructed pulmonary veins (especially infra-diaphragmatic)
        - Mitral stenosis
        - Cor-triatriatum
- Untreated congenital heart defects with a persistent systemic to pulmonary artery shunt (See Adult Guidelines on Pulmonary Hypertension in Adults with Congenital Heart Disease and Eisenmenger Syndrome))
    - Leads to physiological changes from long-term exposure of pulmonary vasculature to high pressure and high flow physiology
        - Thickened pulmonary endothelium
        - Muscularization of pulmonary arterioles
        - Platelet dysfunction.
    - Results in increased pulmonary vascular resistance
        - Increased secretion of endothelin, a potent vasoconstrictor
        - Decreased secretion of vasodilators – prostacyclin and others
    - Includes:
        - Adults with large atrial septal defect
        - Unrepaired left-to-right shunt defects
        - Large left-to-right shunt defects repaired after infancy

    - Long-term result
        - Pulmonary vascular disease/Eisenmenger syndrome
        - Pulmonary arterioles unresponsive to vasodilator therapy
        - Prevents repair of their CHD
            - Resultant increase in afterload not tolerated by right ventricle (RV)
            - PVR not responsive to any therapy
        - At high risk for acute right ventricular failure and premature death
- Known preoperative PH
    - Vulnerable to pulmonary hypertensive crises
    - Especially during:
        - Intubation/extubation
        - Immediate postoperative period.
- Effects of cardiopulmonary bypass (CPB)
    - May result in PH even in the absence of preoperative risk factors
    - Include atelectasis, sequestration of leukocytes, microemboli, production of thromboxane, adrenergic stimulation and decreased levels of nitric oxide
- Idiopathic pulmonary hypertension (IPAH)(See section on ILPAH in this guideline)
    - High risk for pulmonary hypertensive crises after both cardiac and non-cardiac surgery
    - Increased risk associated with anesthesia risk and PH physiology

Diagnosis

- "Gold standard" is cardiac catheterization
    - Evaluate pulmonary artery pressures
    - Calculate PVR
        - Normal - PVR of <3 Wood's Unit/m^2
        - Significant risk of post-operative PH - PVR of >6 Wood's units/m^2
        - High risk for operative mortality (may not be operable) - PVR>10Wood's unit/m^2
    - Allows for testing of pulmonary vasoreactivity using pulmonary vasodilator therapy.
- Triggers for cardiac catheterization
    - Preoperative risk factors
    - Symptoms of PH
- Pre- and post-operative echocardiogram to diagnose and/or evaluate severity of PH
    - Evaluate RV function
    - RV pressure with tricuspid valve jet
    - Identify septal motion/and or bowing
    - Evaluate size of the right atrium
    - Look for pericardial effusion

Recognition of Postoperative Pulmonary Hypertension

- Factors that increase risk of post-operative PH
    - Cardiopulmonary bypass
    - Active respiratory viruses at the time of CPB
        - Careful assessment for respiratory illness within 2-3 weeks pre-operatively
        - Ensure respiratory cultures done and results negative before surgery
    - Repair of large left-to-right shunting lesions
        - Large ventricular septal defect
        - Complete atrioventricular Canal
        - Truncus arteriosus
        - Large patent ductus arteriosus
    - Aortopulmonary window
    - D-Transposition of the great arteries (newborn)
    - Total anomalous pulmonary venous return (especially if "obstructed")
- Respiratory maneuvers known to increase intrathoracic pressure and cause increased pulmonary arterial pressure
    - Intubation/Extubation
        - Careful titration of sedation and analgesia during intubation and extubation is key.
        - May require a transition of sedative medications in the peri-extubation period to a fast acting agent.
    - Coughing
    - Suctioning (*HIGH* risk for provoking pulmonary hypertensive events)
- Invasive procedures, pain
    - Activate the sympathetic nervous system and stress response
    - May cause an elevation in PVR
- Physiology of pulmonary hypertensive events leading to a "crisis"
    - Results from severe pulmonary vasoconstriction
    - Causes an acute rise in RV afterload, RV coronary ischemia, RV failure, decreased LV filling and a sudden deterioration in cardiac output (CO)
- Clinical signs
    - Tachycardia early, then followed by bradycardia during a "crisis"
    - Elevated right atrial pressure and low left atrial pressure
    - Oxygen saturations decrease (right-to-left intracardiac shunting or as mixed venous oxygen saturations drops)
    - Poor perfusion progressing to systemic hypotension during a "crisis"
        - Atrial level communication present – progressive desaturation precedes acute hypotension
            - Right to left intracardiac shunt
                - May maintain LV filling
                - Will see increase in cyanosis
        - Intact atrial septum - hypotension precedes desaturation
            - Poor LV preload
- PH crisis
    - Can occur at any time

    - Recognition & early treatment of pulmonary hypertension "event" important to avoid progression to a "crisis"
    - Immediate recognition of a "crisis" crucial
- Untreated PH crisis
    - Rapidly progresses to cardiovascular collapse, arrest, death

Management of Postoperative Pulmonary Hypertension

- Goals of care
    - Decrease PVR
    - Optimize/ support RV function
    - Optimize CO
- Actions
    - Eliminate stimuli that cause pulmonary vasoconstriction
        - Agitation
        - Excessive suctioning
        - Hypercarbia
        - Hypoxia
        - Acidosis
    - Promote pulmonary vasodilation
        - Administer inhaled oxygen
        - Use inhaled nitric oxide (iNO)
            - Confirm adequate, continuous administration of 100% Fi02 prior to administration of iNO
            - Dose 20-40 ppm
            - Caution – wean may result in rebound PH
                - May consider transition to enteral pulmonary vasodilator (sildenafil) during weaning
        - Nonspecific agents: nitroprusside, milrinone (Primacor), sildenafil, isoproterenol, inhaled prostacyclins (Iloprost)
    - Tracheal suctioning
        - Block stress response with pre-medication with intravenous analgesic or sedation
        - Reduce suction-induced hypoxia - pre-oxygenate with 100% FiO2
        - Promote pulmonary vasodilation – pre-oxygenate with 100% FiO2
        - Use of an in-line, closed suctioning system
            - Allows for airway clearance
            - Provides constant ventilation
            - Can be used by single person
        - Use of an open suctioning system
            - Two people need to be available
            - One to suction, one to ventilate
    - Prevent noxious stimulation of PH events
        - Analgesia, sedation prior to painful, invasive procedures
        - May require deep sedation, analgesia, muscle relaxants for several days post-operatively
    - Support RV function

        - Afterload reduction (milrinone)
        - Inotropic support (dopamine, low dose epinephrine)
        - Vasopressor support
    - Maintain sinus rhythm
    - Maintain normothermia
    - Prevent complications from intracardiac shunts
        - Cerebral vascular events
        - Systemic emboli
        - Requires
            - Air filters on all IV lines
            - Meticulous care of IV lines, connectors, access sites with blood draws and medication administration

Management of an Acute Pulmonary Hypertensive Crisis

- Rapid recognition of a PH event imperative to avert deterioration into a PH crisis
    - If the patient clinically deteriorates during a procedure i.e. suctioning
        - Stop procedure
        - Immediately initiate treatment
- Treatment goals
    - Increase RV coronary driving pressure
    - Decrease RV afterload
    - Improve cardiac output
    - Avoid acidosis
- Management
    - Focus on immediate, simultaneous actions:
        - Ensure patent airway, rule out obstruction/dislodgement
        - Optimize oxygenation with hand bag ventilation with 100% FiO2
        - Administer sedation to decrease airway resistance
            - Reduces oxygen demand
            - Provides muscle relaxation and facilitates ventilation
        - Administer fluid bolus to increase pulmonary blood flow and LV filling
        - Administer vasoactive infusions to improve ventricular contraction
            - Epinephrine, Dopamine, Phenylephrine, Vasopressin
        - ECMO preparations if persistent crisis
- After PH crisis resolves
    - Wean all therapies gradually
    - Careful weaning of iNO
        - Consider using sildenafil for preventing rebound PH
    - Close monitoring of trends in heart rate, O2 saturations, right atrial pressure, perfusion status, serum lactates, and blood pressure

Associated Complications

- Thromboembolic event
    - Anticoagulation to prevent thrombus formation
- Arrhythmias

    - Normal sinus rhythm optimal
    - Aggressive management of arrhythmias in post-operative period
        - Prevent further stress response and potential pulmonary hypertensive event/crisis
- Renal Dysfunction
    - Secondary to poor perfusion
    - Related to clearance of medications aimed at treatment
- Liver Dysfunction
    - Related to clearance of medications aimed at treatment

Critical thinking

- Understanding the patient's anatomy and physiology essential to ***anticipating***, recognizing and appropriately treating PH
- Effects of atrial level communication during PH crisis
    - Open atrial septum – rapid increase in cyanosis with right-to-left shunt
        - Increases risk of cerebral and systemic emboli
        - Requires air filters on all IV lines
        - Provide meticulous IV care
    - No atrial level communication - more likely to be hypotensive first because of a lack of left sided preload
- Prevention of a PH events and crisis critical in the postoperative period
    - Use of oxygen
        - Prevent pulmonary vasoconstriction from hypoxia
        - Encouraged in the postoperative period
        - Encouraged during any respiratory illness or complication after surgery
    - Use of sedation while on mechanical support
        - Positive pressure ventilation
            - Increases intrathoracic pressure
            - Can be a noxious stimulus in a lightly sedated patient
        - Helps to prevent episodes of agitation leading to a PH crisis
    - Ensure adequate RV preload
        - Decreased RV preload with positive pressure ventilation
        - May require additional volume administration to augment RV preload while on ventilator
    - Use of nitric oxide as a prophylactic pulmonary vasodilator in the postoperative period
        - Common in patients with known preoperative pulmonary hypertension
        - Dose 20-40 ppm
- Acidosis - respiratory or metabolic
    - Causes pulmonary vasoconstriction
    - Must be addressed quickly
    - Respiratory acidosis will require an escalation of ventilator support
    - Metabolic acidosis may require administration of sodium bicarbonate, fluid or vasoactive medication

Special Considerations

- Risk factors
    - Genetic risk factors - Trisomy 21 (Down syndrome)
        - Pulmonary Artery Hypertension (PH)
            - Increased growth of small pulmonary arteries
                - Narrower in diameter
                - Increases resistance to pulmonary blood flow
        - Increased risk of postoperative pulmonary hypertension
            - In CHD surgical procedures
            - Also in other non-heart surgery
    - Living at high altitudes
        - Long term exposure to hypobaric hypoxia
    - Asplenia
        - Thought that the lack of a vascular filter allows abnormal cells and activated platelets to reach the lungs.
    - Medications with Serotonergic effects
        - Dopamine, fluoxetine, lithium, protamine, etc.

Primary Pulmonary Hypertension

Idiopathic pulmonary artery hypertension (IPAH) is a diagnosis of exclusion, with evidence of pulmonary artery pressure elevation (>25mmHg) in the absence of left sided congenital heart lesions, disease of lung parenchyma, pulmonary emboli or other causes. This can be inherited, labeled as heritable pulmonary artery hypertension (HPAH) in the presence of positive family member. IPAH can be a devastating diagnosis and is associated with poor outcomes. (Pediatric Pulmonary Hypertension Guidelines from the American Heart Association and American Thoracic Society, 2015)

Diagnosis and Imaging Evaluation

- Initial work up:
    - Comprehensive history and physical exam
        - Identify etiology
            - Familial
            - Genetic
            - Congenital heart disease
        - Evaluate cardiac function
    - Imaging to rule out pulmonary disease - Pulmonary embolism, pulmonary artery stenosis, pulmonary vein stenosis, pulmonary vascular obstructive disease (PVOD) and lung parenchymal disease
- Initiating pulmonary artery hypertension therapy
    - Cardiac catheterization – unless contraindicated or patient unstable
        - Test pulmonary vasoreactivity
            - Measure pulmonary artery pressure
                - Assess change in mean pulmonary artery pressures
                - In room air (21% FiO2)

        - In 100% FiO2
        - In inhaled nitric oxide (iNO)
    - Evaluate any change in mean pulmonary artery pressure
        - Positive response = decrease $\geq$ 20% in the pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR) or systemic vascular resistance (SVR) without a decrease in cardiac output (CO)
        - Negative response = no change in PAP, PVR or SVR
- Ongoing imaging evaluation of management
    - Serial echocardiograms
        - Baseline prior to initiation of treatment
        - Scheduled evaluation of therapy
        - Increased frequency if therapy or clinical changes occur
    - Repeat cardiac catheterization
        - Within 3-12 months of initiation of therapy
        - Scheduled evaluation of therapy
        - Evaluate therapeutic response or for worsening of pulmonary hypertension
    - MRI
        - Initial evaluation of RV function and RV dilation/chamber dimensions
        - Scheduled evaluations of therapy
- Additional testing
    - BNP
        - Can be trended
        - Used to supplement clinical decision making
    - 6 minute walk test
        - Used to evaluate exercise tolerance
        - Appropriate use based upon patient age
    - Sleep study
        - Used if the patient is at risk for obstructive sleep apnea or disorder of breathing during sleep
        - Used if the patient has poor responsiveness to therapies
- Genetic considerations
    - Genetic testing and counseling recommended
    - Non-affected carriers should be screened with serial echocardiograms
    - Family members who develop new cardiorespiratory symptoms should be evaluated immediately for PAH
    - Family education for child with genetic syndrome at risk for PH
        - Symptoms of PH
        - Seek immediate evaluation if symptoms noted

Management Considerations

- Primary IPAH
    - Irreversible
    - Management aim to slow progression of disease

- Non-pharmacologic measurements
    - Avoid strenuous exercise
    - Avoid high altitudes
    - Use caution when flying, may need supplemental oxygen
- Improve exercise tolerance
    - Stable IPAH
    - Exercise training programs with monitoring and low-intensity aerobic exercise
- Avoid over-the-counter medications with alpha-adrenergic properties (decongestants)
- Avoid pregnancy
    - Must consider birth control options
    - Avoid oral contraceptives
- General guidelines for medication management (2015 Pediatric Pulmonary Hypertension: Guidelines from the American Heart Association and American Thoracic Society)
    - Include prevention and inhibition of active pulmonary vasoconstriction
    - Support of right ventricular function
    - Promotion of regressive remodeling of structural pulmonary vascular changes
    - Goal-directed therapy towards therapeutic targets
    - Gradual addition of therapies until hemodynamic parameters and/or symptom relief achieved
    - Lower pulmonary artery pressure with pulmonary specific vasodilators
        - For lower-risk patients, oral therapy should be used – either PDE5 inhibitor or endothelin receptor antagonist
            - Characteristics of Lower Risk:
                - No evidence of RV failure
                - WHO class I, II
                - No syncope
                - Minimal RV enlargement/dysfunction by echocardiography
                - Hemodynamics: PVRI<10 Wood Units/m^2, CI> 3.0 L/min/m^2 , PVR/SVR<0.5
                - Minimally elevated BNP
                - Longer 6 minute walk distance (>500 m)
        - Higher-risk patients should be initiated on IV or SQ therapy immediately
            - Characteristics of Higher Risk:
                - Clinical evidence of RV failure
                - WHO class III, IV
                - Recurrent syncope
                - Significant RV enlargement/dysfunction by echocardiography
                - Hemodynamics: PVRI>20 Wood Units/m^2, C< 2.0 L/min/m^2 , PVR/SVR>1

        - Significantly elevated BNP
        - Shorter 6 minute walk distance (<300 m)
    - Transition from parenteral to oral or inhaled is safe when:
        - Asymptomatic children with PAH who have near-normal pulmonary hemodynamics for a sustained time period[1]
        - MUST be done with close monitoring at experienced PH center
  - Avoid systemic vasodilators
  - Manage congestive heart failure with diuretics and digoxin
    - Diuretics may help to control symptoms of right heart failure
    - Digoxin may have a role with supraventricular arrhythmias with RV failure
  - Manage arrhythmias (Sinus rhythms are optimal)
  - Manage risk of thromboembolism in severe disease with warfarin
  - Preventive care
    - Annual influenza vaccine
    - RSV prophylaxis
    - Pneumococcal vaccine
    - SBE prophylaxis in patients with cyanosis, central lines
- Non-medical therapy: Lung, or heart-lung transplantation
  - Reduces PVR, helps RV function
  - Bilateral preferred to single lung
  - Criteria to refer to a lung transplant center
    - PH medication therapy optimized
    - Disease at WHO Class III or IV
    - Consider if rapid progression of disease
    - Consider if confirmed PVOD or capillary hemangiomatosis by lung biopsy

Specific Medication Management (2015 Pediatric Pulmonary Hypertension: Guidelines from the American Heart Association and American Thoracic Society)

Inhaled Agents

- Oxygen: Provide to avoid hypoxia by vasoconstriction in pulmonary bed
  - Use to dilate pulmonary arteries
  - Reasonable if O_2 saturation <92%
  - Keep O_2 saturation >90%
  - Consider nighttime oxygen therapy
    - May evaluate using a sleep study
    - May help with symptoms in WHO Class IV patients
  - May use supplemental oxygen therapy if needed for airplane travel
- Inhaled nitric oxide (iNO): selective pulmonary vasodilator
  - PH patients deficient in nitric oxide
  - Therapy enhances endogenous effects of nitric oxide on pulmonary vasculature
- Treprostinil (Tyvaso): synthetic prostacyclin
  - Inhaled 4 treatments per day, titrate up to 9 puffs per treatment

    - Benefits include delivery to lungs only, used in combination with oral therapies
    - Side effects of cough, jaw pain, headaches
    - Worse gastrointestinal (GI) side effects with oral administration
    - Method limited by age of patient due to compliance with inhalation treatments
- Iloprost: synthetic prostacyclin
    - Inhaled 6-9 times per day while awake
    - Dose of 2.5-5 mcg
    - Benefits include delivery of prostacyclin to lungs only, used in combination with oral therapies
    - Side effects: cough, jaw pain, headache, flushing
    - Disadvantages
        - Frequent dosing
        - Delivery device
            - Requires education
            - Affects the compliance
        - Inhaled drug can affect reactive airway disease
        - Therapy takes 10-15 minutes per treatment
        - Short duration of action (30-60 minutes), necessitating frequent administration

Oral Agents

Calcium channel blockers

- Inhibits calcium flux into the cardiac and smooth muscle
    - Cause relaxation of vascular smooth muscle
    - May decrease cardiac contractility
- Indicated only in patients who demonstrate an acute response to vasodilator testing during cardiac catheterization
- Beneficial hemodynamic effects in nearly half of children who show vasodilatory response in cardiac catheterization lab
- Diltiazem and verapamil have negative inotropic effects with hypotension
- Use
    - Older than 1 year of age
    - AVOID if pulmonary vascular bed nonreactive or PVR not yet studied
    - AVOID if RV dysfunction or less than one year of age (especially with negative inotropic effects of diltiazem and verapamil)
- Duration of benefit limited
- Requires ongoing assessments for therapeutic result
- Careful follow-up essential - patients may deteriorate over time on CCB therapy alone
- When initiating these meds: always titrate up from lower dose
- Significant adverse effects
    - Bradycardia
    - Decreased cardiac output
    - Hypotension (especially with nifedipine or amlodipine)

- Additional adverse effects: peripheral edema, dizziness, rash, gum hyperplasia, constipation
- Medications
    - Nifedipine - first widely accepted therapy before phosphodiesterase 5 inhibitors became available
    - Amlodipine – comparable to long-acting nifedipine, may increase heart rate
    - Diltiazem – increased risk of bradycardia and negative inotropic effects
    - Verapamil - contraindicated

Phosphodiesterase 5 Inhibitors

- Adverse effects: headache, nasal congestion, flushing, agitation, hypotension, vision/hearing problems, priapism
    - Dose related ocular effects
        - Blurred vision
        - Changes in light perception
        - Transient blue/green visual abnormalities
    - Contraindicated if on nitrates or riociguat
- Monitoring – Include periodic vision and hearing screening
- Medications
    - Sildenafil (Revatio): phosphodiesterase 5 inhibitor, selective pulmonary vasodilator with effects similar to iNO
        - Brief 12 month study demonstrated improved hemodynamics and exercise tolerance
        - FDA safety warning in pediatrics
            - Should not be prescribed in children ages 1-17
                - Due to study showing higher morality at higher doses in children with IPAH
                - No control group of children with IPAH NOT treated for comparison
            - Still recommended for treatment by Pediatric IPAH experts
        - Pediatric dosing is 1mg/kg/dose every 8 hours or adult dose is 20mg three times/day (TID)
        - Side effects
            - Epistaxis, headache, flushing, diarrhea
            - Do not give with nitrates
            - May need to titrate dosing upwards to desired effects
    - Tadalafil (Adcirca): phosphodiesterase-5 inhibitor
        - Adult dosing is 40mg daily
        - Not well studied in children
        - Side effects
            - Headache, dizziness, edema
            - Contraindicated with nitrates

Endothelin Receptor Antagonist (ERA)

- Endothelin
    - Excessive in PH
    - Pulmonary vasoconstrictor in vascular smooth muscle

    - Medical therapy blocks endothelin receptors, reducing the amount of pulmonary vasoconstriction
- Common systemic side effects
    - Liver dysfunction
    - Male infertility
    - Teratogenic
    - Fluid retention/edema
    - Headache
    - Flushing
- Medications
    - Bosentan (Tracleer): non selective endothelin receptor blocker
        - Dosing oral is 62.5mg and 125mg BID
        - Pediatric dosing is 1-2mg/kg BID
        - Side effects
            - Headache, dizziness, edema
            - Contraindicated with cyclosporine and glyburide (potential interaction and liver damage) – more common in adults
            - Decreases oral hormonal contraceptive effectiveness
            - Decreases sildenafil level (drugs interact)
            - Teratogenic
        - Monitoring
            - LFTs - monthly (metabolized by CYP450)
            - Hemoglobin - every 3 months
            - HCG and pregnancy tests - monthly
        - Additional considerations
            - Use 2 forms of birth control
            - Data supports use in Eisenmenger syndrome
            - Special handling precautions: caregivers should handle with gloves; do not crush tablets to avoid inhaling drug particles, may dissolve tablet in solution within a syringe
    - Ambrisentan (Letairis): endothelin receptor antagonist (selective for ET_A)
        - Dosing oral 5 or 10mg daily
        - Side effects
            - Peripheral edema, nasal congestion, sinusitis
            - Increased edema compared to other ERAs reported
            - Decreased effectiveness of oral hormonal contraceptives
            - Teratogenic
        - Monitoring
            - Hemoglobin, LFTs,
            - Monthly HCG and pregnancy tests
        - Not studied in children less than 5 years old
        - Special handling precautions: caregivers should handle with gloves; do not crush tablets to avoid inhaling drug particles, may dissolve tablet in solution within a syringe

Continuous Infusions – Prostacyclin

- Prostacyclin
    - Metabolite of arachidonic acid produced endogenously by the vascular endothelium
    - Potent vasodilator
    - Has anti-thrombotic, anti-proliferative, and anti-inflammatory effects
    - Decreased in patients with severe PAH
- Characteristics
    - Endogenous vasodilator
    - Deficient in PAH
    - Continuous infusion medication increases circulating prostacyclins leading to pulmonary vasodilation
- High risk medication
    - Changes in administration may cause extreme patient response
        - Do not interrupt intravenous (IV) administration
        - Do not flush IV lines
        - Do not add other medications to prostacyclin line
    - Set up unit protocol to manage safe medication administration
        - Multi professional protocol
        - Nursing for IV line maintenance, changing medication administration systems, infection prevention, nurse education for IV pump operation and medication properties, patient education
        - Pharmacy for medication preparation, verifying patient dose and solution concentration, patient education
        - Medicine for correct medication dosing order and back-up orders for system safety (to provide for medication to be available within minutes if IV pump fails, IV line breaks or clots, or other problem with medication delivery)
- Epoprostenol (Flolan)(Veletri - thermostable): synthetic prostacyclin
    - Administered intravenously via tunneled central line
    - Standard of care for severe IPAH
    - Concerns:
        - Effective medication but difficult to manage for family
        - Not stable at room temperature
        - Needs to be kept cold with ice while infusing
        - Stable for only 24 hours (required new solution every 24 hours)
        - Needs refrigerated storage
        - Half-life is < 6 minutes – therefore, any interruption in therapy can be life-threatening (PH crises) due to hemodynamic changes
    - Dosing
        - Starts at 1-2 ng/kg/min
        - Titrated upwards to 25-40ng/kg/min
        - Requires careful monitoring for side effects, especially when increasing dose
        - May require right heart cath to ensure patient is not in high output heart failure (may happen with high doses or chronic overdose)
    - Side effects: headache, flushing, jaw pain, calf pain, nausea, diarrhea

- Treprostinil (Remodulin): synthetic prostacyclin
    - IV therapy less complicated to manage
    - Subcutaneous via catheter or intravenous via surgically placed central line
        - Subcutaneous infusions
            - Pain, erythema at infusion site
            - Used more frequently in adult patients
        - Stable at room temp for 48 hours
        - Half-life 4.5 hours
        - Longer stability if stored in refrigerator
    - Dosing
        - Initiated at 1-2ng/kg/min
        - Titrate to desired clinical effects (maximum is patient dependent)
        - Monitor for side effects: jaw pain, leg pain, headache, nausea, diarrhea
        - Doses are 1.5-2 times higher in treprostinil (Remodulin) – consider if switching from epoprostenol (Flolan)(Veletri - thermostable)
    - Side effects
        - Less frequently reported than with epoprostenol
        - Jaw pain, headache, flushing, diarrhea, nausea, leg pain

Associated Complications

- Clot formation/stroke: IPAH patients can have abnormal coagulation and fibrinolysis
    - Consider long term anticoagulation with warfarin
        - Low cardiac output
        - Long-term indwelling access
        - Hypercoagulable condition
    - Increased risk of clot formation/stroke
        - Abnormal coagulation and fibrinolysis
        - Prothrombotic state from line sepsis with blood stream infection
    - Increased risk of cerebrovascular accidents (CVA)
        - Rare
        - Increases with right-to-left intracardiac shunting lesions
        - Monitor closely for signs/symptoms of CVA
        - Provide patient/family education on signs/symptoms of CVA
    - Patient history of abnormal coagulation factors
        - Initiate warfarin therapy earlier in management plan
    - Target INR
        - Initial goal INR of 1.5-2
        - Advanced disease goal INR of 2-2.5
        - History of thrombus individualize goal INR
- Infection/sepsis: related to required long-term need for central line for administration of IV prostacyclins
    - Prevention of central line infection
        - Meticulous attention to best practice for inpatient management of IV lines

        - Empower patient/family to monitor hospital staff for best practices, especially hand washing and IV line access
    - Provide patient/family education on best practices
        - Importance of good hand washing
        - Proper line care
            - Dressing changes
            - Protection of central site during shower/bathing
        - Signs and symptoms of infection
        - Provide instruction on where/when to seek medical care
            - Emergency care for signs/symptoms of infection
            - Respiratory and febrile illnesses
    - Discharge planning includes:
        - Home nursing
        - Supplies for dressing changes, central line care
        - IV pump for safe medication delivery
        - Outpatient pharmacy for preparation and delivery of IV medications
- Failure to Thrive: related to multiple factors
    - RV failure/dysfunction
    - GI side effects of medications necessary to manage this disease
    - Altered perfusion to GI tract due to altered hemodynamics in end stages
    - Decrease feeding tolerance/desire to eat
    - Must provide consultation with a pediatric cardiac nutritionist to obtain calorie goals and food guidelines
- Anxiety: related to multiple factors
    - Fatal diagnosis
    - Long-term survival depends on many factors, including the patient
        - Produces anxiety for the patient, (if developmentally aware)
        - Produces anxiety in family with untimely/unpredictable loss of child/family member
        - Additional stressors
            - Hospital and medical costs
            - Maintaining working status and balancing family leave time
            - Learning about this disease and how to provide technical care for lines/pumps
            - Genetic testing and pulmonary/cardiac evaluation of other family members
    - Ensure support for family/siblings
    - Refer to social work
- Teen noncompliance: related to lack of control, changes in physical appearance
    - Prescribed medications
        - Have undesirable side effects including altered physical appearance
        - Methods of delivery that alter physical appearance
    - IPAH limits the life of an otherwise “normal” teenager

        - Essential to stress the necessity of life-sustaining medications
        - Empower patient
            - To control those areas of care where they can make a choice
            - Provide safe choices in areas of mandatory care
    - Female patients should not become pregnant
        - Provide counseling
        - Provide OB/Gyn consult for appropriate contraception

Ongoing Care

- Preventative care
    - Immunizations for RSV prophylaxis, influenza and pneumococcal vaccines
        - Yearly influenza vaccine for all family members > 6 mo. old
    - Growth monitoring
    - Prompt evaluation if upper respiratory symptoms
    - SBE prophylaxis if cyanotic or have an indwelling central line
- Pulmonary/cardiac evaluation
    - Frequent evaluations
        - At least every 3 to 6 months
        - Increased with advanced disease
        - After therapy changes or increase medication dose
        - Should be seen if increase in symptoms
        - Should be seen with onset of respiratory illness or signs/symptoms of sepsis
        - Include periodic imaging studies and cardiac catheterizations to evaluate treatment and/or to initiate new treatment
    - See in a comprehensive, multidisciplinary clinic

Special Considerations

- Intravenous medical therapy: Changing medication solution or changing lines is a high risk procedure, especially with epoprostenol (Flolan)/(Veletri - thermostable)
    - Needs to be switched quickly due to the very short half-life of medication
    - See above section on Medications, Continuous Infusion for added considerations, storage, and stability
- All surgical, sedation, or invasive procedures
    - High risk – should be done in a center with pediatric pulmonary hypertension experience
    - Higher than average mortality rates
    - Anesthesia
        - Pre-procedure consultation
        - Provided by cardiac anesthesia specialists
        - Continue medications for PH on day of surgery or cardiac catheterization

                - Ensure back up medication available
                - Ensure OR nursing knows how to operate infusion pump
            - NPO times are: 2 hours for clears, 4 hours for breast milk, and 6 hours for solids or formula
            - Induction of anesthesia
                - Can lead to PH "Crisis" with acute right ventricular failure and cardiovascular collapse
                - Regional anesthesia preferred
            - Goals during/after anesthesia
                - Prevent hypoxia/hypercarbia, acidosis, and other factors that would increase PVR
                - Maintain preload
                - Maintain sinus rhythm
        - Should recover from anesthesia in an intensive care unit (ICU) setting
- Exercise/increased physical activity
    - High risk of syncope and sudden death
    - Exercise testing required prior to any clearance for increased physical activity or participation in sports
    - Activity should be limited by increase in patient symptoms
        - Competitive exercise guidelines - Class III or IV or syncope
            - Competitive exercise should be avoided
            - Exercise should not be strenuous or isometric
            - Important to stay well-hydrated

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Useful pharmacy site with mechanisms of actions for medications:
http://cvpharmacology.com/clinical%20topics/pulmonary%20hypertension

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