Pediatric Cardiac Intensive Care Society 2014 Consensus Statement: Pharmacotherapies in Cardiac Critical Care Pulmonary Hypertension

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Objective: To review the pharmacologic treatment options for pulmonary arterial hypertension in the cardiac intensive care setting and summarize the most-recent literature supporting these therapies.

Data Sources and Study Selection: Literature search for prospective studies, retrospective analyses, and case reports evaluating the safety and efficacy of pulmonary arterial hypertension therapies.

Data Extraction: Mechanisms of action and pharmacokinetics, treatment recommendations, safety considerations, and outcomes for specific medical therapies.

Data Synthesis: Specific targeted therapies developed for the treatment of adult patients with pulmonary arterial hypertension have been applied for the benefit of children with pulmonary arterial hypertension. With the exception of inhaled nitric oxide, there are no pulmonary arterial hypertension medications approved for children in the United States by the Food and Drug Administration. Unfortunately, data on treatment strategies in children with pulmonary arterial hypertension are limited by the small number of randomized controlled clinical trials evaluating the safety and efficacy of specific treatments. The treatment options for pulmonary arterial hypertension in children focus on endothelial-based pathways. Calcium channel blockers are recommended for use in a very small, select group of children who are responsive to vasoreactivity testing at cardiac catheterization. Phosphodiesterase type 5 inhibitor therapy is the most-commonly recommended oral treatment option in children with pulmonary arterial hypertension. Prostacyclins provide adjunctive therapy for the treatment of pulmonary arterial hypertension as infusions (IV and subcutaneous) and inhalation agents. Inhaled nitric oxide is the first-line vasodilator therapy in persistent pulmonary hypertension of the newborn and is commonly used in the treatment of pulmonary arterial hypertension in the ICU. Endothelin receptor antagonists have been shown to improve exercise tolerance and survival in adult patients with pulmonary arterial hypertension. Soluble guanylate cyclase stimulators are the first drug class to be Food and Drug Administration approved for the treatment of chronic thromboembolic pulmonary hypertension.

Conclusions: Literature and data supporting the safe and effective use of pulmonary arterial hypertension therapies in children in the cardiac intensive care are limited. Extrapolation of adult data has afforded safe medical treatment of pulmonary hypertension in children. Large multicenter trials are needed in the search for safe and effective therapy of pulmonary hypertension in children. (*Pediatr Crit Care Med* 2016; 17:S89–S100)

Key Words: calcium channel blockers; nitric oxide; pharmacotherapy; phosphodiesterase inhibitor; prostacyclin; pulmonary hypertension

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Dr. McSweeney disclosed off-label product use: no pulmonary hypertension (PH) drug is Food and Drug Administration (FDA) approved for pediatric use (this is noted several times throughout the article). Dr. Lee disclosed off-label product use: PH medications in pediatrics (many medications are not FDA approved for pediatrics. This is disclosed in the article). Dr. Ivy has disclosed other support from the University of Colorado contracts with Actelion, Bayer, Gilead, Lilly, and United Therapeutics (Dr. Ivy to be a consultant); served on the steering committee for pediatric PH studies being performed by Actelion, Bayer, Lilly, and United Therapeutics; enrolled patients in research studies sponsored by Actelion, Bayer, Gilead, Lilly, and United Therapeutics; received financial support from the National Institutes of Health (NIH); served as a board member of the Pulmonary Hypertension Association; received restricted financial contributions from the Jayden de Luca Foundation, the Frederick and Margaret Weyerhaeuser Foundation, and the Leah Bult Foundation to perform pediatric PH research; received support for this article research from the NIH, Jayden de Luca Foundation, Frederick and Margaret Weyerhaeuser Foundation, and Leah Bult Foundation; and disclosed off-label product use: ambrisentan, bosentan, macitentan, sildenafil, tadalafil, epoprostenol, treprostinil, and iloprost. His institution received funding from Actelion, Bayer, and Gilead. Dr. Kim disclosed that he does not have any potential conflicts of interest.

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Pulmonary arterial hypertension (PAH) is a life-threatening disease characterized by a progressive increase in pulmonary vascular resistance (PVR) leading to right heart failure and death. In the past decade, specific targeted

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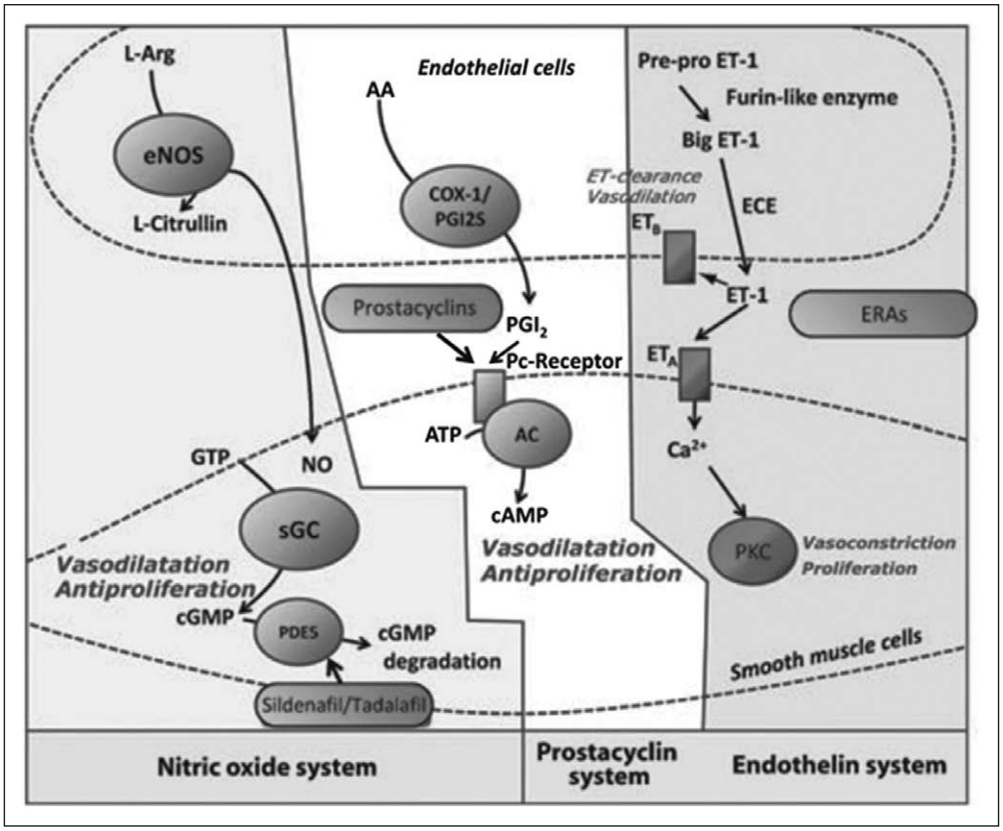

Figure 1. Endothelial pathways for currently approved pulmonary arterial hypertension therapies. ATP = adenosine triphosphate; cAMP = cyclic adenosine monophosphate, cGMP = cyclic guanosine monophosphate, eNOS = endothelial nitric oxide synthase, ERA = endothelin receptor antagonists, ET = endothelin, GTP = guanosine triphosphate, sGC = soluble guanylate cyclase. Adapted from Diller and Baumgartner (1). Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

therapies have been developed and have improved survival in adult patients with PAH. These therapies have also benefited children with PAH. The most common etiologies of PAH in children differ from those of PAH in the adult population. PAH is associated with congenital heart disease, idiopathic PAH (formerly known as "primary PH"), and heritable PAH in the majority of children. Unrepaired congenital heart diseases, such as ventricular septal defects or a patent ductus arteriosus and more complex diseases, such as truncus arteriosus or single ventricle, may cause PAH. Although PAH associated with congenital heart disease resolves in most children after early surgical correction, irreversible pulmonary vascular disease develops in some children. Thus, the natural history of PAH due to congenital heart disease has a wide range of survival. In contrast to children with congenital heart disease, the survival rate in children with idiopathic or heritable PAH is worse. The diagnosis of idiopathic PAH is difficult as the symptoms are nonspecific and include breathlessness, syncope, or seizures. Unfortunately, there are limited data on treatment strategies in children with PAH because of the small number of randomized controlled clinical trials evaluating the safety and efficacy of specific treatments. Currently approved PAH therapies impact one of three endothelial-based pathways, including nitric oxide (NO)-cyclic guanosine monophosphate (cGMP), prostacyclin, or endothelin-1 (ET-1) (**Fig. 1**) (1). This statement summarizes currently available therapies based on adult data and a limited number of clinical trials in children with PAH (**Tables 1 and 2**).

CALCIUM CHANNEL BLOCKERS

1. Physiologic rationale: Calcium channel blockers (CCBs) cause relaxation of vascular smooth muscle by inhibition of calcium influx to the cardiac and smooth muscle. Recent data suggest that CCB treatment for PAH is only indicated and efficacious in 10–30% of children (2). "Responders" to vasoreactivity testing at cardiac catheterization may have a good response to treatment with CCBs, but "nonresponders" should not be treated with CCBs as they are associated with worse survival and may lower cardiac output.
2. Mechanism of action: Calcium channel antagonists inhibit calcium flux into cardiac and smooth muscle by binding to the calcium channels and may have negative inotropic effects. The effects on systemic blood pressure are consequence of a dose-related decrease of systemic vascular resistance.
3. Pharmacokinetics: Pharmacokinetic data are available only for the children with pulmonary hypertension and bronchopulmonary dysplasia (3). Nifedipine, diltiazem, and amlodipine undergo significant hepatic metabolism via the CYP3A4 enzyme system (4), and concomitant use with inhibitors of CYP3A4 should be cautioned.

   Monitoring variables and adverse effects: High-dose CCB therapy has a potential risk for systemic hypotension and should be avoided in children with low blood pressure, low cardiac output, or high right atrial pressure. The use in neonates and infants is controversial.
4. Evidence to support the therapy: It is rare that CCBs should be used as new therapy in the ICU setting. The beneficial effects of CCBs have been reported in pediatric and adult patients with PAH (2, 5), but patients should be monitored closely as they may deteriorate later in the disease process. Furthermore, nifedipine, amlodipine, and diltiazem have been used for treatment of pulmonary hypertension, but there have been no large series of patients comparing these agents. Verapamil should not be used to treat PAH.

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TABLE 1. Food and Drug Administration–Approved Vasodilator Therapies

Prostacyclin	Generic Name Epoprostenol Iloprost Treprostinil	Brand Name Flolan Veletri Ventavis Remodulin Tyvaso Orenitram	Route IV Inhaled IV/subcutaneous Inhaled Oral	Food and Drug Administration–Approved Adult Maximum Dose Unknown 5 μg per treatment session Unknown 54 μg per treatment session Unknown	Frequency Continuous 6–9 times daily Continuous 4 times daily 2–3 times daily
Phosphodiesterase type-5 inhibitor Endothelin receptor antagonist Soluble guanylate cyclase stimulator	Sildenafil Tadalafil Bosentan Ambrisentan Macitentan Riociguat	Revatio Adcirca Tracleer Letairis Opsumit Adempas	Oral IV Oral Oral Oral Oral Oral	20 mg 10 mg 40 mg 125 mg 10 mg 10 mg 2.5 mg	3 times daily 3 times daily Once daily 2 times daily Once daily Once daily 3 times daily

None of these medications are Food and Drug Administration approved for pediatric use. Safety and dosing of these medications are not well established in children.

PROSTACYCLIN

1. Physiologic rationale: Prostacyclin, a member of the endogenous prostanoid family, is a potent vasodilator and has antithrombotic, antiproliferative, and anti-inflammatory effects.
2. Mechanism of action: Prostacyclin is produced from arachidonic acid in the vascular endothelium (6). The elaborated prostacyclin has an extremely short biological half-life of between 2 and 3 minutes in the pulmonary circulation. The biological functions of prostacyclin are mediated by cell-surface G-protein receptors on pulmonary endothelial cells or platelets, and increased intracellular cyclic adenosine monophosphate leads to smooth muscle relaxation and inhibition of platelet aggregation (7). Prostacyclin metabolites and prostacyclin synthase are decreased in PAH (8–10).
3. Pharmacokinetics:
   a) Epoprostenol has a rapid onset of action, reaching plasma steady-state concentrations within 15 minutes. Epoprostenol is obligated to a continuous IV therapy due to the elimination half-life of 2–3 minutes. In human blood, epoprostenol is rapidly hydrolyzed and metabolized to 6-keto-prostaglandin F1α. This metabolite is biologically inactive and eliminated in the urine (11, 12).

      Monitoring variables and adverse effects: Severe adverse events, such as bradycardia, systemic hypotension, and thrombocytopenia, may occur and should be monitored at initiation of administration. Patients with pulmonary venoocclusive disease or pulmonary vein disease may develop life-threatening pulmonary edema. Patients with pneumonia or other parenchymal lung disease may develop worsening ventilation-perfusion matching. Epoprostenol also inhibits platelet aggregation with a potentially increased risk of bleeding with concomitant anticoagulant or antiplatelet therapy (13, 14). Serious complications of "rebound" pulmonary hypertension can occur on acute discontinuation. Dyspnea, chest pain, pallor, and syncope may result from insufficient drug delivery.

   b) Iloprost, an inhaled prostacyclin analogue, has low risk of systemic hypotension, minimizing the effect on ventilation-perfusion mismatch compared with IV prostacyclin (15–21). Iloprost achieves maximum serum concentration at 5–10 minutes after inhalation. The serum elimination half-life of inhaled iloprost is 6.5–9.4 minutes with a pharmacodynamic half-life of 20–25 minutes (22, 23). Approximately 80–90% of metabolites are eliminated in the kidney.

      Monitoring variables and adverse effects: Inhaled iloprost requires caution in patients with concomitant pulmonary diseases, such as asthma and interstitial lung disease. The liver and kidney metabolize iloprost, and dosage adjustments may be necessary in hepatic or renal insufficiency. No significant events of serious bleeding have been noted in patients during coadministration with warfarin. There are no significant drug-to-drug pharmacokinetic interactions between iloprost and other pulmonary vasodilators (2).

   c) Treprostinil, an alternative prostacyclin analogue, was initially approved by the Food and Drug Administration (FDA) for subcutaneous use and subsequently approved for IV, inhaled, and oral use. The advantages of treprostinil therapy compared with epoprostenol include stability at room temperature, longer half-life, fewer side effects, and small pump options for outpatient use.

IV and subcutaneous treprostinil infusions are bioequivalent with a terminal elimination half-life of approximately 4.5 hours. Treprostinil is rapidly and completely absorbed with subcutaneous infusion. Steady-state concentrations occur in 10 hours (24–27).

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TABLE 2. Treatment Options for Pediatric Pulmonary Hypertension

Prostacyclin	Medication	Dose	Side Effects	Consideration
	Mechanism of action: increases cyclic adenosine monophosphate, pulmonary and systemic vasodilation, inhibition of vascular remodeling, and antiplatelet aggregation			
	Epoprostenol	Initial infusion rate: 1–3 ng/kg/min Maintenance infusion rate: 50–80 ng/kg/min	Flushing, headache, nausea, diarrhea, jaw discomfort, rash, and hypotension thrombocytopenia	Potential risk of hypotension and bleeding in children receiving concomitant drugs, such as anticoagulants, platelet inhibitors, or other vasodilators
	Iloprost	Initial dose: 2.5 μg per inhalation 6 times daily Maintenance dose: 5 μg per inhalation 9 times daily	Cough, wheeze, headache, flushing, jaw pain, diarrhea, rash, and hypotension (at higher doses)	Potential risk of exacerbating reactive airway disease
	Treprostinil (IV/ subcutaneous)	Initial infusion rate: 1.25–2 ng/kg/min Maintenance infusion rate: 50–80 ng/kg/min	Flushing, headache, nausea, diarrhea, musculoskeletal discomfort, rash, hypotension, thrombocytopenia, and pain at subcutaneous infusion site	Similar to epoprostenol
	Treprostinil (inhaled)	Initial dose: 3 breaths (18 μg) 4 times daily Maintenance dose: 9 breaths (54 μg) 4 times daily	Cough, headache, nausea, dizziness, flushing, and throat irritation	Reactive airway symptoms and hypotension possible at high dose
	Treprostinil (oral)	Initial dose: 0.25 mg PO BID Maintenance dose: determined by tolerability	Headache, nausea, diarrhea, jaw pain, extremity pain, hypokalemia, abdominal discomfort, and flushing	If BID dosing increment is not tolerated, consider TID dosing
PDE-5 inhibitor	Mechanism of action: inhibits PDE-5, pulmonary vasodilation, and inhibition of vascular remodeling			
	Sildenafil	Pediatric (oral) Initial dose: 0.5 mg/kg per dose PO TID Maintenance dose: 1–2 mg/kg per dose PO TID Adult (oral) 20 mg PO TID Pediatric (IV) Loading dose 0.4 mg/kg over 3 hr Followed by continuous infusion: 1.6 mg/kg/d	Headache, flushing, rhinitis, dizziness, hypotension, peripheral edema, dyspepsia, diarrhea, myalgia, and back pain	Coadministration of nitrates is contraindicated Sensorineural hearing loss has been reported Ischemic optic neuropathy has been reported
	Tadalafil	Pediatric (preliminary studies suggest) 1 mg/kg per dose PO QD Adult 40 mg PO QD	Similar to sildenafil No significant effect on vision	Coadministration of nitrates is contraindicated Sensorineural hearing loss has been reported Ischemic optic neuropathy has been reported

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TABLE 2. (*Continued*). Treatment Options for Pediatric Pulmonary Hypertension

Endothelin receptor antagonist	Mechanism of action: ET_A/ET_B receptor antagonist, pulmonary vasodilation, and inhibition of vascular remodeling			
	Bosentan	Pediatric	Abdominal pain, vomiting, extremity pain, fatigue, flushing, headache, edema, nasal congestion, anemia, and decreased sperm count	Monitor liver enzymes and hemoglobin (required)
		2 mg/kg per dose PO BID	Potential risk of dose-dependent increases in aminotransaminase levels	
		10–20 kg: 31.25 mg PO BID 20–40 kg: 62.5 mg PO BID		Not recommended in patients with moderate or severe hepatic impairment
		> 40 kg: 125 mg PO BID		Caution with concomitant use of CYP3A4 inducers and inhibitors
		Adult Initial dose: 62.5 mg PO BID Maintenance dose: 125 mg PO BID		Teratogenecity REMS*
	Ambrisentan	Pediatric < 20 kg: 2.5–5 mg PO QD > 20 kg: 5–10 mg PO QD	Peripheral edema, nasal congestion, headache, flushing, anemia, nausea, and decreased sperm count	Obtain baseline liver enzymes and hemoglobin and monitor as clinically indicated
		Adult: Initial dose: 5 mg PO QD Maintenance dose: 10 mg PO QD	The incidence of serum aminotransferase elevation is low	Teratogenecity REMS*
	Macitentan	10 mg PO QD	Nasal congestion, headache, flushing, anemia, and decreased sperm count The incidence of serum aminotransferase elevation is low	Obtain baseline liver enzymes and hemoglobin and monitor as clinically indicated Teratogenicity REMS*
sGC stimulator	Mechanism of action: stimulates sGC, pulmonary vasodilation, and inhibition of vascular remodeling			
	Riociguat	Initial dose: 0.5–1 mg PO TID	Headache, dizziness, dyspepsia, nausea, diarrhea, hypotension, vomiting, anemia, gastroesophageal reflux, and constipation	Coadministration of nitrates and/or PDE-5 inhibitors is contraindicated
		Maintenance dose: 2.5 mg PO TID		In growing rats, effects on bone formation were observed Teratogenecity REMS*

PDE-5 = phosphodiesterase type-5, ET = endothelin, REMS = Risk Evaluation and Mitigation Strategies, sGC = soluble guanylate cyclase.

*The Food and Drug Administration (FDA) Amendments Act of 2007 gave the FDA authority to require Risk Evaluation and Mitigation Strategies (REMS) from manufacturers to ensure the benefits of a drug or biological product outweigh its risks. These medications require REMS due to teratogenicity.

None of these medications are FDA approved for pediatric use. Safety and dosing of these medications are not well established in children. Recommended pediatric dosing is included if available.

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Monitoring variables and adverse effects: Systemic blood pressure, heart rate, and side effects should be monitored with IV treprostinil initiation, thus requiring hospital initiation. Major side effects of treprostinil include headache, diarrhea, nausea, rash, flushing, jaw pain, and foot pain. Following transition from epoprostenol to IV treprostinil, children exhibited less prostanoid side effects, with the exception of leg/muscle pain (28). Prostanoid side effects are similar with subcutaneous administration with the addition of infusion site pain and reaction being the most-common side effects (with a negative impact on tolerability). The clearance of treprostinil is decreased in patients with hepatic insufficiency, and caution with dosing is needed in children with liver disease. Gram-negative bacteremia has been associated with IV treprostinil therapy. The use of protected connections and an alkaline buffer may decrease the risk (29, 30). Treprostinil has no pharmacokinetic interactions with endothelin receptor antagonists (ERAs) or phosphodiesterase inhibitors. Coadministration of treprostinil may have a potential risk of bleeding and systemic hypotension in children receiving concomitant anticoagulants or vasodilators, respectively (31).

Inhaled treprostinil has an unknown half-life that cannot be estimated given the low plasma concentration achieved (when compared with parenteral treprostinil) due to direct lung delivery. Patients requiring rates of parenteral treprostinil greater than or equal to 15 ng/kg/min should not be transitioned to inhaled treprostinil given the decreased exposure. Inhaled treprostinil T_{max} is achieved in 5–10 minutes.

Monitoring variables and adverse effects: In contrast to its IV formulation, inhaled treprostinil has less systemic effects and has been started in the outpatient setting in stable patients as add-on therapy. Inhaled treprostinil requires caution in patients with concomitant pulmonary diseases, such as asthma and interstitial lung disease (32).

Oral treprostinil was recently approved, and there is little experience in children. Oral treprostinil is an osmotic tablet delivered orally. The pill must be swallowed whole and may not be chewed or broken as the entire dose will be delivered. There is no suspension. The maximum dose is determined by tolerability.

Monitoring variables and adverse effects: Oral treprostinil may cause prostanoid side effects similar to other prostacyclins (33).

4. Evidence to support the Therapy:

   a) Epoprostenol is indicated for the treatment of adult patients with PAH to improve exercise tolerance and survival (34–36). Although epoprostenol is not approved in children, continuous IV epoprostenol therapy is effective for improving symptoms, hemodynamics, and survival in children with idiopathic PAH or PAH associated with congenital heart disease (2, 37–39). Inhaled epoprostenol has been effectively used in the ICU setting in place of inhaled NO.

   b) Iloprost is indicated for adults with PAH to improve a composite endpoint consisting of exercise tolerance, functional class symptoms, and lack of deterioration (32). Although iloprost is not approved in children, several studies have evaluated the use of aerosolized iloprost in children with PAH (15–21). There is currently only one study showing chronic iloprost efficacy in children with idiopathic PAH or PAH associated with congenital heart disease (16). In this study, iloprost caused sustained functional improvement in select children with PAH; however, bronchoconstriction led to discontinuation in some patients. One small study retrospectively reviewed seven children who transitioned from inhaled NO to inhaled iloprost in the postoperative period after congenital heart surgery. Systolic pulmonary artery (PAP) or systemic arterial (SAP) pressures did not differ between inhaled NO versus iloprost treatment, but the PAP/SAP ratio was reduced on iloprost therapy (from 0.61 on NO to 0.49 on iloprost; $p = 0.03$). Although this is a modest improvement, this study shows that children on inhaled NO can be successfully transitioned to inhaled iloprost therapy (40). A prospective study in 2008 evaluated 12 children at risk for pulmonary hypertensive crisis after congenital heart surgery in whom iloprost was administered in place of inhaled NO. Eight children had a pulmonary hypertensive crisis that was responsive to inhaled iloprost with a fall in mean PAP (47.9–30.2; $p = 0.012$) and a rise in arterial saturation (82.2–93.4; $p = 0.012$) with no fall in SAP (19).

   c) Treprostinil has four delivery options and is FDA approved for subcutaneous (2002), IV (2004), inhaled (2009), and oral (2013) administration in adults with PAH to diminish symptoms associated with exercise (41–44). Treprostinil therapy is not approved in the pediatric population. However, recent studies have demonstrated safety in transitioning pediatric patients from epoprostenol to subcutaneous or IV treprostinil therapy for the advantages of stability at room temperature and a longer half-life when compared with epoprostenol (28, 45). Inhaled treprostinil has been studied both in acute and long-term treatment of children (46, 47). There are no published studies of oral treprostinil in children.

PHOSPHODIESTERASE TYPE 5 INHIBITORS

1. Physiologic rationale: Phosphodiesterase type 5 (PDE-5) inhibitors increase the concentration of cGMP in pulmonary smooth muscle vasculature, thus resulting in pulmonary vasodilation.
2. Mechanism of action: PDE-5 is abundantly expressed in lung and penile tissue; in PAH, the PDE-5 enzyme is increased in the lung vasculature. PDE-5 inactivates cGMP leading to attenuated vasodilation (48). PDE-5 inhibitors have antiproliferative, proapoptotic, and vasodilating effects in pulmonary vasculature through an increase in cGMP (49).

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3. Pharmacokinetics:

   a) Sildenafil is absorbed rapidly after oral administration with maximum plasma concentrations achieved after 1–2 hours and a half-life of approximately 4 hours in adults. Metabolism of sildenafil occurs primarily by hepatic cytochrome P450 (CYP) enzymes, such as CYP3A4 and CYP2C9. CYP3A4 inducers and medications, such as bosentan, decrease the levels of sildenafil, thus monitoring may be advisable with coadministration with CYP3A4 inducers. Alternatively, CYP3A4 inhibitors increase serum concentrations of sildenafil.

      Monitoring variables and adverse effects: Oral sildenafil has less systemic effects and has been started in the outpatient setting. Eye and hearing screening in extremely premature infants should be considered (50–53). Hearing and visual disturbances in older patients have been described. Patients with a creatinine clearance less than 30 mL/min, hepatic cirrhosis, or concomitant use of CYP3A4 inhibitors may require a reduction in their sildenafil dose (54). Although serum levels can rise in severe impairment of renal or hepatic function, dosage adjustments are usually not necessary. Sildenafil should not be used concomitantly with systemic nitrates. Coadministration of sildenafil with bosentan leads to decreased sildenafil plasma concentrations and increased bosentan concentrations (55). There is no significant pharmacokinetic interaction between sildenafil and warfarin. Erections may occur in 10% of boys taking sildenafil but are usually not serious.

   b) Tadalafil reaches a maximal concentration of 2 hours with a half-life of 35 hours after oral administration in adults (56). Steady-state plasma concentrations are achieved within 5 days of initiation of tadalafil at 20 mg or 40 mg daily. Metabolism of tadalafil occurs primarily by hepatic cytochrome P450 CYP3A4 enzyme.

      Monitoring variables and adverse effects: The use in children less than 4 years has not been described, and the use in neonates and infants is contraindicated because of the lack of maturation of glucuronidation pathway (57, 58). Tadalafil has little effect on PDE-6, and thus, it has a minimal influence on visual effects. Concomitant use of potent inducers or inhibitors of CYP3A is not recommended. The dose should be reduced in patients with mild to moderate renal or hepatic impairment. Tadalafil is not recommended in patients with severe renal or hepatic disease and should not be used in patients taking nitrates. Tadalafil exposure is decreased with concomitant bosentan by 41.5% in healthy adult volunteers (59). Coadministration of tadalafil with bosentan leads to decreased tadalafil plasma concentrations and increased bosentan concentrations. No pharmacokinetic drug interactions between tadalafil and ambrisentan have been noted (60).

4. Evidence to support the therapy:

   a) Sildenafil was FDA approved in 2005 for the treatment of adult PAH to improve exercise ability and delay time to clinical worsening at a dose of 20 mg TID (61). Although sildenafil is approved for use in children with PAH in Europe, the U.S. FDA released a strong warning in 2012 against the chronic use of sildenafil in children with PAH with concerns for increased mortality at higher doses. The Sildenafil in Treatment-Naive Children Aged 1-17 years with pulmonary arterial hypertension (STARTS)-2 trial (an extension of the STARTS-1 trial) is a worldwide randomized, double-blind, placebo-controlled study of 234 treatment naive children evaluating outcomes of low (10 mg), medium (10–40 mg), or high (20–80 mg) doses of oral sildenafil or placebo TID (62). Survival on sildenafil monotherapy was similar for the first year for all dosage groups in the STARTS-2 study (63, 64). At 3 years, however, an increase in mortality was noted at the high-dose range. Deaths were related to etiology and baseline disease severity (idiopathic and familial PAH with above-median values for PVR, mean PAP, and right atrial pressure at baseline). In response to the FDA warning, clinical pediatric PAH experts put forth a consensus statement highlighting the limitations of the STARTS-2 extension study and recommending continued but cautious use of oral sildenafil in pediatric patients with a strong recommendation to avoid the use of high doses (65). The FDA published a clarification in 2014 stating that the risks and benefits of sildenafil should be considered in treating children with PAH. IV sildenafil has also been studied in children. A double-blind, multicenter, placebo-controlled study of IV sildenafil in pediatric patients with congenital heart disease and postoperative pulmonary hypertension showed favorable results, such as shorter time to extubation and ICU stay, although the study was stopped early because of poor enrollment (66). Sildenafil is approved for pediatric PAH in Europe.

   b) Tadalafil, a long-acting PDE-5 inhibitor, is a once-daily oral alternative to sildenafil and was FDA approved for adults in 2009. Tadalafil is currently approved for the treatment of adult PAH (World Health Organization [WHO] group 1) to improve exercise ability. Although little is known of the use of tadalafil in children with PAH, a recent retrospective study suggested clinical efficacy and safety in children with PAH. In this study, 33 pediatric patients with PAH were retrospectively evaluated and 29 of 33 patients who transitioned from sildenafil (3.4 ± 1.1 mg/kg/d) to tadalafil (1.0 ± 0.4 mg/kg/d) successfully continued tadalafil therapy without the need to return back to sildenafil. Only two patients stopped tadalafil because of side effects, including migraine and allergic reaction (discontinuation rate, 6%). Furthermore, tadalafil statistically improved hemodynamic data, including mean pulmonary arterial pressure (53.2 ± 18.3 vs 47.4 ± 13.7; $p < 0.05$) and PVR index (12.2 ± 7.0 vs 10.6 ± 7.2; $p < 0.05$) compared with sildenafil in 14 of 29 patients with repeated catheterization (58).

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INHALED NO

1. Physiologic rationale: Inhaled NO is the first-line vasodilator treatment for persistent pulmonary hypertension of the newborn (67–70). Similar to endogenously produced NO, inhaled NO diffuses rapidly across the alveolar-capillary membrane and induces vasodilation through a cGMP-dependent pathway (71, 72). Although FDA approval for inhaled NO therapy is restricted to newborns with hypoxemic respiratory failure, inhaled NO has been used in the management of postoperative PAH associated with congenital heart disease, congenital diaphragmatic hernia, bronchopulmonary dysplasia, and severe PAH presenting with hemodynamic instability and right heart failure (73–76).
2. Mechanism of action: NO is produced endogenously from L-arginine by NO synthases. Inhaled NO diffuses rapidly across the alveolar-capillary membrane into the pulmonary smooth muscle. The pathophysiologic effects of NO are mediated through the increased intracellular concentrations of cGMP, leading to smooth muscle relaxation.
3. Pharmacokinetics: No Pharmacokinetic Data Are Available.

    a) Dosing: NO is administered by mask, nasal cannula, or tracheal tube. A randomized, placebo-controlled, dose-response trial compared three different doses of inhaled NO (5, 20, or 80 ppm) and placebo in term newborns with respiratory failure. In this study, all regimens of inhaled NO improved oxygenation compared with the placebo group; however, there was no difference in responses among the three regimens, and 35% of patients who received 80 ppm of inhaled NO had methemoglobinemia. The study suggested that 5–40 ppm of inhaled NO therapy may be appropriate and safe, whereas sustained treatment with 80 ppm NO increases the risk of adverse events (77, 78).

    b) Monitoring variables and adverse effects: Patients receiving inhaled NO should be monitored for formation of nitrogen dioxide (NO_2) and methemoglobinemia. NO_2 is easily converted to nitric acid that is highly toxic to the respiratory tract. Methemoglobinemia may occur under high concentrations of inhaled NO (80 ppm) (77, 78). Inhaled NO combines with hemoglobin and is rapidly oxidized to methemoglobin, leading to tissue hypoxia without cyanosis. The acute withdrawal of inhaled NO therapy may precipitate rebound PAH, which may be avoided with the use of PDE-5 inhibitors. There are no known drug interactions.
4. Evidence to support the therapy: Multicenter, randomized clinical studies have demonstrated that inhaled NO reduces the need for extracorporeal membrane oxygenation in Pediatric Pulmonary Hypertension Network (69). Furthermore, inhaled NO is used for the acute vasoreactivity testing during the assessment of pulmonary hemodynamics at cardiac catheterization (16, 47, 78–80).

ENDOTHELIN RECEPTOR ANTAGONISTS

1. Physiologic rationale: ET-1, a potent vasoactive peptide produced primarily in the vascular endothelial and smooth muscle cells, is considered the predominant pathophysiologic isoform in PAH. The overexpression of ET-1 protein has been demonstrated in patients with PAH (81). Expression of plasma and lung tissue ET-1 is increased in PAH and correlate with the degree of pulmonary remodeling. ET-1 is a potent vasoconstrictor and is mediated by two types of endothelin receptors, including type A (ET_A) and type B (ET_B). Bosentan shows an almost equal affinity for both receptors. In contrast, ambrisentan is highly selective for ET_A. Bosentan and ambrisentan can improve hemodynamics and survival in adult patients with PAH. Although the use of oral bosentan in pediatric patients with idiopathic or associated PAH has been reviewed previously (82–87), bosentan has not been approved in pediatric populations.
2. Mechanism of action: The ET_A and ET_B receptors on vascular smooth muscle mediate vasoconstriction and cell proliferation in pulmonary vascular smooth muscle cells. The ET_B receptor on endothelial cells mediates vasodilation, antiproliferation, and ET-1 clearance. Bosentan and macitentan are highly specific, competitive, dual ET-1 receptor antagonists, which bind to ET_A and ET_B receptors (81). Ambrisentan is a selective antagonist of ET_A with a 4000-fold greater affinity for ET_A over the ET_B receptor (88, 89). The possible impact of higher selectivity for the ETA receptor includes greater vasodilation and ET-1 clearance.
3. Pharmacokinetics:

    a) Bosentan: Bosentan is rapidly absorbed after oral administration, and the median time to maximum plasma concentration is 1–3 hours (82, 90). Bosentan is metabolized in the liver by CYP2C9 and CYP3A4.

        Monitoring variables and adverse effects: Bosentan has the potential risk of dose-dependent increase in aminotransferase in adults (81), but the incidence of this is low in children (84), liver function tests must be monitored monthly, and bosentan should be used with caution in critically ill children with liver dysfunction. Concomitant use of bosentan with inhibitors of CYP2C9 or CYP3A4 should be cautioned (83). The pharmacokinetics of bosentan was not affected by coadministration with warfarin, but bosentan can decrease anticoagulant response from warfarin and must be monitored closely. Because sildenafil inhibits CYP3A4 activity, the coadministration of sildenafil leads to an increase in bosentan concentrations (91). Likewise, bosentan reduces the concentration of sildenafil. Therefore, adjusting the dose of sildenafil or bosentan should be considered in patients treated with combination therapy. Bosentan is teratogenic.

    b) Ambrisentan: Ambrisentan is rapidly absorbed after oral administration with mean time to maximal concentrations of 1.7–3.3 hours. Steady state is achieved after 3–4 days of therapy. The half-life of ambrisentan

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is approximately 15 hours for the 5 mg once-daily dosing in adults patients. The primary metabolic pathway of ambrisentan is hepatic glucuronidation. Ambrisentan is also metabolized by CYP3A4 and CYP2C19 isozymes (60, 92, 93).

Monitoring variables and adverse effects: Monthly liver function testing for ambrisentan is no longer on the FDA label after a recent study found no difference in hepatic aminotransferase level elevation when compared with placebo (88, 89), but most pediatric centers still perform routine monitoring, every 3–4 months. Ambrisentan is partially metabolized by CYP3A4 and CYP2C19, and caution should be exercised with concomitant use of medications that are strong inhibitors of CYP3A4 or CYP2C19. Administration of ambrisentan with warfarin does not have significant drug interactions. There are no drug-to-drug interactions between ambrisentan and sildenafil (60, 93–95). Ambrisentan should be used with caution in critically ill children with liver dysfunction. Ambrisentan is teratogenic.

c) Macitentan: Macitentan is slowly absorbed after oral administration with time to peak concentration of 8 hours. The half-life of macitentan is approximately 16 hours (active metabolite approximately 48 hours) (96, 97). Macitentan is metabolized by CYP3A4 and CYP2C19 isoenzymes.

Monitoring variables and adverse effects: ERAs are known to cause hepatotoxicity and liver failure; baseline liver enzymes should be obtained and monitored as clinically indicated. Macitentan is a major substrate of CYP3A4, and caution should be exercised with concomitant use of medications that are strong inhibitors or inducers of CYP3A4. Macitentan does not cause clinically relevant changes in sildenafil or warfarin exposure. There are currently no published studies in children. Macitentan is teratogenic.

4. Evidence to support the therapy:

a) Bosentan: Bosentan, an oral endothelin ET_A/ET_B receptor antagonist, improves exercise capacity, hemodynamics, and survival in adult patients with PAH (98–100). Bosentan was FDA approved in 2001 and is recommended as treatment for adult patients with PAH. Twice-daily doses of bosentan at 31.25, 62.5, or 125 mg (10–20, > 20–40, or > 40 kg, respectively) for 12 weeks significantly improved hemodynamics in pediatric patients with PAH (aged 3–15 yr) with WHO functional class II or III in a noncomparative, multicenter, pharmacokinetic trial (Bosentan randomized trial of endothelin antagonist therapy for pulmonary hypertension-3) (82). Although the use of oral bosentan in pediatric patients with idiopathic or associated PAH has shown clinical efficacy (82–87), bosentan has not been approved in pediatric populations in the United States. A pediatric formulation is approved in Europe.

b) Ambrisentan: Ambrisentan, an oral endothelin ET_A/ET_B receptor antagonist, was approved as treatment for adult patients with PAH in 2013. Ambrisentan has demonstrated improved exercise tolerance, WHO functional class, and Borg dyspnea score in adults (88, 91). The clinical efficacy and safety of ambrisentan therapy have not been well studied in children with PAH. A recent retrospective study suggested clinical efficacy and safety of ambrisentan in 38 children with PAH (101).

c) Macitentan: Macitentan, a selective oral endothelin ET_A receptor antagonist, was approved as treatment for adult patients with PAH in 2013. A trial of 250 patients revealed improved survival in patients randomized to 3 mg of macitentan daily when compared with placebo (with further improvement at 10 mg daily compared with placebo) (102). There are currently no studies in children.

SOLUBLE GUANYLATE CYCLASE STIMULATORS (RIOCIGUAT)

1. Physiologic rationale: NO induces vasodilation through a cGMP-dependent pathway (71, 72). Riociguat increases cGMP levels, thus inducing vasodilation of the pulmonary vasculature.
2. Mechanism of action: Riociguat stimulates soluble guanylate cyclase (sGC) independently of NO and increases the sensitivity of sGC to NO, resulting in increased cGMP levels.
3. Pharmacokinetics: Riociguat is rapidly absorbed, and maximum plasma concentration is reached between 0.5 and 1.5 hr. The mean elimination half-life is 5–10 hr.

Monitoring Variables and Adverse Effects. The most common serious adverse events associated with riociguat use include right ventricular failure and syncope (103, 104). Patients should not take riociguat with any nitrates or PDE-5 inhibitors as this combination may lead to severe hypotension. Riociguat alters the regulation of bone homeostasis in juvenile rats, and the riociguat-related bone findings are of concern with respect to potential pediatric use, especially in infants and younger children. Riociguat has no pharmacodynamic interaction with warfarin (105). Riociguat is teratogenic.

4. Evidence to support the therapy: Riociguat was FDA approved in 2013 for the treatment of PAH and is the first drug to be approved for the treatment of PH associated with chronic thromboembolic pulmonary hypertension (CTEPH). In Arterial Hypertension Soluble Guanylate Cyclase-Simulator Trial-1, 443 patients with symptomatic PAH were randomized to receive placebo or riociguat. After 12 weeks, the riociguat group had improved 6-minute walk distance by 30 m ($p < 0.001$), and the placebo group had decline by 6 months ($p < 0.001$). There were also significant improvements in PVR ($p < 0.001$), N-terminal of the prohormone brain natriuretic peptide (NT-proBNP) levels ($p < 0.001$), WHO functional class ($p = 0.003$), and time to clinical worsening ($p = 0.005$) (103). In the Chronic Thromboembolic Hypertension Soluble Guanylate Cyclase-Stimulator-1 study, 261

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patients with inoperable CTEPH or persistent or recurrent pulmonary hypertension after pulmonary endarterectomy were randomized to receive placebo or riociguat. By week 16, the 6-minute walk distance had increased by a mean of 39 m in the riociguat group ($p < 0.001$), when compared with a mean decrease of 6 m in the placebo group ($p < 0.001$). Riociguat was also associated with significant improvements in the NT-proBNP level ($p < 0.001$) and WHO functional class ($p = 0.003$) (104).

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