Published in final edited form as:

Prog Pediatr Cardiol. 2009 December 1; 27(1-2): 3–6. doi:10.1016/j.ppedcard.2009.09.002.

Towards improving the care of children with pulmonary hypertension: The rationale for developing a Pediatric Pulmonary Hypertension Network

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Abstract

Pulmonary hypertension (PH) and related pulmonary vascular diseases contribute to high morbidity and mortality and treatment options remain limited. Despite the availability of new drug therapies, the long-term outcomes of patients with severe PH remain poor. This may be especially true for many children with PH. Although most clinical studies have emphasized studies of adult patients, PH in pediatrics can be devastating and often contributes to poor outcomes in diverse clinical settings in newborns, infants and children. Unfortunately, studies that address the safety and efficacy of PH therapies in children are rare, as most pharmaceutical studies have focused on the adult population and only in patients with a fairly limited range of associated conditions. Thus, pediatric PH has been understudied and little is understood regarding the natural history, mechanisms of disease, and treatment of childhood PH. Limitations regarding current translational approaches to children with PH are partly due to the relatively small numbers of patients with PH associated with specific pediatric disorders at each center; the small number of well-established, multidisciplinary programs in pediatric PH; little communication between translational and clinician-scientists; and limited interactions between existing PH programs. There is clearly a need to develop clinical infrastructure to better define the natural history and course of pediatric PH, to develop new strategies to identify at-risk patients early in their course, and to establish novel approaches to diagnose, monitor disease progression and treat children with PH. This article discusses the rationale, goals and initial steps in the establishment of an interactive network of investigators, care providers and multidisciplinary teams from several pediatric PH centers.

Keywords

Pulmonary hypertension; Pulmonary vascular diseases; Persistent pulmonary hypertension of the newborn; Idiopathic pulmonary arterial hypertension; Bronchopulmonary dysplasia; Cystic fibrosis; Interstitial lung disease; Sickle cell disease

1. Introduction

Despite advances over the past decades, pulmonary hypertension (PH) and related pulmonary vascular diseases (PVD) continue to cause significant morbidity and mortality in diverse pulmonary, cardiac, and hematologic disorders of childhood [1]. Whereas the impacts of pulmonary hypertension (PH) on the clinical course of children with congenital heart disease, persistent pulmonary hypertension of the newborn (PPHN), and idiopathic pulmonary arterial hypertension (IPAH) are most clearly appreciated, the contribution of pulmonary hypertension to the course and ultimate outcome of children with lung disease is often overlooked or underestimated. Structure and function of the pulmonary circulation can be altered by primary aberrations of lung growth and development (such as lung hypoplasia, pulmonary capillary hemangiomatosis, arteriovenous malformations, anomalous pulmonary venous return, pulmonary veno-occlusive disease (PVOD), pulmonary vein stenosis, and others), or secondary to injury associated with acute respiratory failure, chronic lung disease after premature birth, chronic hypoventilation, congenital heart disease and chronic hemolysis.

PH is often an unrecognized or silent contributor to morbidity and mortality of many chronic lung disorders in pediatrics, including bronchopulmonary dysplasia (BPD), cystic fibrosis (CF), sickle cell disease (SCD), and various childhood interstitial lung diseases (chILD). For example, 42% of pediatric patients with chILD have evidence of PH early in their clinical course [2]. Progressive PH, which appears to predict early death in adults with SCD, is already present by echocardiogram in 10–20% of young children with SCD [3,4]. In general, clinical strategies that anticipate the development of PH may allow earlier recognition and more aggressive therapy, thereby slowing the development of PH in many chronic lung parenchymal and vascular diseases, especially in children.

Despite some similarities, many aspects of PH in children are distinct from adult PH (Table 1). First, pediatric PH is intrinsically linked to issues of lung growth and development, including many prenatal and early postnatal influences [5]. The development of PH in the neonate and young infant is often related to impaired functional and structural adaptations of the pulmonary circulation during transition from fetal to postnatal life. Second, the timing of pulmonary vascular injury is a critical determinant of the subsequent response of the developing lung to such adverse stimuli as hyperoxia, hypoxia, hemodynamic stress, inflammation, and others. Third, abnormalities of the lung circulation are significant beyond the adverse hemodynamic effects of PH alone. The developing lung circulation plays critical roles in lung organogenesis and development of the distal airspace, maintenance of lung structure, metabolism, gas exchange, the ability to tolerate increased workloads imposed by exercise, and others. Recent studies have clearly shown that disruption of lung vascular growth can impair distal airspace structure during development and contributes to the pathobiology of diverse lung diseases. Fourth, there are apparent differences in function, structure, genetics, and perhaps responsiveness to therapies between adults and children with PH. Therapeutic strategies for adult PH have not been sufficiently studied in children especially regarding potential toxicities or optimal dosing, and age-appropriate endpoints for clinical use and research are lacking in this population.

2. Current barriers to improving clinical research and outcomes in pediatric PH

Gaps in our current knowledge of basic and clinical science behind pediatric PH were recently highlighted in an NIH Workshop that evaluated priorities for improving translational approaches to pediatric lung diseases more broadly [6]. With regard to pulmonary vascular diseases in children, this workshop outlined the critical need to link bench and translational studies. Both short- and long-term strategies are needed to enhance the diagnosis, management or prevention of PH in children (Table 2). These include the need for: 1) identification of current gaps in our basic knowledge of normal and impaired lung vascular development and interactions between vascular and alveolar growth; 2) better characterization of unique aspects of the developing pulmonary circulation and related basic mechanisms underlying pediatric PH; and 3) overcoming barriers that limit the successful translation of basic science findings to clinical trials and improving outcomes of children with PH or related PVD. Such approaches must include studies of disease mechanisms that can establish biomarkers in the clinical setting that can predict disease risk, severity, monitor disease progression, improve outcome measures that are especially applicable to young children with PH. Additional work is needed to develop and apply novel age- and disease-specific therapies for pediatric PH. In addition to the need for multicenter, randomized clinical trials, much can be learned through alternate strategies such as comparative effectiveness research (CER) between known PH therapies, bench-marking approaches, and the application of standardized clinical assessment and management plans [7].

Despite recognition of these issues, significant barriers continue to limit our ability to improve outcomes in pediatric PH (Table 3). One of the major challenges is the extremely small number of patients at each center, making it nearly impossible to successfully conduct studies at a single site. As a result, there is a striking lack of data on the natural history of many forms of pediatric PH, and that most of the scientific literature is based on anecdotal reports or case studies. In addition, there is a lack of quality data about current care patterns in pediatric PH. Before meaningful comparisons between interventions can be made, it is helpful to have a sense of what treatment strategies are currently being utilized. Limited information is available regarding useful endpoints for assessing the effects of different interventions, especially in infants and young children with PH.

In addition, the lack of well-organized, multidisciplinary care teams has further impaired clinical care and research (Tables 4 and 5). For example, interactions between neonatologists, pediatric intensivists, pulmonologists, and cardiologists are essential to optimize care of children with severe PH in many settings, such as PPHN, BPD, CDH and others. Successful strategies require extensive knowledge of the optimal management of associated lung disease and cardiac dysfunction in addition to the use of PH-specific drug therapies, yet such collaborations to promote such efforts are often lacking at many centers. Thus, there is a clear need for developing multidisciplinary approaches within each medical center. To better develop clinical programs, apply successful care guidelines and promote clinical research, there are clear needs for developing better infrastructure at individual

centers and for enhancing interactions between pediatric PH centers, through the formation of a network of large clinical PH programs.

3. The Pediatric Pulmonary Hypertension Network (PPHNet)—mission, goals and approach

To achieve these broad and long-ranging goals, there is clearly a need to develop a network of pediatric PH centers that will develop and plan long-term strategies that will promote effective translational research and enhance the clinical care of children with PH. To meet these ends, we have established a *Pediatric Pulmonary Hypertension Network* (PPHNet), which consists of 8 core centers with established expertise in pediatric PH, and provides a multidisciplinary, interactive working group. Its overall mission (Table 6) and goals (Table 7) are described below. Together, this network will establish a clinical database, initiate the collection of biomarkers and genetic/genomic or proteomic samples in combination with disease phenotyping, and institute multicenter observational (natural history) and interventional studies.

The initial organizational structure for PPHNet is illustrated below (Fig. 1). Core centers were initially selected based on the presence of well-established, multidisciplinary clinical programs in pediatric pulmonary hypertension as a starting point. Once established, the overall plan is to add programs to more centers to the PPHNet. The current structure of the group includes an Executive Committee led by the PPHNet Director and site PIs from each core center (Table 8). This committee is responsible for the overall operation and administration of the network, establishes organizational rules and policies, and sets priorities for research, education and training activities, and related missions. An External Advisory Board will also meet regularly with the Executive Committee to advise and provide oversight to the PPHNet. Members of this board have extensive research experience, including basic, translational and clinical studies, and will further serve to provide a key source of ideas for priorities and new directions of PPHNet. The Data Coordinating Center (DCC) is responsible for the overall management of the database, as well as all phases of subsequent protocol development and use; training database personnel; working directly with oversight committees to ensure the quality, integrity and security of databases; and related roles. Initial standing committees include a Clinical Care Guidelines Committee, a Scientific Committee, and a Lung Pathology Consortium (Fig. 1). Satellite Centers will be selected for collaborations in specific studies to expand patient enrollment in future studies.

In conclusion, there is clearly a need to develop clinical infrastructure to better define the natural history and course of pediatric PH, to develop new strategies to identify at-risk patients early in their course, and to establish novel approaches to diagnose, monitor disease progression and treat children with PH. The establishment of an interactive network of multidisciplinary teams from several pediatric PH centers may provide an effective mechanism for advancing the care of children with PH.

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PPHNet Organizational Chart

Fig. 1.
PPHNet organizational chart.

Table 1

Critical differences between pediatric and adult pulmonary hypertension.

<ul style="list-style-type: none">• Intrinsically linked to developmental biology of the cardiopulmonary system;• Timing of vascular injury during susceptible periods of adaptation and development (e.g., hyperoxia, hypoxia, inflammation, infection, hemodynamic stress, others);• Role of vascular disease beyond PH alone (e.g., distal lung growth as in BPD, CDH, lung hypoplasia)• Differences in genetics, vascular function and structure, and responsiveness to therapeutic strategies;• Developmental differences in drug metabolism, pharmacokinetics and pharmacodynamics;• Additional importance of “preventive” strategies as well as approaches targeting “reverse remodeling.”• Maturational changes in right and left ventricular function.

Table 2

Gaps in clinical science and translational research in pediatric PH.

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- Define *natural history*, *epidemiology* of pediatric PH and related pulmonary vascular diseases (PVD);
 - Link well-defined phenotypes with *biomarker*, *genetic*, *epigenetic* and *gene–environment* studies;
 - Develop and apply known or *novel biomarkers* to predict clinical course and monitor disease activity;
 - Develop better *outcome measures*: molecular, biochemical, cellular, physiologic (exercise, vasoreactivity, and assessments of distal lung growth), right heart function and lung vascular imaging;
 - Study the *pharmacology* of drug therapy: risk/benefit assessments;
 - Perform *pharmacogenetic studies* to predict response to therapy;
 - Plan and perform multicenter randomized clinical trials (MRCTs)
 - Develop clinical care guidelines and establish standards for PH centers;
 - Establish “Personalized Medicine” approaches to pediatric PH.
-

Table 3

Current barriers to clinical care of children with pulmonary hypertension.

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- Limited understanding of unique, disease-specific mechanisms in pediatric pulmonary hypertension
 - Heterogeneity of conditions
 - Lack of organized, multidisciplinary care
 - Small number of patients at each center
 - Lack of hard clinical endpoints for assessing clinical course and response to interventions
 - Anecdotal-based strategies, often based on adult data
 - Absence of systematic, centralized database
 - Lack of infrastructure for multicenter trials
 - Lack of resources to coordinate collaborations and to plan group projects
 - Disincentives for and lack of support of pharmaceuticals to support pediatric PH studies
-

Table 4

Priorities for clinical research and care of children with pulmonary hypertension.

<ul style="list-style-type: none">• Establishing strong multidisciplinary, translational PH programs at leading academic medical centers• Network of large clinical programs for<ul style="list-style-type: none">– Establishing industry-independent databases and tissue banks;– Developing clinical care guidelines– Defining prevalence, natural history of diseases– Performing well-planned, sufficiently powered, multicenter, randomized trials– Performing comparative efficacy research (CER) studies• Developing “Personalized Medicine” approaches linking phenotyping with biomarkers, genetic and genomic approaches, pharmacogenomics;• Development of novel, disease-specific and age-appropriate endpoints and therapies.• Maintain strong interactions with basic science advances to allow for more rapid translation of “bench to bedside” strategies

Table 5

Key components of comprehensive pediatric pulmonary hypertension centers.

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- Multidisciplinary
 - Inpatient consultation
 - Outpatient consultation
 - Long-term follow-up
 - Pro-active care
 - Outcomes assessments (database)
 - Patient advocacy
 - Clinical research
 - Education and training
 - Links with basic research
-

Table 6

PPHNet: mission statement.

<ul style="list-style-type: none">• To improve the health, quality of care and outcomes of children with pulmonary hypertension by enhancing collaborations among centers, in order to develop and apply novel strategies for early recognition and initiation of treatment to reverse, prevent or slow the progression of disease.• To promote and conduct collaborative activities in research, education and training that leads to the development of effective therapies and their successful application.
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Table 7

Overall goals of PPHNet.

<ul style="list-style-type: none"> • Develop and apply evidence-based approaches to pediatric PH and related pulmonary vascular diseases • Develop collaborative multidisciplinary network of leading, well-established clinical pediatric PH centers; • Plan short-term and long-term projects for addressing novel therapies to pediatric PH • Create longitudinal database to define the natural history of diseases, benchmark therapies and provide basis for prospective studies <ul style="list-style-type: none"> – Natural history studies – Biomarkers, genetics, genomics to identify novel mechanisms of disease or predict responses to therapy (“Personalized Medicine”) – Interventional trials – Perform comparative efficacy response studies between known PH therapies
<p>Establish clinical care guidelines to define PH care (centers, diagnostics, endpoints, therapies, others)</p> <ul style="list-style-type: none"> • Education and training • Advocacy programs • Dissemination of new knowledge to the community through seminars, publications, educational programs.

Table 8

PPHNet: core centers, site investigators and external advisory board.

University of Colorado Denver
<ul style="list-style-type: none"> • Steven Abman, MD • Dunbar Ivy, MD • John Kinsella
Boston Children's Hospital
<ul style="list-style-type: none"> • Tom Kulik, MD • Mary Mullen, MD
Children's Hospital of Philadelphia
<ul style="list-style-type: none"> • Brian Hanna, MD
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