Published in final edited form as:

Paediatr Drugs. 2014 February ; 16(1): 43–65. doi:10.1007/s40272-013-0052-2.

Drug Treatment of Pulmonary Hypertension in Children

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Abstract

Pulmonary arterial hypertension (PAH) is a rare disease in infants and children that is associated with significant morbidity and mortality. The disease is characterized by progressive pulmonary vascular functional and structural changes resulting in increased pulmonary vascular resistance and eventual right heart failure and death. In the majority of pediatric patients, PAH is idiopathic or associated with congenital heart disease and rarely is associated with other conditions such as connective tissue or thromboembolic disease. Although treatment of the underlying disease and reversal of advanced structural changes has not yet been achieved with current therapy, quality of life and survival have been improved significantly. Targeted pulmonary vasodilator therapies, including endothelin receptor antagonists, prostacyclin analogues and phosphodiesterase type 5 inhibitors, have demonstrated hemodynamic and functional improvement in children. The management of pediatric PAH remains challenging as treatment decisions continue to depend largely on results from evidence-based adult studies and the clinical experience of pediatric experts. This article reviews the current drug therapies and their use in the management of PAH in children.

Keywords

pulmonary hypertension; pediatric; prostacyclin; epoprostenol; iloprost; treprostinil; phosphodiesterase type 5 inhibitors; sildenafil; tadalafil; endothelin receptor antagonists; bosentan; ambrisentan

Introduction

Pulmonary arterial hypertension (PAH) is a rare but life-threatening disease. It is characterized by progressive structural changes to the pulmonary vascular bed with resultant increase in pulmonary vascular resistance and pulmonary arterial pressures that ultimately result in right heart failure and death. [1] The pathogenesis of the disease remains incompletely defined but includes a combination of vasoconstriction, inflammation, structural remodeling, in situ thrombosis and an imbalance of vasoactive mediators. [2–4] Important proliferative mediators include increased thromboxane A₂ and endothelin-1 (ET-1), and decreased vasodilator and antiproliferative vasoactive mediators, such as prostacyclin and nitric oxide (NO). [3, 5, 6] Improving the balance of these mediators has

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Disclosures: None

driven the development of the current pulmonary vasodilatory and antiproliferative therapies for PAH.

The etiology of PAH in the pediatric population remains variable and the distribution of etiologies is very different from adults with a predominance of idiopathic cases (IPAH) or associated with congenital heart disease (PAH-CHD). [7–10] In contrast to adults, PAH associated with connective tissue disease remains a rare cause in children. [7–10] Large registries of pediatric pulmonary hypertension, including the Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension (TOPP) registry [8], the Nationwide Netherlands PH service registry [11], and the combined adult and pediatric U.S. REVEAL registry (*Registry to Evaluate Early and Long-Term PAH Disease Management*) [7] have been developed to better define the etiologies of pediatric PAH.

The most current classification of pulmonary hypertension was established at the 4th World Symposium held in 2008 in Dana Point. [12, 13] The Dana Point classification is difficult to use in the pediatric population as it does not completely reflect the complexity of pediatric disease nor does it include the heterogeneity of factors that contribute to pediatric pulmonary vascular disease. [14–16] A classification system of pediatric pulmonary hypertensive vascular disease was therefore developed by the Pulmonary Vascular Research Institute Pediatric Taskforce at the 2011 Panama meeting [14], and recognized the concepts of the contribution of abnormalities of lung growth and development to pediatric pulmonary hypertension and highlighted multifactorial causes of pulmonary hypertension such as congenital heart disease, chromosomal anomalies, sleep disorder, chronic aspiration, and prenatal contributions to postnatal lung disease (Fig. 1). Although it has not yet been widely integrated into clinical practice, this classification system provides a more comprehensive classification of almost all causes of pediatric PAH, and may ultimately be integrated into pediatric treatment algorithms.

The conventional definition of PH, based on the criteria established at the 4th World Conference on pulmonary hypertension at Dana point, CA, USA in 2008, includes a mean pulmonary artery pressure (mPAP) ≥ 25 mmHg; patients with a normal pulmonary capillary wedge pressure (< 15 mmHg) are subclassified as having PAH. [17, 18] Pulmonary vascular resistance (PVR) is currently not included in the definition of adult patients with PAH, but an increase in pulmonary vascular resistance index (PVRI) >3 Wood units $\times m^2$ is important to include in the pediatric PAH definition due to the predominance of patients with PAH due to unrepaired congenital heart disease. As pediatric patients have lower systemic blood pressures, PAH may also be described according to the ratio of pulmonary artery systolic pressure divided by systemic artery systolic pressure with a ratio greater than 0.4, but this definition has not been globally accepted or validated. [18] These definitions are easily applied to children with biventricular circulation but cannot be used on children with single ventricle defects, as many develop elevated PVR after a cavopulmonary anastomosis without elevation of pulmonary artery pressure beyond 25 mmHg. [14] As elevated pulmonary pressures >20 mmHg have proven to be detrimental in these patients [19, 20], pediatric pulmonary hypertensive vascular disease following cavopulmonary anastomosis has been defined as a PVRI >3.0 Wood units $\times m^2$ or a transpulmonary gradient >6 mmHg, whereas PAH in biventricular circulations is defined as a mPAP >25 mmHg, a pulmonary capillary wedge pressure < 15 mmHg, and a PVRI >3.0 Wood units $\times m^2$ in the Panama classification. [14]

Incidence data from the Netherlands has revealed an annual incidence and point prevalence of 0.7 and 4.4 for IPAH and 2.2 and 15.6 for PAH-CHD cases per million children (Fig. 2). [11] Without appropriate treatments, median survival rate in children after diagnosis with IPAH might be worse compared to adults, and was 10 months for children in the NIH

registry of patients with IPAH. [21] In 1995, prior to the availability of targeted PAH therapies, a single center cohort study showed the estimated median survival of children and adults with idiopathic PAH were similar (4.12 years versus 3.12 years, respectively). [22] With targeted pulmonary vasodilators, the survival rate has continued to improve in pediatric patients with PAH. Children in the combined adult and pediatric U.S. REVEAL registry (*Registry to Evaluate Early and Long-Term PAH Disease Management*) demonstrated 1-, 3-, and 5-year estimated survival rates from diagnostic catheterization of 96+/-4%, 84+/-5%, and 74+/-6%, respectively. [7] Retrospective reports from the United Kingdom and Netherlands have shown variable but improved survival rates in children with PAH. [9, 11, 23] The retrospective study from the UK Pulmonary Hypertension Service for Children (n= 216) has shown the 5-year survival rates in children with idiopathic PAH to be 85.6%, 79.9% and 71.9% at 1, 3 and 5 years, respectively, whereas associated PAH survival rates were 92.3%, 83.8% and 56.9% at 1, 3 and 5 years, respectively (Fig. 3). [9] Amongst children with associated PAH, those with PAH and repaired CHD have shown worse outcomes compared to all other subgroups (Fig. 4). [9] For all children with PAH-CHD, outcomes remain heterogeneous. Cumulative survival has been shown to be better than those with IPAH, however survival is variable amongst subgroups. Only PAH-CHD with post-tricuspid shunt or abnormal pulmonary vasculature development have shown better survival than IPAH. [11] Despite the variability in reported outcomes, survival has appears to have improved in patients with Eisenmenger syndrome using advanced PAH therapies [24].

Therapeutic options have increased in the past several years but remain limited. Management strategies include the prevention and inhibition of active pulmonary vasoconstriction, support of right ventricular function, and promotion of regressive remodeling of structural pulmonary vascular changes. Currently approved PAH therapies impact one of three endothelial-based pathways including NO, prostaglandin, or ET-1 (Fig. 5). Although treatments approved for PAH in adults have shown favorable affects in children, pediatric treatment decisions largely depend on results from evidence-based adult studies and the experience of clinicians. The purpose of this review is to summarize the current knowledge regarding PAH drug therapies and their clinical use in the management of pediatric PAH.

Challenges in the Treatment of Pediatric PAH

Despite recent advances, the management of pediatric PAH remains challenging. Various characteristics of the pediatric population including variable drug metabolism, growth, and development make it difficult to extrapolate conclusions from adult data to children. Therapeutic strategies for adult PAH have not been sufficiently studied in children, especially regarding potential toxicities or optimal dosing, and appropriate endpoints for goal-oriented therapy in children are lacking. Nevertheless, children with PAH are currently treated with targeted PAH drugs and have been shown to benefit from these new therapies.

Clinical Presentation

Establishing the diagnosis of PAH in children remains difficult because their presentation is often non-specific. Failure to thrive, tachypnea and irritability due to low cardiac output are often seen in infants with PAH where as older children present with similar symptoms as adults and complain of exercise intolerance and occasionally chest pain. The most frequent initial presenting symptom in IPAH and PAH-CHD is dyspnea on exertion. [7, 8] Near syncope or syncope is a marker of severe disease and is more frequently seen in IPAH and familial PAH patients. [7, 8] Cyanosis is only seen in patients with significant lung disease or intra-cardiac shunting. Due to the variable presentation and often non-specific symptoms, a high index of suspicion is required to improve the time to diagnosis in children.

Diagnostic Evaluation

Due to the many diseases associated with PAH, a methodical and comprehensive evaluation is important. The most successful strategy in treatment of PAH is correction of an underlying abnormality, rather than addition of vasodilator therapy. A complete evaluation to rule out underlying diseases that may contribute to the development of PAH, including investigations for obstructive sleep apnea and gastroesophageal reflux disease, is recommended in all patients prior to initiation of pulmonary vasodilatory therapy. A diagnostic algorithm is shown in Figure 6. [25]

Conventional Therapies

Despite the introduction of advanced pulmonary vasodilatory therapies, conventional therapies continue to play an important role in the management of PAH. Diuretic therapy is often necessary in children with heart failure but should be initiated carefully as children with PAH may be pre-load dependent to maintain adequate cardiac output. The use of diuretics remains essential in the management of patients with PH related to left ventricular diastolic dysfunction. The use of digitalis has not shown clear benefits, though it may be beneficial in the management of right heart failure. [26] Although its role is not well studied in children, chronic anticoagulation may be beneficial in patients with low cardiac output, central venous lines or hypercoagulable states at risk of thrombosis in situ. Risks and benefits of anticoagulation should be weighed, particularly in younger children that may be at higher risk of hemorrhagic complications. The use of anticoagulation in patients with Eisenmenger physiology is controversial as it has not been shown to impact long-term survival. [27] Oxygen supplementation is used to avoid chronic hypoxemia and is considered in patients with severe right heart failure or significant hypoxemia with exercise.

Calcium Channel Blockers

Historically, calcium channel blockers (CCBs) were used primarily in the management of PAH due to the absence of any alternative therapy. By inhibiting calcium flux into the cardiac and smooth muscle, CCBs cause relaxation of vascular smooth muscle but may decrease cardiac contractility. CCB therapy for PAH is only indicated in patients who demonstrate an acute response to vasodilator testing. The reported proportion of children with acute vasoreactivity varies from 7–40% and depends highly on the criteria used. [18, 28] The most commonly used vasoreactivity criteria include the Barst criteria (decrease in mPAP of $\geq 20\%$, unchanged or increased cardiac index, and decreased or unchanged pulmonary to systemic vascular resistance ratio (PVR/SVR) [29], Rich criteria (decrease in mPAP and PVR of $\geq 20\%$) [30], and Sitbon criteria (decrease in mPAP of ≥ 10 mmHg reaching a mPAP value of ≤ 40 mmHg and an increased or unchanged cardiac output) [31]. Nifedipine, diltiazem and amlodipine are the preferred CCBs for PAH therapy, while verapamil is contraindicated. Recommended pediatric dosing is shown in Table 1. CCBs should be avoided in patients with severe ventricular dysfunction, high right atrial pressure, decreased cardiac output, or those < 1 year of age. The benefits of CCB therapy have been reported in pediatric patients, including improved survival in acute vasoreactive responders [18, 28], but careful follow-up is essential as patients may deteriorate over time on CCB therapy alone. [32]

Inhaled Nitric Oxide

Inhaled NO is used commonly in the acute management of PAH and is recognized as the first line pulmonary vasodilatory agent in the treatment of persistent pulmonary hypertension of the newborn. [33–35] Similar to endogenously produced NO, inhaled NO diffuses rapidly across the alveolar-capillary membrane and induces vasodilation through a

cyclic guanosine monophosphate (cGMP) dependant pathway. [36, 37] Although FDA approval for inhaled NO therapy is restricted to newborns with hypoxemic respiratory distress, inhaled NO has been used in the management of postoperative PAH associated with CHD, congenital diaphragmatic hernia, bronchopulmonary dysplasia and severe PAH presenting with hemodynamic instability and right heart failure. [38–44] In multicenter randomized clinical studies, inhaled NO has improved outcomes in neonatal hypoxic respiratory failure by decreasing the need for extracorporeal membrane oxygenation. [45, 46] In the cardiac catheterization lab, inhaled NO has also proven to be an ideal agent for acute vasoreactivity testing (Fig. 7). [47, 48] Despite its growing indications in acute care management, inhaled NO has not been used in the long-term management of PAH given its risk of toxic metabolites, short half-life and complicated delivery system, [49] but trials are underway to determine feasibility. [50]

Targeted Pharmacological Therapies

The prognosis of children with PAH has improved in the past decade owing to new therapeutic agents and off-label application of adult PAH specific therapies to children. Use of targeted pulmonary vasodilators in children is primarily based on experience with increasing evidence from an emerging number of pediatric clinical trials. Targeting one of three endothelial-based pathways (Fig. 5), three drug classes have been well studied in PAH treatment including phosphodiesterase inhibitors, endothelin receptor antagonists and prostacyclin analogues. [51]

Phosphodiesterase Type 5 Inhibitors

Phosphodiesterase-5 (PDE-5) inhibitors have been used for over a decade in the treatment of children with pulmonary hypertension. PDE-5 inhibitors have antiproliferative, proapoptotic, and vasodilating effects in pulmonary vasculature through an increase in cyclic guanosine monophosphate (cGMP). [52, 53] PDE-6 inhibition can also occur with therapeutic dosing of sildenafil. [54, 55] PDE-5 inhibitors are most commonly administered orally and are well tolerated. Most frequent adverse effects include headache, agitation, and flushing. [56–58] Dose related ocular effects, including blurred vision, changes in light perception and transient blue/green visual abnormalities, rarely occur with therapeutic dosing due to PDE-6 inhibition. Erections occur in about 10% of males. Rare cases of sensorineural hearing loss have only been reported in adults on PDE-5 inhibitors but the physiologic mechanism remains unclear. [59] Sildenafil is the only PDE-5 inhibitor available for intravenous administration and is used solely in the acute care setting due to the risks of systemic effects. Serial monitoring is not required but routine vision and hearing assessments should be considered with long-term PDE-5 therapy, especially in premature infants.

Sildenafil—Sildenafil was approved by the U.S. Food and Drug Administration (FDA) in 2005 for the treatment of adult PAH as it was found to improve exercise ability and delayed time to clinical worsening at a dose of 20 mg three times daily. [57] Pediatric use of sildenafil was initially studied in the outpatient setting in 14 children with PAH. During sildenafil therapy, the mean 6 minute walk (6MW) distance increased at 6 months with a decrease in mPAP and PVR. [60] In children with IPAH and PAH-CHD, sildenafil was also found to improve oxyhemoglobin saturation and exercise capacity without significant side effects. [61]

The STARTS-1 trial, a worldwide 16-week randomized, double blind placebo-controlled study of treatment naïve children, studied the effects of oral sildenafil monotherapy in pediatric patients with PAH. [56] Children (n=235) with PAH (aged 1–17 yrs.; 8 kg) received low (10 mg), medium (10–40 mg), and high (20–80 mg) dose sildenafil or placebo

orally three times daily (Fig. 8). The primary comparison was percent change in peak oxygen consumption (pVO_2) for the three sildenafil doses combined from baseline to week 16; exercise testing was performed only in children able to exercise reliably. Secondary endpoints, including mPAP, PVR, and functional class, were assessed in all enrolled patients, including those unable to reliably exercise. The estimated mean $\pm$ standard error percentage change in pVO_2 for the low-, medium- and high-doses combined versus placebo was $7.7\% \pm 4.0\%$ (95% CI, -0.2% to 15.6% ; $P=0.056$) (Fig. 9). Thus, the pre-specified primary outcome measure was not statistically significant. Peak VO_2 only improved with the medium dose. Secondary outcomes showed a varied response to sildenafil. Functional capacity only improved with high dose sildenafil. PVRI improved with medium and high dose sildenafil, but mean PAP was lower only with medium dose sildenafil. [56]

In the long-term extension study (STARTS-2), children on therapy remained on the dose of sildenafil received during STARTS-1 but subjects were no longer blinded to the dose after the STARTS-1 study ended in 2008. Children receiving placebo were randomized to low, medium or high dose. Of note, sildenafil dose could be uptitrated by the treating physician and was also increased for weight gain. [62] At three years, an increase in mortality was noted at the higher doses. As of August 2011, 37 deaths (15% mortality) occurred during the extension phase: 26 patients died while still on therapy and 11 were off treatment. Deaths appeared to be dose-related, with 3-year Kaplan-Meier (K-M) survival rates of 94%, 93% and 88%. Hazard ratios for mortality were 3.50 (95% CI, 1.29–9.51) for high versus low dose sildenafil. Review of this data by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) resulted in disparate recommendations. Sildenafil was approved by the European Medicines Agency in 2011, with a later warning on avoidance of use of the high dose. [63] In August 2012, the FDA recently released a strong warning against the (chronic) use of sildenafil for pediatric patients (ages 1 through 17) with PAH. (<http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm317743.htm>). The FDA warning states that "... this recommendation against (sildenafil) use is based on a recent long-term clinical pediatric trial showing that: (1) children taking a high dose of Revatio had a higher risk of death than children taking a low dose and (2) the low doses of Revatio are not effective in improving exercise ability. Revatio has never been approved for the treatment of PAH in children, and in light of the new clinical trial information, off-label (not approved by FDA) use of the drug in pediatric patients is not recommended..."

In response to the FDA warning, clinical pediatric PH experts put forth a consensus statement highlighting the limitations of the STARTS-2 extension study. Similar to the conclusions made by the EMA after evaluating the STARTS-2 data, the group recommended continued but cautious use of oral sildenafil in pediatric patients with a strong recommendation to avoid the use of high doses. [64]

Sildenafil may also be useful in the setting of inhaled NO therapy withdrawal [65] [66] [67], in post-operative pulmonary hypertension [68], in the presence of PH related to chronic lung disease [69], or in single ventricle physiology with high PVR. [19, 20, 33, 34, 40, 45, 48, 55, 58, 70–73] In children with PAH associated with chronic lung disease, sildenafil is well tolerated and has also been shown to improve hemodynamics in 88% of patients without a decline in oxyhemoglobin saturation (Fig. 10). [74] A study of sildenafil in Japanese children has also suggested safety and efficacy. [75]

Although no definitive dosing guidelines have been established in the United States, conservative sildenafil dosing is recommended based on the STARTS-1/2 data and the current EMA dosing recommendations [63] (Table 1). An oral sildenafil dose of 10 mg three times daily is recommended in children between 8 and 20kg and a dose of 20 mg three times

daily in children greater than 20kg. Higher dosing of oral sildenafil is strongly discouraged based on the STARTS-2 mortality data. For children less than 8 kg, sildenafil doses of 0.5–1.0mg/kg three times daily have been beneficial. [74] In some centers, sildenafil has been dosed four times daily in the neonatal population. An oral suspension of sildenafil is available (2.5mg/mL) that is stable at room temperature and can be used in children that cannot tolerate pill format. [76] The current FDA warning only applies to children 1–17 years of age and does not apply to the use of sildenafil in the critical care setting.

As sildenafil is primarily metabolized by hepatic cytochrome P450 (CYP) enzymes, co-administration of sildenafil with potent CYP3A inducers or inhibitors such as ketoconazole or rifampin should be avoided. Bosentan decreases the maximum plasma concentration (C_{max}) of sildenafil by 55.4%, where as sildenafil increases the C_{max} of bosentan by 42.0% but the clinical effect of this interaction is unclear. [77] Recommendations for dose adjustment are not available, so monitoring may be advisable with co-administration.

Intravenous sildenafil has been studied in children with persistent pulmonary hypertension of the newborn (PPHN) and in postoperative CHD. In an open-label, dose-escalation trial in infants with PPHN and an oxygenation index (OI) > 15, intravenous sildenafil improved OI compared to placebo in infants with severe PPHN. [78] Use of intravenous sildenafil for the management of postoperative pulmonary hypertension in children with CHD has also showed favorable results including shorter time to extubation, shorter intensive care unit stay, and augmentation of pulmonary vasodilatory effects when co-administered with inhaled NO. [79–81] Dosing recommendations are based on a small double-blind, placebo-controlled, dose-ranging trial (Table 1). [78] Use in premature infants is not well studied. Cautious use is recommended in postoperative patients with CHD and those with significant lung disease due to the risk of increased intrapulmonary shunting and systemic delivery. [80]

Tadalafil—Tadalafil, a selective PDE-5 inhibitor with a longer duration of action, was FDA approved for use in adults with PAH in 2009 after it was shown to improve exercise capacity and quality of life measures while reducing clinical worsening in adults. [82] The use of tadalafil in children has recently increased based on the results of a retrospective study that suggested clinical efficacy and safety in children with PAH and the FDA warning. [83] In this open-label study, most patients were successfully transitioned from sildenafil to tadalafil and demonstrated statistically improved hemodynamic data, including mPAP and PVRI, compared with sildenafil (Fig. 11). [83]

Tadalafil administered orally once daily may lead to overall improved compliance for pediatric patients with PAH. [83, 84] Although pediatric dosing is not available, a retrospective study demonstrated 1 mg/kg/day of tadalafil is well tolerated in children with clinical improvement with a favorable side effect profile (Table 1). [83] Tadalafil can be compounded into a stable suspension (5mg/mL) to facilitate use in children. [85] Recommended dosing of tadalafil in adults is 40mg once daily. [82] The reported adverse events are similar to those seen with sildenafil use but tadalafil has little effect on PDE-6 so visual effects are rarely seen. [82, 83] Similar to sildenafil, concomitant use of potent inducer or inhibitors of CYP3A is not recommended and co-administration with bosentan will decrease plasma concentration of tadalafil. [86] Use in the neonatal and infant population is contraindicated due to lack of maturation of the glucuronidation pathway. There is no data on the use of tadalafil in infants and young children, thus caution is advised.

Endothelin receptor antagonists (ERA)

Endothelin-1 (ET-1), a potent vasoactive peptide produced primarily in the vascular endothelial and smooth muscle cells, is considered the predominant pathophysiological

endothelin isoform in PAH. The over-expression of ET-1 protein has been demonstrated in patients with PAH and correlates with the degree of pulmonary remodeling. [87, 88] Vasoconstriction by ET-1 is mediated by 2 types of endothelin receptors, type A (ETA) and type B (ETB), located on vascular smooth muscle; ETB receptors on endothelial cells facilitate clearance of ET-1 and cause release of NO and prostacyclin. [89] Bosentan, a dual ET-1 receptor antagonist, and ambrisentan, a selective ETA receptor antagonist, have both been shown to improve hemodynamics and survival in adult patients and have been approved by the FDA for oral PAH therapy in adults. Oral ERA therapy is well tolerated and the most common adverse events include abdominal pain, nausea, flushing, headache, peripheral edema, and nasal congestion. [87, 90–92] Important clinical side effects of ERA therapy include transaminitis, anemia, seminiferous tubular atrophy and impaired fertility. Due to the risk of teratogenicity, ERA therapy is contraindicated in pregnancy and appropriate contraception is required in sexually active patients. Caregivers who may be pregnant should wear gloves while handling ERAs. Effectiveness of oral contraception is decreased with ERA therapy so use of two reliable methods of contraception is recommended. Although the use of bosentan and ambrisentan in pediatric patients with IPAH or associated PAH has demonstrated clinical benefit, neither ERA has been approved for use in pediatric populations in the United States.

Bosentan—Bosentan, an oral dual ERA, is approved in adult patients with PAH. [91] Several pediatric studies have demonstrated clinical utility of bosentan therapy, including improvement of exercise capacity, functional class, and long-term outcomes in children with IPAH and PAH-CHD. [9, 23, 90, 93–105] A retrospective study of children on bosentan for a median exposure of 14 months as single or combination therapy demonstrated sustained clinical and hemodynamic improvement with no significant adverse events and an estimated 2 year survival of 91%. [102] In the United Kingdom, a retrospective, observational study of 101 children with IPAH and PAH-CHD showed improvement in World Health Organization (WHO) functional class and six minute walk (6MW) distance with bosentan; the K-M survival estimates for the 101 patients were 96, 89, 83 and 60% at 1, 2, 3 and 5 yrs., respectively. [98] Likewise, in a retrospective cohort study from the United States, 86 consecutive children with idiopathic/heritable or associated PAH, treated with bosentan had a 4 year survival estimate of 82% and K-M estimate of disease progression of 54%. [100]

Bosentan has also demonstrated improvement in patients with PAH-CHD. In a study that included both children and adults with PAH and a systemic-to-pulmonary shunt, bosentan produced short-term improvements in WHO functional class and 6MWD. [104] The Bosentan Randomized Trial of Endothelin Antagonist Therapy-5 (BREATHE-5) was a 16-week, multicenter, randomized, double-blind, placebo-controlled study that evaluated the effect of bosentan on systemic pulse oximetry and pulmonary vascular resistance in 54 patients with WHO functional class III Eisenmenger syndrome. Compared with placebo, bosentan reduced PVRI (−472.0 dyne.s.cm(−5); $P=0.0383$) (Fig. 12) and increased exercise capacity (53.1 m; $P=0.0079$) (Fig. 13). Overall bosentan was well tolerated by patients with Eisenmenger syndrome and improved exercise capacity and hemodynamics without compromising peripheral oxygen saturation. [106] In a small number of patients with single ventricle physiology after staged cavopulmonary anastomosis, bosentan has demonstrated improvement in functional class, systolic ventricular function and hemodynamics. [105, 107]

Clinical studies, including the *BREATHE-3* and *FUTURE-1* trials, have demonstrated the pharmacokinetics of bosentan with twice daily dosing in pediatric patients with PAH. [90, 108] In the *FUTURE-1* trial, bosentan concentrations following doses of 2 and 4 mg/kg were similar, and were lower than adult exposure (Fig. 14). [108] Based on the results in a noncomparative, multicenter, pharmacokinetic trial (*BREATHE-3*), bosentan doses of 31.25

mg, 62.5 mg, or 125 mg (10–20 kg, >20–40 kg, or >40 kg, respectively) twice daily are currently recommended for pediatric PAH therapy (Table 1). [90] A pediatric formulation has only been approved in Europe. [108]

Bosentan has the potential risk of dose-dependent increases in amino transaminase levels, but these risks are lower in children than adults. [95] In pediatric studies, the incidence of elevated aminotransaminase levels (>3x ULN) were 3% in extended *FUTURE-2* trial [90] and 16% in the *BREATHE-3* trial. [87] Although the incidence of serum aminotransferase elevation due to bosentan therapy is low in children, liver function tests should be monitored monthly.

Ambrisentan—Ambrisentan, an oral selective ETA receptor antagonist, has demonstrated improvements in exercise tolerance and WHO functional class with a good safety and side effect profile in adult patients. [91, 92, 109, 110] The clinical efficacy and safety of ambrisentan therapy has been not well studied in children with PAH, but its use in children is increasing due to its favorable once daily dosing, lack of drug interaction with PDE-5 therapy, and decreased risk of elevated aminotransaminase levels. A retrospective study of children with PAH that were either transitioned from bosentan to ambrisentan therapy or started on adjunctive ambrisentan therapy suggested clinical efficacy and safety of ambrisentan by improved mPAP and WHO functional class in 31% of patients with no elevation of aminotransferase levels. [111, 112] In a single center study, ambrisentan therapy was safe in patients with Eisenmenger syndrome and showed increasing exercise capacity at short-term follow-up without a decrease in systemic saturation and no significant evidence of clinical deterioration at longer term follow-up. [112] Larger, controlled studies are required to better determine the safety and clinical efficacy of ambrisentan therapy for pediatric patients.

Ambrisentan is initiated at 5 mg once daily and may be increased to 10 mg once daily in adult patients as tolerated. [91, 92, 109] Pediatric dosing is not available due to insufficient clinical data, but a current retrospective study demonstrated pediatric patients can be started on ambrisentan at 2.5 mg (<20 kg) or 5 mg (≥20 kg) and considered for an up-titration to the 5 mg to 10 mg dose if tolerated (Table 1). [111] Although monthly liver function testing for ambrisentan is no longer on the FDA label as the incidence of elevated hepatic aminotransferase levels was similar to the placebo group in the ARIES study [91], most pediatric centers still perform routine monitoring every 3 to 4 months. Similar to bosentan, teratogenicity remains a concern. Ambrisentan is contraindicated in pregnancy and contraception should be discussed in women who may become pregnant. There are no drug interactions between ambrisentan and sildenafil, which facilitates combination therapy. [113]

Prostacyclins

Prostacyclin, a metabolite of arachidonic acid produced endogenously by the vascular endothelium, is a potent vasodilator and has anti-thrombotic, anti-proliferative, and anti-inflammatory effects. [114–116] The biological functions of prostacyclin are mediated by cell-surface G-protein receptors on pulmonary endothelial cells or platelets causing increased intracellular cyclic adenosine monophosphate (cAMP) and resultant activation of protein kinase A. Protein Kinase A increases smooth muscle relaxation and inhibition of platelet aggregation. [117] In patients with severe PAH, prostacyclin metabolites and prostacyclin synthase are decreased. [116] Epoprostenol was the first approved prostacyclin therapy for PAH in 1995 and was followed by treprostinil (subcutaneous 2002, intravenous 2004, inhaled 2009), iloprost (2004) and most recently room temperature stable epoprostenol (2010). Prostacyclin therapy has formed the main stay of PAH therapy for

many years and has improved functional status and survival for both adult and pediatric patients.

Epoprostenol—Epoprostenol, a prostacyclin analogue delivered by intravenous infusion, has been used for over two decades for the treatment of PAH with good results. [9, 28, 32, 99, 118–123] Epoprostenol is recommended for first-line treatment of adult PAH patients with New York Heart Association (NYHA) functional class III–IV symptoms. [13, 124] Although epoprostenol is not approved in children, continuous intravenous epoprostenol therapy is effective for improving symptoms, hemodynamics, and survival in children with IPAH or PAH-CHD. [28, 32, 99, 121–123, 125] Clinical effects occur with long-term use even in patients without a response during vasodilator testing. Pediatric studies have shown improved survival with long-term intravenous epoprostenol therapy, with a 4-year survival rate for treated children of 94% [28] and a reported 10-year treatment success rate (freedom from death, transplantation, or atrial septostomy) of 37%. [32] Experience in the United Kingdom has shown cumulative survival on epoprostenol at 1, 2 and 3 years of 94%, 90% and 84% with significant improvement in growth. [122] Patients treated with intravenous epoprostenol that showed marked improvement in hemodynamics have also been successfully transitioned to oral or inhaled targeted PAH therapy without deterioration of clinical and hemodynamic parameters. [126]

Epoprostenol has a short elimination half-life of approximately 3 to 5 minutes that necessitates administration by continuous intravenous infusion, placement of a permanent central venous catheter and delivery by a portable infusion pump. Due to the complicated nature of dose titration, epoprostenol therapy should be initiated during hospitalization by a pulmonary hypertension specialist. In a monitored hospital setting, intravenous epoprostenol is initiated at 1–3 ng/kg/min and the dose is rapidly increased over the first few days, then steadily increased by 1–2 ng/kg/min every 1 to 2 weeks as tolerated (Table 1). Dose titration can be managed on an outpatient basis with the goal to maximize efficacy while side effects remain tolerable. Children often require higher doses than adults, commonly in the range of 50–80ng/kg/min, with further uptitration on an individual basis.

Side effects of epoprostenol therapy are dose-dependent and usually occur within hours of dose titration. Common side effects include flushing, headache, nausea, diarrhea, jaw discomfort with first bite when eating, foot pain, rash, and thrombocytopenia. [119, 127, 128] Severe adverse events such as bradycardia, systemic hypotension, and profound thrombocytopenia may occur, resulting from insufficient or excessive dosage of epoprostenol. Patients with PAH due to pulmonary veno-occlusive disease or pulmonary vein disease may develop life threatening pulmonary edema. Systemic desaturation due to ventilation-perfusion matching can occur in patients with significant lung disease. Serious complications, including sepsis secondary to infection of the indwelling catheter, catheter dislodgement, or catheter thrombosis can occur and may result in “rebound” pulmonary hypertension with acute discontinuation of therapy. [129, 130] Given the complexity of intravenous therapy, risk and benefits should be cautiously weighed with family prior to initiation of epoprostenol therapy in any child, however there remains the strongest base for improved survival with this therapy.

Treprostinil—Treprostinil, an alternative prostacyclin analogue, was initially approved by the FDA for subcutaneous use and subsequently approved for intravenous and inhaled use. The advantages of treprostinil therapy compared to epoprostenol include stability at room temperature, longer half-life, fewer side effects and smaller pump options. Subcutaneous treprostinil offers the advantage of no central venous catheter and has been evaluated in children. [131] Favorable experiences of switching from epoprostenol to intravenous treprostinil therapy have been demonstrated in children. [121] In children with PAH,

outcomes (Fig. 15) and hemodynamic changes (Fig. 16) over time on intravenous treprostinil have been demonstrated to be similar to epoprostenol. [132] Despite higher doses, children exhibited less prostanoid side effects, with the exception of leg pain when transitioned to intravenous treprostinil therapy. [121] Use of subcutaneous treprostinil therapy in children after failure of combined oral treatment or due to severe complications with intravenous epoprostenol, resulted significant improvement in functional class, hemodynamics, and 6MW distance. [131] Although injection site pain due to subcutaneous infusion remains a major disadvantage, subcutaneous treprostinil may be tolerated in some children. [131] To date, inhaled treprostinil has been used primarily as add-on therapy or for patients who have injection site pain due to subcutaneous infusion. [133–135] Inhaled treprostinil has also been shown to be effective and well tolerated for acute vasoreactivity testing in children (Fig. 20). [136]

Intravenous and subcutaneous treprostinil are bioequivalent with a terminal elimination half-life of approximately 4.5 hours. Intravenous and subcutaneous treprostinil are generally initiated at 1.25 to 2 ng/kg/min and the dose is gradually increased based upon clinical status, hemodynamic changes and side effect profile (Table 1). A stable dose is commonly around 50 to 80 ng/kg/min with doses of intravenous treprostinil typically higher than intravenous epoprostenol. Due to the risk of systemic vasodilation and placement of an indwelling catheter, intravenous treprostinil initiation requires in hospital initiation.

Prostacyclin side effects noted with intravenous treprostinil are similar to subcutaneous administration and include headache, diarrhea, nausea, rash, flushing, jaw pain, and foot pain. [121, 131] Continuous infusion of treprostinil through a central venous catheter has been found to expose children to an increased risk of catheter related blood stream infections by gram negative organisms. [137] The risk of bacteremia is reduced with the use of an alkaline buffer, closed hub systems, and protection of catheter connections while showering. [130, 138, 139] Infusion site pain and reaction are the most common side effects with subcutaneous therapy, which can negatively impact tolerability. Incidence and severity of site pain appears to improve 5–7 days after subcutaneous catheter placement and by maintaining the infusion volume as low as possible (<1ml/24 hours). Additional techniques to control site pain include: initiation of systemic H1 and H2 histamine blockers, placing a “dry” site without medication 24 hours prior to infusion start, application of topical anti-inflammatory agents prior to site initiation, and administration of oral analgesics during the first 5–7 days of a new site. It is not uncommon for sites to last 1–2 months.

Inhaled treprostinil has less systemic effects and can started in the outpatient setting in stable patients as add-on therapy. Inhaled treprostinil is dosed in breaths (1 breath = 6 mcg treprostinil). The starting dose of inhaled treprostinil for an adult is 3 breaths (18 mcg) 4 times per day, given approximately 4 hours apart during waking hours. The dose is generally increased by an additional 3 breaths every 1–2 weeks as tolerated to a target maintenance dose of 9 breaths (54 mcg) per treatment (Table 1). Smaller children (<20kg) should be monitored for systemic hypotension and may require slower up titration of 1 breath every 2–4 weeks with an initial target maintenance dose of 5–6 breaths (30 – 36 mcg) per treatment. Proper inhalation technique is required for effective drug delivery, so patient education and family support are essential to optimize administration in children. Common side effects include cough, headache, throat irritation, nausea, and flushing. Acute inhalation of inhaled treprostinil is as effective as iNO in lowering mean PAP and PVRI (Figure 17). [136] Worsening respiratory symptoms have been reported in patients with reactive airway disease with inhaled treprostinil therapy but have been improved with bronchodilators prior to administration. [135]

Iloprost—Similar to inhaled treprostinil, iloprost is an inhaled prostacyclin analogue and has several advantages over intravenous prostacyclin therapy including less risk of systemic hypotension and minimizing the effect on ventilation-perfusion mismatch. [125, 140–145] Iloprost has been shown to improve hemodynamics and WHO functional class in IPAH and PAH-CHD (Fig. 18). [142, 143, 146] Due to a short biologic half-life, low risk of toxic metabolites and ease of delivery in the acute care setting, inhaled iloprost has been considered as an alternative to inhaled NO for postoperative care and vasodilator reactivity testing. [143, 144, 146, 147] Although the clinically effective dose of inhaled iloprost is not established in children, a study suggested that the initial dose of iloprost 2.5 mcg inhaled 5 to 9 times daily, could be increased to 5 mcg per inhalation, and could be maintained at that dose for chronic therapy (Table 1). [142] Side effects, such as bronchospasm and poor compliance with frequent administrations (6–9 times daily), have discouraged its integration into the outpatient management of PAH in children. [142]

Beraprost—Beraprost is an oral prostacyclin analogue that is not currently available in the United States or Europe. In few studies, beraprost has been shown to improve hemodynamics and exercise capacity in patients with IPAH. [148–150] A double-blind randomized placebo control trial in 116 patients with PAH suggested benefits in early phases of treatment but did not persist with time. [151] Evidence to support the use of beraprost in children is limited.

Novel Therapies

Although current PAH therapies have improved outcomes, the need for additional therapies still exists to optimize the care of patients with PAH. Imatinib, an oral receptor tyrosine kinase antagonist, is a potent antiproliferative agent that may have a role in the treatment of PAH. In the randomized efficacy study (IMPRES) in adult patients with advanced PAH on 2 therapies, imatinib improved exercise capacity and hemodynamics. [152] Study drug discontinuations and serious adverse events, including subdural hematoma formation in patients on anticoagulation, were common thereby questioning the long-term safety of imatinib in patients with PAH. [152]

Macitentan, a novel dual ERA with tissue targeting properties, is thought to have improved receptor binding capacity and fewer drug-drug interactions than bosentan. [153, 154] A phase III trial (SERAPHIN) has been completed with preliminary results showing improved morbidity and mortality. [155] Complete results are pending release prior to consideration for FDA approval.

Riociguat, an oral agent with dual mode of action that synergizes with endogenous NO and also directly stimulates soluble guanylyl cyclase, is another promising therapy. [156, 157] In phase III trials of PAH therapy in patients with chronic thromboembolic pulmonary hypertension (CHEST-1) and in patients with symptomatic PAH (PATENT-1), riociguat demonstrated improved hemodynamics, functional class and time to clinical worsening. [158, 159] FDA approval for the use of riociguat in the management of PAH (WHO group 1 and 4) recently occurred. No pediatric studies have been completed.

Selexipeg, an oral selective prostacyclin receptor (IP receptor) agonist [160], is a promising new therapy as its high functional selectivity for the IP receptor may help minimize gastric side effects. [161] In the phase II study, selexipeg was well tolerated with a favorable side effect profile and showed significant reduction in PVR compared to placebo. [162] A phase III study (GRIPHON) is currently in progress.

Statins have also received growing attention in the treatment of PAH. The results of a randomized, double-blind, placebo-controlled clinical trial of aspirin and simvastatin in patients with PAH did not support the use of these medications in the treatment of PAH as no improvement in 6MW distance was demonstrated. [163] Fasudil, a Rho-kinase inhibitor, has been shown to improve hemodynamics but has not been studied in larger clinical trials. [164–167]

Regeneration of lung vascular endothelium by treatment with bone-derived endothelial progenitor cells (EPCs), has shown marked improvement in survival in animal PAH models. [168] Use of EPCs has not been adequately studied in humans but offers the hope of a curative therapy for PAH. [169, 170]

Treatment Algorithms

As no definitive cure exists to date for PAH, treatment goals focus on improving survival, quality of life, exercise tolerance and hemodynamics. Treatment options for children with PAH are currently extrapolated from evidence-based adults guidelines. Many challenges, including determination of functional status using the WHO classification, limit the use of adult algorithms in children and highlight the need for pediatric specific treatment algorithms.

A treatment algorithm in children with severe PAH has been proposed (Fig. 19). [124] Acute vasodilatory response is found in only a limited number of pediatric IPAH patients but remains an important determinant in treatment approach and has been shown to have long-term prognostic value. [7, 18] Use of the adaptation of the conventional pediatric definition (Barst criteria) [29] for an acute responder is the most reasonable approach at this time to determine patients who should be considered for initial treatment with long-term high-dose CCB therapy and for identifying patients who appear more likely to have a favorable outcome. [7] Although CCBs should be considered in responders to acute vasodilator testing, most children will ultimately require additional forms of PAH therapy.

Continuous prostacyclin therapy should be considered for non-responders to acute vasodilator testing with symptomatic right heart failure, while other oral PAH medications are first line therapy in the non-responders without significant exercise intolerance or functional impairment. Pediatric treatment algorithms for PAH are being proposed that will include more relevant pediatric risk factors that support initiation of intravenous over oral PAH therapy in children. Although pediatric studies remain limited, combination therapy has shown improved outcomes in adults with PAH and should be considered in children with progressive disease and functional decline (see Combination Therapy section). Co-administration of PAH therapies should be done cautiously due to the risk of drug interactions. Atrial septostomy, palliative pulmonary-to-systemic shunts and transplantation are additional therapeutic options for children but should be reserved for patients with WHO functional class IV, who have progressed despite maximal medical therapy. Unfortunately, only limited data of treatment strategies in children with PAH exists due to few randomized controlled clinical trials evaluating the safety and efficacy of specific treatments.

Combination therapy

In patients with progressive disease, combination therapy is an attractive option. By simultaneously addressing the multiple pathophysiological pathways present in PAH, combination therapy may be more efficacious due to additive or synergistic effects. Concomitant use of targeted PAH therapies has been well tolerated and has been shown to improved exercise capacity, hemodynamic measurements and time to clinical worsening in adults. [171–174] In adult patients, combination therapy has also allowed reduction of

epoprostenol dosing and subsequent decrease in prostacyclin side effects with stabilization of hemodynamics. [126] Its use in children is increasing as most patients in the REVEAL registry received combination therapy for pediatric PAH. [7] In the limited number of studies that have included pediatric patients, combination therapy has proven to be safe and effective. [126, 175] Whether combination therapy should be used as a first step by simultaneous initiation of two or more drugs or by addition of a second treatment to a previous therapy considered insufficient is still not known. More studies are needed to help establish guidelines for combination therapy in children.

Conclusion

In the last two decades, the long-term survival of children with PAH has improved with the introduction of targeted pulmonary vasodilatory drug therapies. Although recent treatment strategies in children have improved their prognosis dramatically, the management of pediatric PAH remains challenging in the current era. Vasodilator therapies in children are based on experience or expert opinion, whereas the therapies in adults are evidence based from randomized trials. With growing collaboration, the number of multicenter trials for children with PAH is increasing which may ultimately improve the development of specific treatment strategies and clinical endpoints for children with pulmonary hypertension.

Acknowledgments

Sources of Funding: None

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1. Prenatal or developmental pulmonary hypertensive vascular disease
2. Perinatal pulmonary vascular maladaptation
3. Pediatric cardiovascular disease
4. Bronchopulmonary dysplasia
5. Isolated pediatric pulmonary hypertensive vascular disease (isolated pediatric PAH)
6. Multifactorial pulmonary hypertensive vascular disease in congenital malformation syndromes
7. Pediatric lung disease
8. Pediatric thromboembolic disease
9. Pediatric hypobaric hypoxic exposure
10. Pediatric pulmonary vascular disease associated with other system disorders

Fig. 1.

Pulmonary Vascular Research Institute Classification of Pediatric Pulmonary Hypertensive Vascular Disease (Panama 2011) (From Del Cerro MJ, et al. *Pulm Circ.* 2011, with permission)

Fig. 2.

Annual incidence rates for pediatric pulmonary hypertension based on epidemiological data from the Netherlands during a 15-year period. PH, pulmonary hypertension; PAH, pulmonary arterial hypertension; PAH-CHD, PAH associated with congenital heart disease; iPAH, idiopathic PAH. (From Van Loon RL, et al. *Circulation*. 2011, with permission)

Fig. 3. Survival curves for idiopathic pulmonary arterial hypertension (IPAH) and associated pulmonary arterial hypertension (APAH). Cases were censored for time in the study and transplantation. (From Haworth SG, et al. *Heart*. 2009, with permission)

Fig. 4.

Survival curves for the subgroups within the APAH group. Shown is the number in each group (brackets), and the predicted survival out of a possible 5 years. APAH, associated pulmonary arterial hypertension; CT, controls. (From Haworth SG, et al. *Heart*. 2009, with permission)

Fig. 5. Schematic diagram of endothelial vascular biology depicting the relevant vasoactive mediators that have led to targeted treatment of pulmonary hypertension, including the nitric oxide-cGMP system, the endothelin system and the prostacyclin system. (Reproduced with permission from Diller GP, et al. *IJCP*. 2010.)

Fig. 6.

A diagnostic algorithm for investigating pulmonary hypertension. CXR, chest x ray; PH, pulmonary hypertension; V/Q, ventilation/perfusion. (From Haworth SG, et al. *Arch Dis Child*. 2008, with permission)

Fig. 7.

Percentage of pediatric patients with pulmonary hypertension that demonstrated acute vasodilatory response to the evaluated agents. The greatest number of acute responders was seen with the use of iNO and oxygen. iNO, inhaled nitric oxide; O₂, oxygen. (Reproduced with permission from Barst RJ, et al. *Pediatr Cardiol.* 2010.)

	Placebo	Low Dose		Medium Dose		High Dose	
Body Weight(kg)	Allocation Ratio	Dose	Allocation Ratio	Dose	Allocation Ratio	Dose	Allocation Ratio
≥8 - 20	1			10 mg	1	20 mg	2
>20 - 45	1	10 mg	1	20 mg	1	40 mg	1
>45	1	10 mg	1	40 mg	1	80 mg	1

Fig. 8.

Treatment allocation in the STARTS-1 trial. Patients were randomized to placebo, low, medium or high dose oral sildenafil. (From Barst RJ, et al. *Circulation*. 2012, with permission)

Fig. 9.

Percent change in peak oxygen consumption ($\dot{V}O_2$) from baseline to week 16 of sildenafil monotherapy in treatment-naïve children, aged 1–17 years, with pulmonary arterial hypertension (STARTS-1). Given the small number of developmentally able children in the 8- to 20-kg group, this group was combined with the 20- to 45-kg group. Greatest improvement in $\dot{V}O_2$ was demonstrated with medium and high doses of sildenafil. (From Barst RJ, et al. *Circulation*. 2012, with permission)

Fig. 10.

Changes in systolic pulmonary artery pressures (sPAP) (A) and pulmonary/systemic systolic artery pressure (sPAP/ssBP) (B) as determined by echocardiogram in response to prolonged sildenafil therapy in infants with chronic lung disease. Median duration of treatment between studies was 58 days (range: 25 – 334). Individual data plotted together with mean $\pm$ SD. (Reproduced with permission from Mourani PM, et al. *J Peds*. 2009.)

Fig. 11.

Change in hemodynamic measures after transition from sildenafil to tadalafil for 14 pediatric patients with PAH. Hemodynamic data, including mPAP, PVRI and Rp/Rs, improved in comparison to the last catheterization data on sildenafil therapy during follow-up period (23.5 ± 8.3 months). mPAP, mean pulmonary arterial pressure; PVRI, pulmonary vascular resistance index; Rp/Rs (From Takatsuki S, et al. *Pediatr Cardiol.* 2012, with permission)

Fig. 12.

Change in indexed pulmonary vascular resistance (PVRi) from baseline to week 16 in placebo and bosentan groups (BREATHE-5). PVRi, the secondary endpoint, was significantly improved with bosentan therapy demonstrating a treatment effect of -472 (SE 221.9) $\text{dyn}\cdot\text{sec}\cdot\text{cm}^{-5}$. TE, treatment effect. (Reproduced with permission from Galie N, et al. *Circulation*. 2006)

Fig. 13.

Change in 6 minute walk distance (6MWD) from baseline to week 16 in placebo and bosentan groups (BREATHE-5). Exercise capacity measured by 6MWD was significantly improved with bosentan therapy demonstrating a treatment effect of 53.1 (SE 19.2) m. TE, treatment effect. (Reproduced with permission from Galie N, et al. *Circulation*. 2006)

Fig. 14. Pharmacokinetics in FUTURE -1. Arithmetic mean ($\pm$ SD) plasma concentration vs. time profiles of bosentan in patients with pediatric pulmonary arterial hypertension after multiple dose administration of bosentan at a dose of 2 and 4mg/kg twice daily. (n = 11). 2mg kg⁻¹ (■); 4mg kg⁻¹ (□)(Reproduced with permission from Beghetti M, et al. *Br J Clin Pharmacol.* 2009.)

Fig. 15.

Kaplan-Meier survival curve for a cohort of pediatric PAH patients receiving prostacyclin therapy, comprising patients on epoprostenol, treprostinil, and those who transitioned, with 95% confidence intervals (CI) depicted. Transplant-free 5-year survival was 70% (95% CI, 56% –80%). (Reproduced with permission from Siehr SL, et al. *J Heart Lung Transplant*. 2013.)

Fig. 16.

Change in pulmonary-to-systemic vascular resistance ratio (R_p/R_s) over time in pediatric PAH patients receiving intravenous epoprostenol or treprostinil. Initial improvement was seen in R_p/R_s at 1 to 2 years on therapy that was not sustained long-term. (Reproduced with permission from Siehr SL, et al. *J Heart Lung Transplant*. 2013.)

Fig. 17.

Hemodynamic change in the mean pulmonary artery pressure and the pulmonary vascular resistance index during acute pulmonary vasodilator testing with inhaled nitric oxide and inhaled treprostinil in children with PAH. Inhaled nitric oxide and inhaled treprostinil significantly decreased the mean pulmonary artery pressure and the pulmonary vascular resistance index. iNO, inhaled nitric oxide; NS, not significant. (From Takatsuki S, et al. *Pediatr Cardiol.* 2013, with permission)

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Fig. 18. Change in pulmonary-to-systemic vascular resistance ratio (R_p/R_s) in children with congenital heart disease and pulmonary hypertension in response to inhaled nitric oxide (iNO) and aerosolized iloprost. (Reproduced with permission from Rimensberger P, et al. *Circulation* 2001.)

Fig. 19.

Treatment algorithm in children with severe pulmonary arterial hypertension. (From Tissot C, et al. *J Pediatr* 2010, with permission)

Table 1

Treatment options for pediatric pulmonary arterial hypertension (PAH). Safety and dosing of these medications is not established in children.

Agent	Dose	Side effects	Cautions
Calcium Channel blockers			
Nifedipine	Initial dose: 0.6–0.9 mg/kg/day in 3 divided doses Maintenance dose: 2–5 mg/kg/day Maximum adult dose: 120–240 mg/day	headache, constipation, dizziness, fatigue, nausea, edema, rash, gum hyperplasia, bradycardia, and systemic hypotension.	Uptitrate from a lower dose If possible use extended release preparations Potential risk of hypotension
Diltiazem	Initial dose: 1.5–2 mg/kg/day in 3 divided doses Maintenance dose: 3–5 mg/kg/day in 3 divided doses Maximum adult dose: 240–720 mg/day		
Amlodipine	Initial dose: 2.5–5 mg/day Maintenance dose: 2.5–5 mg/kg/day twice daily Maximum adult dose: 20 mg/day		
Prostacyclin			
Epoprostenol	Initial dose: 1 to 3 ng/kg/min Maintenance dose: 50 to 80 ng/kg/min (may be higher)	flushing, headache, nausea, diarrhea, jaw discomfort, foot pain, rash, 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 6–9 times per day Maintenance dose: 5 µg per inhalation Maximum 9 times per day	Cough, headache, flushing, jaw pain, diarrhea, rash, and hypotension	Reactive airway symptoms, hypotension possible at high dose
Treprostinil	<i>Intravenous/subcutaneous</i> Initial dose 1.25 to 2 ng/kg/min Maintenance dose: 50 to 80 ng/kg/min <i>Inhaled</i> Initial dose: 3 breaths (18 µg) 4 times per day Maintenance dose: 9 breaths (54 µg) 4 times per day	<i>Intravenous infusion</i> Similar to epoprostenol but may require higher doses <i>Subcutaneous</i> Pain at the infusion site <i>Inhaled</i> Cough, headache, nausea, dizziness, flushing, throat irritation	<i>Intravenous/subcutaneous</i> Similar to epoprostenol <i>Inhaled</i> Reactive airway symptoms, hypotension possible at high dose
Phosphodiesterase type 5 inhibitor			
Sildenafil	<i>Oral</i> <8kg Initial dose: 0.5 mg/kg/dose Maintenance dose: 1 mg/kg/dose tid (max dose 10mg tid) European Medicines Agency (EMA): 8–20 kg = 10 mg tid > 20 kg = 20 mg tid <i>Intravenous</i> 0.4mg bolus over 3 hours 1.6mg/kg/day: continuous infusion	Headache, flushing, rhinitis, dizziness, erections, hypotension, peripheral edema, dyspepsia, diarrhea, myalgia, back pain, visual disturbances, hearing loss	FDA warning of chronic use in children 1–17 years of age Caution in concomitant use of CYP3A4 inhibitors reduce clearance of sildenafil Co-administration of bosentan leads to decreased sildenafil concentrations and increased bosentan concentrations Use in premature neonates not well studied
Tadalafil	Pediatric studies suggest: 1mg/kg/day	Similar to sildenafil No significant influence on vision	Concomitant use of CYP3A4 inhibitors reduce clearance of tadalafil No clinically significant alterations in co-administered bosentan or ambrisentan
Endothelin receptor antagonist			
Bosentan	2 mg/kg bid 10–20 kg: 31.25 mg bid 20–40 kg: 62.5 mg bid >40 kg: 125 mg bid after up titration	Abdominal pain, vomiting, extremity pain, fatigue, flushing, headache, edema, nasal congestion. Potential risk of dose-dependent increases in aminotransaminase levels Teratogenicity May decrease effectiveness of birth control	Routine monitoring liver enzymes required Not recommended in patients with moderate or severe hepatic impairment Teratogenic; requires birth control Anemia Caution in concomitant use of CYP3A4 inducers and inducers

Agent	Dose	Side effects	Cautions
			Co-administration of sildenafil leads to decreased sildenafil concentrations and increased bosentan concentrations Decreases in sperm count have been observed in patients taking endothelin receptor antagonists
Ambrisentan	2.5 / 5 / 10 mg daily	peripheral edema, nasal congestion, headache, flushing, and nausea The incidence of serum aminotransferase elevation is low Teratogenicity May decrease effectiveness of birth control	Routine monitoring liver enzymes recommended Not recommended in patients with moderate or severe hepatic impairment Teratogenic: requires birth control Anemia Caution in concomitant use of CYP3A4 inducers and inhibitors No drug to drug interactions between ambrisentan and sildenafil or tadalafil Decreases in sperm count have been observed in patients taking endothelin receptor antagonists