Curr Treat Options Cardio Med (2018) 20: 8
DOI 10.1007/s11936-018-0597-z

Pediatric and Congenital Heart Disease (G Singh, Section Editor)

Treatment of Pediatric Pulmonary Hypertension

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Published online: 20 February 2018

This article is part of the Topical Collection on *Pediatric and Congenital Heart Disease*

Keywords Pediatric pulmonary hypertension · Potts shunt

Abstract

Pulmonary hypertension (PH) is an increasingly recognized problem in children, particularly within tertiary pediatric hospitals. This increase is, in large part, due to ever improving survival among previously fatal conditions, such as extreme prematurity and complicated congenital heart disease. This increased recognition has paralleled burgeoning pharmacologic and interventional PH-specific treatment options. Unfortunately, most PH-specific therapies have not been tested in children with rigorous, randomized, controlled trials. As a result, most treatment of PH in children is based upon expert consensus and practitioners' experience. In this article, we highlight some of the current and recent advances in therapies available for children with PH. The role that a Potts shunt may have in ameliorating severe PH in children is highlighted.

Introduction

Once felt to be a relatively rare disease, the diagnosis of pulmonary hypertension (PH) in children has escalated dramatically in the last 10 years, especially in tertiary pediatric hospitals. [1, 2•, 3•]. This rise lies in part due to increased awareness and improved diagnostic acumen. Additionally with ever improving therapeutic skills, previously fatal childhood diseases are now transitioning into chronic disorders often incurring new problems such as pulmonary hypertension (PH). This is most evident in the Neonatal Intensive Care Unit (NICU) where extremely low gestational age neonates (ELGANs) are surviving, often with resultant chronic lung disease and a high susceptibility to developing PH. Other pediatric populations where PH is being recognized with escalating frequency include children with congenital heart disease, genetic disorders, sickle cell disease, and post-chemotherapy [4–7]. The recognition of the increasing relevance of pediatric PH has led to the recent publication of a comprehensive guideline to help practitioners with the diagnosis and treatment of pediatric PH [3•].

Interest in PH, both in adults and children, has no doubt been accelerated by the development of PH-specific therapies. From the initial approval of epoprostenol to treat PH in 1995, there has been an increasing array of PH-specific medications available. In general, these medications fall into three categories

based upon their mechanism of action within the pulmonary vasculature: (1) utilization of the prostacyclin pathway and the upregulation of intracellular cAMP levels, (2) utilization of the nitric oxide pathway with upregulation of intracellular cyclic guanosine monophosphate (cGMP) levels, and (3) inhibition of endothelin-1, a potent vasoconstrictor [8•]. Use of these medications have undoubtedly improved the overall survival in children from a median survival of less than 1-year to a 5-year survival of 50–70%, depending on etiology [9, 10••]. While clearly an improvement, a 5-year survival as low as 50% still makes PH a devastating diagnosis in a child. Complicating the use of these medications in children is the fact that, despite their use for over a decade, very few of these medications have undergone randomized control trials assessing efficacy and safety in the pediatric population. Thus, most treatment guidelines for children rely on expert consensus and helps explain why there still exists a fair amount of variability in how different centers treat children with PH. Further adding to management concerns is that these medications are extraordinarily expensive. Intravenous prostacyclin alone can cost over $100,000 a year not including the supplies needed for delivery. Not surprisingly therefore, treatment options can be significantly influenced by what a family's insurance is willing to cover.

Our goal in this article is to highlight some of the recent advances made in treating children with PH and to point out areas of possible disagreement. We will also emphasize the role of interventional therapies, especially that of recently introduced Potts shunt, which we feel is a potent but under-utilized tool in the practitioner's armamentarium.

Treatment

Nitric oxide/cGMP modulators

Sildenafil is the first drug in this class approved by the FDA in 2005 for treating PH. It inhibits phosphodiesterase-5 within pulmonary vascular smooth muscle and endothelial cells thereby preventing the breakdown of cGMP which has both vasodilatory and anti-proliferative effects. Though these are the newest class of medication in children, they are undoubtedly the most commonly PH-specific medication owing to their oral formulation, minimal side effects (headaches and GI upset most common) and relatively low cost. Adding to their appeal, especially in infants and young children, is its availability in liquid form. A number of studies have argued for its efficacy in relatively short-term studies in adults with improved exercise capacity, reduced pulmonary pressures and slowing of disease progression [11]. However, no study to date has shown it to reduce mortality.

Sildenafil stands alone as the only PH-specific medications actually tested in children in a randomized, double-blind, placebo-controlled trial. The STARTS-1 and STARTS-2 trials involved treatment naïve children with PH aged 1–17 years of age comparing various dosages of medication [12, 13•]. Short-term benefit included improved clinical functioning and hemodynamics and while critically, long-term survival was also improved in the treatment group of children. While all doses of sildenafil used in the study increased survival compared to controls, those children receiving the highest dose had an unexplained higher mortality compared to lower doses. This prompted the Food and Drug Administration (FDA) to initially release its strictest, i.e., a "black box" warning against the chronic use of sildenafil (Revatio) at any dose in children from 1 to 17 years of age for PH. The ensuing hue and cry among practitioners and families led to a "clarification" from the FDA that "…there may be situations in which the benefit-risk profile of Revatio may be acceptable in individual children, for example, when other treatment options are limited and Revatio can be used

with close monitoring." While the FDA black box warning remains, sildenafil is widely prescribed for pediatric PH albeit at relatively lower doses: a maximum of 10 mg three times a day for children < 20 kg and 20 mg three times a day maximum for those > 20 kg. Tadalafil, another PDE-5i drug, has a longer duration of action than sildenafil, thus allowing once a day dosing. It does not have similar data for its efficacy in children as sildenafil, although many prescribers treat them similarly [14, 15]. While it does not fall under the same FDA proscription as sildenafil, lack of a convenient liquid preparation makes its use more problematic in younger children. Riociguat, a drug that enhances production of cGMP levels through stimulation of guanylate cyclase was approved for treatment of PH by the FDA IN 2013. While short-term results in adults have been encouraging, where this new and expensive drug fits in the pediatric world remains to be seen, especially since it cannot be given along with a PDE5i due to resulting hypotension [16]. Studies comparing riociguat to sildenafil as well as a pediatric study evaluating its use are currently recruiting patients.

Due to the ease of administration and relatively low side effects, sildenafil has become the first-line medication in premature infants who develop pulmonary hypertension. Though initial guidelines suggested that these medications should not be utilized without a catheterization, follow-up literature does not give the same mandate [3•, 17]. It is clear, however, that many practitioners utilize these medications prior to obtaining a cardiac catheterization [18]. If additional therapy is needed, cardiac catheterization is more often utilized.

Endothelin receptor antagonists

Endothelin receptor antagonists (ERAs) are orally active medications that block activation of the endothelin system. There are two target receptors, types A and B, with activation of type A receptor resulting in pulmonary vasoconstriction. Bosentan is a dual receptor antagonist that was first approved for PH treatment by the FDA in 2001. It is the most widely used ERA in pediatrics and is readily compounded in liquid form. There are no randomized, double-blind, placebo-controlled studies in children nor are there studies in adults that show it reduces mortality. Nonetheless, there are a number of smaller scale studies showing both safety and efficacy in slowing the progression of pediatric PH [19, 20]. Interestingly, bosentan is the only PH-specific medication shown to have efficacy in PH related to congenital heart disease [21]. Generally, bosentan is well tolerated in infants and children. Nonetheless, the relatively rare side effect of hepatoxicity and anemia requires monthly blood draws which makes it less likely to be used as monotherapy compared to sildenafil in children. Ambrisentan is a type A selective antagonist with promising data in adults and scant reports in children [22]; however, it is often treated as comparable to bosentan. With once a day dosing and freedom from monthly blood draws, it is an attractive alternative in older children (no liquid preparation is available). Macitentan is a newer generation ERA introduced in 2013 that is a dual receptor antagonist with selectivity to the type A receptor. Importantly, the study demonstrating its efficacy used the far more rigorous and compelling long-term end-points of morbidity and mortality, rather than short-term end-points such as improved exercise capability [23]. A study of macitentan in

pediatric PH is currently recruiting patients and is comparing its usage to standard therapies.

Currently, for a child with relatively mild PH, i.e., WHO functional class I or II, less than systemic right ventricular (RV) pressures with no evidence of RV failure, monotherapy with either a PDE5i or an ERA is recommended. However, a randomized, double-blind controlled trial in 2015 showed that treatment naïve adults who took ambrisentan and tadalafil together had a lower risk of developing "clinical failure" [24]. Clinical failure was defined as a composite of death, hospitalization, disease progression, or decreased clinical performance. Of note, at the end of the 6-month trial, there was no significant difference in mortality and functional class between the two groups. This trial, and many more that are currently underway, raises the question of treating PH with multiple drugs upfront [25, 26]. Virtually, all of these trials are not designed with children in mind and the risk-benefit of possibly increased side effects, not to mention cost, make this an area of uncertainty in pediatric PH.

Prostacyclins/cAMP modulators

While treating children with "lower risk" PH can be variable among practices, virtually all practitioners would agree that children with severe, "higher risk," disease deserve a trial of prostacyclins. Epoprostenol was first approved for treating PH in 1995. Even after 20 years, it remains a mainstay in treating patients with severe PH and is, along with sildenafil, the only other drug to show a reduction in mortality in children [27]. Treprostinil, introduced in 2002, is also widely used in children. Although not as rigorously tested as epoprostenol, most pediatric practitioners feel they are comparable in effects [28, 29]. Yet despite the proven effectiveness of prostacyclins, a main hesitation for their implementation in children is their delivery, which implies the placement of a central line for continuous intravenous (IV) infusion. The fact the treprostinil can be given subcutaneously (SQ) and be as efficacious as the IV form has made it a popular option. Even infants have tolerated SQ infusion with little of the site pain that can plague adult patients [30]. Despite these modifications, for parents, the idea that their young child may require a continuous infusion of medication for the rest of his or her life is daunting indeed. Inhaled treprostinil has limited data in children and is not felt to be comparable to IV/SQ administration in terms of effectiveness [31]. Nonetheless, it has a niche as an add-on to other oral therapies or as an option for a child weaning off IV/SQ prostacyclin. The most recent prostacyclin analogue to generate significant enthusiasm is selexipag. This unique drug, approved by the FDA in 2015, is an oral, selective agonist to the IP prostacyclin receptor which results in increased intracellular levels of cAMP within pulmonary smooth muscle cells. A randomized, double-blind, placebo-controlled trial in adults showed those taking the drug experienced significantly fewer end-point "events," which included death, hospitalization, disease progression, and lung transplantation [32]. There was not a reduction solely in mortality. Since then, a report using selexipag in 10 children with PH suggests it could be beneficial in the pediatric population as well [33]. The idea that children with severe PH may be free of lines and pumps yet treated effectively makes this drug of acute interest for families and pediatric caregivers.

Glucocorticoids

There is a wealth of basic science knowledge implicating inflammation in the pathophysiology of pulmonary hypertension [34]. Inflammatory cells and elevated inflammatory cytokines have long been identified in tissue and sera from patients with PH. Furthermore, animal models have shown attenuation of PH and even disease reversal when treated with anti-inflammatory medications. Recently, we published the first report utilizing glucocorticoids in children with PH with encouraging results [35]. We utilized prednisone at 2 mg/kg/day for 5 days and a slow tapering of medication if there was echocardiographic and clinical improvement. We found it most successful in children less than 2 years of age often with a diagnosis other than idiopathic pulmonary hypertension, such as PH associated with chronic lung disease of prematurity, Down syndrome, giant omphalocele, pulmonary-veno-occlusive disease, and post-chemotherapy. Further controlled trials are obviously needed; however, proof of the effectiveness of glucocorticoids in treating PH could have a significant impact given how readily available and amazingly inexpensive glucocorticoids are compared to other PH-specific medications.

Interventions

Up until the last 5 years, options for patients with severe PH that failed medical therapy were either creation of an atrial septal defect (ASD) or lung transplantation. ASD creation is seen as a final attempt short of transplantation to rescue a failing right ventricle (RV). Studies in adults have shown it to be successful in reducing symptoms but not in preventing mortality [36, 37]. Its failure to impact mortality is due in large part to the fact that an ASD only helps a RV that has undergone diastolic failure. Diastolic RV failure equates to a high right atrial pressure which older studies have shown is a clear harbinger of imminent mortality [38]. There are no studies on the effect of ASD creation in children. Lung transplantation remains the ultimate palliation for severe PH. In 2011, we published the largest series on outcomes in children undergoing lung transplantation for severe PH [39•]. Over an 18-year span, we transplanted 26 children with a median survival of 5.8 years. One of the more telling analyses of our data was that date of transplant did not affect mortality. In other words, children transplanted 18 years apart had similar outcomes, implying that medical advances over nearly 20 years failed to impact survival in children transplanted due to severe PH.

Potts shunt

In 2012 and 2014, a French led group published on a series of 24 children with severe PH treated with a Potts shunt [40•, 41]. This procedure involves an anastomosis between the left pulmonary artery and the descending aorta as first described by Dr. Willis Potts in 1945. However, instead of providing a source of pulmonary blood flow as originally intended, the French group had the remarkable insight to utilize the Potts shunt to allow blood to flow from the supra-systemic pulmonary system to the systemic arterial system, thus, decompressing the RV to systemic left ventricular pressures. They postulated that by recapitulating the pathophysiology of Eisenmenger syndrome where right and left ventricular pressures equalize, they would also confer upon the treated children the superior life expectancy purported in patients with

Eisenmenger syndrome [42]. While very long-term outcomes remain to be seen, the French group found that children treated with a Potts shunt have improved functional class with the majority weaning completely off prostacyclin therapy. At least 7 of their treated children have lived beyond 8 years, which exceeds the median survival for lung transplant. At our institution, we have now performed 12 Potts shunts in children with an age ranging between 3.5 months and 17 years and with a variety of PH diagnoses [43]. Most of our children experienced improvement similar to the results published by the French. However, we have had four children where the Potts shunt was not successful in significantly improving outcomes. All four children were teenagers who had evidence for severe RV failure at the time of their surgery. Clearly, if a Potts shunt is to be successful, RV systolic function must be relatively preserved with pre-operative data suggesting RV supra-systemic pressures being ideal. Nonetheless, looking at published evidence, Potts shunts clearly help children with severe PH. Furthermore, we believe, in the right situation, it can provide longer term survival with less morbidity than lung transplantation. We also do not feel it precludes a future lung transplantation should that become necessary. Thus, we advocate that a Potts shunt should be considered in any child with supra-systemic RV pressures regardless of etiology who has not responded to medical therapy within a reasonable time period. What that time period is—6 months, 1 year, 2 years?—remains a matter of debate.

Clinical Implications

Pediatric pulmonary hypertension is a severe, progressive disease with many options for treatment. Care for these individuals is enhanced by a multi-disciplinary team familiar with the varied treatment options. As newly available medical and interventional options become available, the treatment community as a whole will have to build understanding of the optimal uses for these therapies.

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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