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# Prostacyclins and pulmonary arterial hypertension in children

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**Abstract. – OBJECTIVE: Despite its low incidence, pulmonary hypertension in children places a substantial burden on families and society because survival can be shorter than 10 months and treatment options are limited and ineffective. Drugs to treat pulmonary hypertension include endothelin antagonists, phosphodiesterase type 5 inhibitors and prostacyclin, which is the most widely used to treat pediatric pulmonary hypertension. The main aim of this study was to provide a comprehensive overview of the advantages and disadvantages of prostacyclin and its analogs for treating pulmonary hypertension in children.**

**MATERIALS AND METHODS: To retrieve a thorough collection of studies, we performed a search in PubMed using the following combination of keywords: (Prostacyclins) or (Epoprostenol) or (Iloprost) or (Treprostinil) or (Beraprost), (children) and (pulmonary arterial hypertension). The time limits used for the search were December 1983 to May 2021.**

**RESULTS: The search retrieved a total of 238 articles. Titles and abstracts of articles were screened for relevance, and all relevant articles published in English were included.**

**CONCLUSIONS: Epoprostenol can be effective against severe pulmonary hypertension. Iloprost can treat severe persistent pulmonary hypertension in newborns and inhaled iloprost can be used in pulmonary vasoreactivity testing. Treprostinil is a long-acting prostacyclin analog, and it shows the highest antiproliferative activity among prostacyclins. Beraprost may be effective in premature infants, but available evidence comes from only one patient, so more clinical testing is needed.**

*Key Words:*
Prostacyclins, Pulmonary arterial hypertension, Children.

## Introduction

Based on the guidelines of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), pulmonary hypertension (PH) is defined as an increase in the mean pulmonary arterial pressure (PAP) ≥25 mmHg at rest, as measured by invasive right heart catheterization (RHC). The diagnosis is instead pulmonary arterial hypertension (PAH) if the PAP increase is accompanied by a decrease in pulmonary arterial wedge pressure (PAWP) ≤ 15 mmHg and pulmonary vascular resistance (PVR) > 3 Wood Units (WU) in the absence of other causes of precapillary PH, such as PH due to lung disease, chronic thromboembolic PH, or other rare diseases[1]. Historically, similar criteria have been used to diagnose PH in children as in adults[2]. However, children are undergoing growth and development, which may influence the cut-off for physiological PAP. Accordingly, at the recent World Symposium on Pulmonary Hypertension in 2018, experts attempted to standardize classification of PH in children and adults[3]. They proposed a definition of PH in adults and children as a mean increase of PAP ≥20 mmHg, and a PVR ≥ 3 WU for adults and PVRI (PVR indexed to body surface area) of ≥ 3 WU • $m^2$ for children[4].

In 2011, the Pulmonary Vascular Research Institute Task Force established a complex classification of PH in children based on birth prematurity, chromosomal anomalies, other genetic abnormalities, coronary heart disease (CHD), breathing-related sleep disorders, and parenchymal disease secondary to chronic aspiration. The experts identified 10 main classes and 109

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subclasses of PH, demonstrating its complexity in growing children[5]. Currently, pediatricians suggest a simpler classification of pediatric PH in only five subtypes: neonatal PH, cardiac PH, idiopathic PAH (IPAH) or PAH of unknown cause, and syndromic PH (coexisting factors)[6]. PAH is the most frequent subtype, accounting for 88% of all pediatric PH cases, while IPAH or familial PAH account for 57%, and other disorders account for 43% in PAH[7]. The main causes of children's PAH are congenital heart disease, primary PH of the newborn (PPHN), and genetic disorders. Adult PH, in contrast, usually does not involve these causes, highlighting the differences between adult and infant PH[8].

Pediatric PH affects about 25.7-32.6 per one million children in the USA[9]. In the United Kingdom and the Netherlands, the incidence of the IPAH subtype was reported to be 0.48 or 0.7 per million children, respectively[10,11]. Hospitalization of children who have PAH as a co-morbidity has increased in the past years[12], which may reflect the increasing survival rates of premature infants[13].

If untreated, children's PAH is associated with very poor prognosis. The US National Institutes of Health (NIH) reported a median survival rate of 10 months for untreated children diagnosed with IPAH, compared to 2.8 years for adults[14]. Although the development of targeted medicine has shown a positive impact on the survival of pediatric PAH patients[15,11], PAH is still defined as an incurable disease. The pathological features of PAH comprise vasoconstriction, inflammation, structural remodeling, *in situ* thrombosis, and an imbalance in levels of vasoactive mediators. Levels of proliferative and vasoconstrictive mediators such as thromboxane A2 and endothelin-1 typically increase, while levels of antiproliferative and vasodilatory mediators such as prostacyclin and nitric oxide (NO) decrease[16]. Accordingly, therapies against PAH have focused on vascular remodeling. Three main drugs are used against PAH: (1) prostanoids (Epoprostenol, Treprostinil, Iloprost, Beraprost), which stimulate cAMP; (2) endothelin receptor antagonists (Bosentan, Ambrisentan, Macitentan), which block endothelin signaling; and (3) phosphodiesterase inhibitors (Sildenafifil, Tadalafifil, and the soluble guanylate cyclase stimulator Riociguat), which stimulate the NO-cGMP system[17]. Of all these drugs, Epoprostenol was the first to be used to treat PAH. Epoprostenol is an analog of prostacyclin. Despite the development of other therapeutic options, the most recent recommendations of the European Societies of Cardiology and Pulmonology consider this potent analog of prostacyclin as the first therapy option for patients with severe PH who fall within WHO functional class IV[18]. In this review, we focus on knowledge about prostacyclin and its analogs for the treatment of pediatric PAH.

### Prostacyclin Derivatives

Prostacyclin (PGI2) was first reported in 1976 by Needleman et al[19] as an end product derived from the sequential metabolism of arachidonic acid via cyclooxygenase-2 (COX-2) and prostacyclin synthase. Arachidonic acid in cells is present in the phospholipids of the cell membrane. In brief, phospholipase A, which can be activated by a variety of stimuli, releases arachidonic acid from the membrane phospholipids. Free arachidonic acid can then be processed by COX proteins. There are two COX isoenzymes in the body, COX-1 and COX-2, both of which act on arachidonic acid to produce the same metabolites prostaglandin G2 (PGG2) and prostaglandin H2 (PGH2). COX-1 is a structural enzyme that exists under normal physiological conditions and mainly mediates the formation of physiological prostaglandins. COX-2 is an inducible enzyme that is produced in large quantities in response to inflammatory cytokines. It exists mainly at inflammatory sites and promotes the synthesis of inflammatory prostaglandins, which can cause inflammatory reactions, fever and pain. Subsequently, TXA2 synthetase in platelets converts the arachidonic acid-derived metabolite PGH2 into thromboxane A2 (TXA2), which has a strong role in promoting platelet aggregation. Vascular endothelial cells can convert PGH2 to PGI2 because they contain prostacyclin (PGI2) synthetase[19]. PGI2 is the active endogenous platelet inhibitor, and it can inhibit platelet aggregation induced by adenosine-5'-diphosphate, collagen or other factors[19]. The body regulates thrombosis through the dynamic balance between TXA2 produced by platelets and PGI2 produced by endothelial cells.

The cell surface receptor for PGI2 is a seven-transmembrane G-protein-coupled receptor termed prostaglandin I2 receptor. When activated by PGI2, this receptor stimulates adenyl cyclase, which leads to an increase in intracellular cyclic AMP (cAMP) levels and subsequent increase in activation of protein kinase A (PKA) and the phosphorylation of further proteins. This cascade results in smooth muscle relaxation, reduced cell

proliferation, and other processes that suppress PAH[19]. Patients with PAH typically show reduced levels of PGI2 and PGI2 synthase. This results in the induction of vasoconstriction and vascular smooth muscle cell proliferation[20]. Thus, prostacyclin and its analogs have been extensively studied to ameliorate PAH, as discussed below.

## Prostacyclin and its Analogs

### *Epoprostenol*

The first isolation of prostacyclin (PGI2) was reported by Moncada et al[21] in 1972. The substance, termed epoprostenol (PGx), was directly prepared from rabbit or pig aortas and was shown to be 30 times more potent in inhibiting human platelet aggregation than prostaglandin E1[21]. Based on the results from phase 2 and 3 trial trials carried out between 1987 and 1992 in adult patients with PAH, epoprostenol was approved for the treatment of severe idiopathic PAH in 1995. The classical mode of delivery of epoprostenol (continuous intravenous infusion via an indwelling central venous line) is associated with adverse events such as bacteremia, sepsis and thromboembolism. Clearly, these events can be fatal in children. In order to solve this problem, some doctors use a totally implantable access port (TIAP) delivery approach. Unfortunately, TIAP-related complications also occur, including local port site infections, bloodstream infections, port site skin perforations and incorrect port placement[22]. Inhalation has also been used to deliver epoprostenol to treat acute PH, even in neonates. Inhaled epoprostenol is an effective therapy for the treatment of certain pediatric patients with acute PH. Evidence[23] suggests that neonates may respond better than older infants and children. Furthermore, under certain conditions (New York Heart Association functional class I or II, mean PAP < 35 mmHg, normal cardiac index, age > 6 years), intravenous epoprostenol can be transitioned to oral/inhaled administration to treat PAH[24].

Apart from the adverse events associated with the delivery mode, epoprostenol can give rise to secondary adverse effects[25], the most common of which in children are pulmonary hemorrhage, cardiac failure, hemoptysis, bradycardia, hypotension, and thrombocytopenia[26,27].

Despite the many adverse reactions described above, epoprostenol still represents an effective and feasible therapy for PAH, even in young children. One study[28] in adults showed that PAH patients who received oral combination of drug therapies had lower survival rates than those who received initial combination therapies that included intravenous epoprostenol. This raises the question of whether we should routinely use intravenous epoprostenol in patients at intermediate risk of PAH. Pediatricians should address this question.

### *Iloprost*

One of the caveats of epoprostenol (i.e., PGI2/PGx) is that it is a chemically unstable compound. Its half-life in blood or physiological solutions is only a few minutes. As a result, one study[29] focused on finding a more stable compound and, in 1981, Schrör et al[29] reported the chemically stable prostacyclin analog iloprost [ZK 36 374; 5-{(E)-(1S,5S, 6R, 7R) -7-hydroxy-6-[(E)-(3S,4RS)-3-hydroxy-4-methyl- oct-l-en-6-yn-yl-bicyclo [3.3.0]-octan-3-yliden}-pentanoic acid]. Intravenous (i.v.) administration of iloprost was shown to mitigate severe persistent PPHN[30]. Median oxygenation index (OI) and alveolar-arterial oxygen levels began to fall after only 2 hours of treatment and continued to decline thereafter. Importantly, iloprost did not affect general blood pressure or heart rate[30].

Iloprost can also be administered by inhalation, typically in six to nine inhalations per day per treatment. Iloprost-loaded liposomes containing di-palmitoyl-phosphatidyl-choline (DPPC) and cholesterol (CH) components are well suited to aerosolization using a vibrating mesh nebulizer[31]. Aerosolized iloprost has similar efficacy as inhaled NO in the management of PH in children who have undergone congenital heart surgery[32]. Indeed, inhaled iloprost in combination with $O_2$ can be useful for correctly identifying pulmonary vasoreactivity without prolonging cardiac catheterization[33]. In children with severe PAH associated with congenital heart disease, iloprost aerosol inhalation followed by surgery with anti-PAH drugs has been reported to be effective[34]. Aerosolized iloprost has also been shown to be an appropriate new agent to identify long-term responders to calcium channel blockers among patients with IPAH[35], as well as an effective way to treat IPAH patients in pulmonary hypertensive crisis (at a dose of 10 μg per administration, for 10-15 min at 2-hour intervals, 8 times per day)[36].

Aside from PH-related diseases, iloprost can also be used for the treatment of Raynaud's phenomenon in children with threatening ischemic digits, aseptic osteonecrosis (AON), reflex sympathetic dystrophy or bone-marrow edema syndrome[37-40].

While inhaled iloprost has been demonstrated to improve pulmonary function of children with PAH and most patients tolerate the transition from intravenous to inhaled prostanoid therapy, iloprost treatment is not exempt from secondary effects. In adults, nausea, vomiting, diarrhea and dry cough are the classical symptoms accompanying treatment[36]. In children, the adverse events of inhaled iloprost include bronchoconstriction, headache and rash around the mouth[41]. In a recent meta-analysis[42], inhaled iloprost was a safe and well-tolerated treatment against PAH in the first 3 months after diagnosis. However, if used for a prolonged period, aerosol iloprost monotherapy could contribute to unsatisfactory vascular remodeling and even lower event-free survival rate[42]. Frequency of treatments, clinical deterioration, side effects, and poor compliance need to be taken into account when considering the chronic use of iloprost, especially in children[43]. Pediatric patients with severe PAH likely need a combination treatment[44].

### Beraprost

In 1985, a new prostacyclin analog, Beraprost sodium (BPS or TRK-100), was described by Sim et al[45]. Beraprost is a potent *in vitro* inhibitor of human platelet aggregation induced by adenosine diphosphate. This inhibitory activity is half of that of PGI2 but eight times that of PGE1, and it is considered a potentially useful antithrombotic therapy[45]. Intratracheal administration of beraprost nanoparticlesin PAH rat models significantly decreased right ventricular pressure, right ventricular hypertrophies, and pulmonary artery muscularization[46].

Oyamada et al[47] described oral BPS given to a 74-day-old premature infant with congenital heart disease and PAH, who was born at a gestational age of 35 weeks and 6 days and weighed 1,489 g at delivery). The oral drug was started at a dose of 0.5 **μg**/kg twice daily, which was gradually increased to 1.3 **μg**/kg twice daily. Due to severe watery diarrhea and vomiting, the dose had to be reduced to 0.8 **μg**/kg twice daily. After 36 months of treatment, ligation of the patent ductus arteriosus (PDA) was successfully performed. In this case report, the patient continued to take 0.5 **μg**/kg oral BPS twice daily and remained asymptomatic[47]. In contrast, in the case of 12-year-old homozygotic twins with primary PH, where one twin received BPS and the other received epoprostenol, the twin treated with beraprost showed progressive worsening[48]. After changing to epoprostenol, this twin showed improvement similar to the twin who had received epoprostenol from the beginning. This discrepancy in the literature about the efficacy of oral BPS in children with PAH highlights the importance of performing more investigations of the compound.

### Treprostinil

In the continuing search for more stable and potent prostacyclin analogs, Mohler et al[49] reported in 2000 the synthesis of treprostinil sodium (UT-15), a potent and long-acting prostacyclin analog with high affinity for the EP2 and DP1 prostacyclin receptors (6.2 ± 1.2 nM and 0.6 ± 0.1 nM EC50, respectively)[49]. Teprostinil demonstrated stronger antiproliferative effects on smooth muscle cells than other compounds (UT-15 > iloprost > cicaprost > beraprost), thus demonstrating an ability to strongly influence vasodilation[50]. In addition, Treprostinil exerts its beneficial effects through inhibition of platelet activation, resulting in smaller numbers of circulating microvesicles that also show weaker procoagulant activity[51].

In a recent investigation[52], treprostinil was the only prostacyclin mimetic that bound mainly to the prostaglandin E2 receptor ($EP_2$). Indeed, $EP_2$ receptor knockdown selectively reduced functional responses to treprostinil. These results indicate that $EP_2$ receptors represent a novel therapeutic target for treprostinil, uncovering a key pharmacological difference from other prostacyclin mimetics.

In February 2002, the US Food and Drug Administration (FDA) first approved treprostinil injection for the treatment of patients with primary or secondary PAH and class II-IV symptoms as defined by the New York Heart Association. For children, treprostinil is administered by inhalation or via intravenous, oral or subcutaneous routes.

Inhaled treprostinil can be used in children ≥6 weeks age. In doses of 3-9 breaths (6 μg/breath) taken 4 times per day, it has been shown to improve the World Health Organization functional class and the exercise capacity[53]. Adverse effects, however, include bronchospasm, cough and sore throat[53]. Inhaled treprostinil can also be administrated via an endotracheal tube, an anesthesia mask, or a laryngeal mask airway during acute vasodilator testing (AVT). These adminis-

tration methods have proven effective and well tolerated[54]. Nevertheless, high-frequency oscillator ventilators with a vibrating mesh nebulizer should be used with caution when delivering inhaled treprostinil to children in order to prevent overdosing[55].

Intravenous treprostinil is well tolerated by neonates and infants and can improve cardiac function and reduce pulmonary circulation resistance in children with PAH[56,57], but dose titration is limited by hypotension and hypoxemia[56]. Treprostinil has fewer side effects than epoprostenol[58], but the need for intravenous administration represents an infection risk. Unfortunately, replacing the central line in pediatric PH patients after a bloodstream infection has not been shown to improve subsequent infection rates or time until the next infection, but instead may actually increase risk of adverse events, including potential loss of vascular access[59]. In this situation, older children can opt for intravenous treprostinil delivery via an implanted pump (LENUS Pro®). However, this pump can produce local pain, inflammation, and local infection; it may not be well tolerated; and it may even severely decrease the quality of life of the child, especially when psychological or psychomotor issues hinder the use of external pumps[60,61].

Oral treprostinil was approved for the treatment of PAH in December 2013[62]. A multicenter study[63] reported that the youngest patient to successfully receive oral treprostinil was a 4-year-old child weighing 16 kg. A recent study[64] showed that, in the transition from parenteral or inhaled treprostinil to oral treprostinil, 96.9% of children with PAH effectively maintained the transition to oral treprostinil. This indicates that oral treprostinil had greater therapeutic efficacy against PAH. However, most patients receiving oral administration suffered from drug-related adverse effects, including headache (81%), diarrhea (69%), nausea (66%), vomiting (66%), or flushing (56%)[64]. This may become an important limitation to the oral use of treprostinil in children.

Because of the complications associated with combined oral treatment or central line administration of treprostinil, delivering the drug subcutaneously may be a good choice for treating refractory pediatric PH[65]. Subcutaneous treprostinil infusion is an effective therapy without serious side effects and with an adaptation age that ranges from 1 to 200 months in cases of severe pediatric PH. The adverse events are local site pain and minor site infections[66]. Long-term use of subcutaneous treprostinil, even at higher doses, is safe and well-tolerated in children with severe PAH. Thus, it may be a good alternative to intravenous prostacyclin treatment in order to avoid the potential complications of permanent central line usage[67]. Indeed, data from 12 independent clinical trials using treprostinil in children with PH showed that subcutaneous administration is the most frequent delivery method[68], and most authors have concluded that subcutaneous treprostinil is effective and well tolerated, making it a suitable replacement for epoprostenol[68].

## Conclusions

Four major prostacyclin compounds are currently used as therapeutics for the treatment of PH. Epoprostenol is still the molecule recommended for severe PAH cases. Iloprost can treat severe PPHN, and inhaled administration can be used for pulmonary vasoreactivity testing. Treprostinil is a long-acting prostacyclin analog, and it shows the highest antiproliferative activity among prostacyclins. Finally, beraprost may be effective in premature infants based on one successful case report, which of course needs to be validated in larger studies. Due to the lower incidence of PAH among children, not many multi-center studies have examined the effects of prostacyclin or its analogs. The available data make clear that different prostacyclin analogs have different advantages and disadvantages (Table I), for which we need further clinical studies. Our deepening understanding of PH, the remarkable development of biological and genetic approaches, new drug research, and better clinical monitoring and record-keeping should help improve the treatment and management of children with PH.

### Conflict of Interests

The Authors declare that they have no conflict of interests.

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**Table I.** Prostacyclin doses in pediatric PAH.

| Prostacyclin | Dosage | Age | Associated adverse events | Adaptation |
|---|---|---|---|---|
| Epoprostenol | Initial: 1-3 ng/kg/min<br>Maintenance:<br>50-80 ng/kg/min[17] | All | Pulmonary hemorrhage, cardiac failure, hemoptysis, bradycardia, hypotension, thrombocytopenia[24,26] | Severe PAH<br>Or intermediate risk[26] |
| Iloprost | Initial: 2.5 mg/ inhalation<br>6-9 times per day<br>Maintenance:<br>5 m g/inhalation<br>Maximum: 9 times per day[17] | Neonatal and older | Bronchoconstriction, headache and rash around mouth[41], flushing, rash, hypotension[16], nausea, vomiting, diarrhea and dry cough[41] | Well-tolerated for PAH in the first 3 months after diagnosis[43] |
| Beraprost | *Oral:*<br>Initial: 0.5 μg/kg bid.<br>Maximum:<br>1.3 μg/kg bid<br>Maintenance:<br>0.5 μg/kg bid[47] | Premature, neonatal and older | Severe watery diarrhea and vomiting | New York Heart Association (NYHA) Class II-IV symptoms |
| Treprostinil | *Inhaled:*<br>Initial: 3 breath (18 μg) 4 times per day<br>Maintenance:<br>9 breath (54 μg) 4 times per day[17]<br>*Intravenous/ subcutaneous:*<br>Initial:1.25-2 ng/kg/min<br>Maintenance:<br>50-80 ng/kg/min<br>*Oral:*<br>Transition dose:<br>2.0 mg per dose,<br>Two or three doses per day | *Inhaled:* ≥6 weeks old.<br>*Intravenous:* neonatal and older[60]<br>*Subcutaneous:*<br>1-200 months<br>*Oral:* ≥4 years | *Inhaled:* bronchospasm, cough and sore throat[53]<br>*Intravenous:* central line infection<br>*Subcutaneous:* pain, inflammation, and local infection<br>*Oral:* headache, diarrhea nausea, vomiting, and flushing[63] | New York Heart Association (NYHA) Class II-IV symptoms |

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