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Persistent Challenges in Pediatric Pulmonary Hypertension

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Pulmonary hypertension and related pulmonary vascular diseases cause significant morbidities and high mortality and present many unique challenges toward improving outcomes in neonates, infants, and children. Differences between pediatric and adult disease are reflected in controversies regarding etiologies, classification, epidemiology, diagnostic evaluations, and therapeutic interventions. This brief review highlights several key topics reflecting recent advances in the field and identifies persistent gaps in our understanding of clinical pediatric pulmonary hypertension. CHEST 2016; 150(1):226-236

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Pulmonary hypertension (PH), defined as an abnormal elevation of pulmonary arterial pressure, causes significant morbidity and mortality in the pediatric population. Although there are similarities in etiology and disease pathogenesis between pediatric and adult forms of PH, many cardiopulmonary and systemic diseases associated with PH are unique to neonates, infants, and children. There has been growing recognition of the important impact of PH after premature birth and in the settings of developmental lung diseases, genetic syndromes, and diverse factors that reflect interactions between prenatal and postnatal influences (Fig 1). PH-related hospitalizations of children are increasing, which likely reflect improved recognition and awareness of the role of PH in diverse settings, or perhaps, an actual increase in the incidence of disease.[1,2] In this review, we briefly discuss important challenges in the definition, classification, diagnosis, evaluation, and treatment of children with PH, highlighting differences from adult PH.

Definition

PH in adults refers to an increased mean pulmonary artery pressure (PAP) > 25 mm Hg. Pulmonary arterial hypertension (PAH) refers specifically to precapillary pathology and is defined by mean PAP > 25 mm Hg with a normal pulmonary artery wedge pressure of 15 mm Hg or less. However, PAP must

ABBREVIATIONS: BPD = bronchopulmonary dysplasia; CDH = congenital diaphragmatic hernia; FDA = US Food and Drug Administration; NT-proBNP = N-terminal pro-brain-type natriuretic peptide; PAH = pulmonary arterial hypertension; PAP = pulmonary artery pressure; PH = pulmonary hypertension; PPHN = persistent pulmonary hypertension of the newborn; PVR = pulmonary vascular resistance; PVRI = Pulmonary Vascular Research Institute; TAPSE = tricuspid annular plane systolic excursion; WHO = World Health Organization

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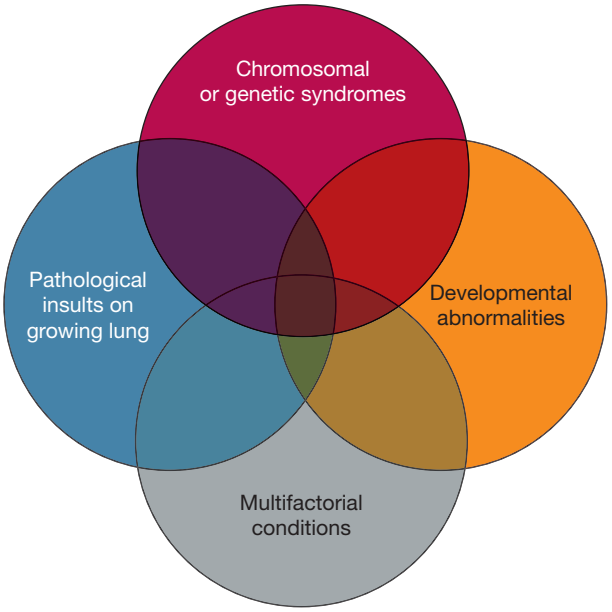

Figure 1 – *Venn diagram illustrating the heterogeneity and multifactorial elements in pediatric pulmonary hypertensive vascular disease. Insults on the growing lung may be due to ventilator-induced lug injury. Developmental abnormalities may include conditions such as bronchopulmonary dysplasia. Examples of multifactorial conditions may include aspiration or congenital heart disease. (From del Cerro et al.[6])*

progressively decline during the first few months after birth from values that match systemic arterial levels in utero to values of mean PAP that are similar to adults. Thus, the definition of PH in children is the same as in adults beyond 3 months of age at sea level.[3] Failure of the normal transition of the pulmonary circulation at birth leads to sustained elevation of PAP to near systemic levels and causes the syndrome of persistent pulmonary hypertension of the newborn (PPHN) (Table 1). PPHN is associated with diverse disorders, such as meconium aspiration, congenital diaphragmatic hernia, and others, and is characterized by extrapulmonary right-to-left shunting of blood across the patent foramen ovale and/or ductus arteriosus, causing severe hypoxemia.[4] Although pulmonary vascular resistance (PVR) is not included in the Nice classification system per se,[5] it is included in the pediatric Panama classification because of the greater prevalence of congenital heart diseases, which have vastly different outcomes depending on PVR but with a similar elevation of mean PAP.[6] Although diagnostic criteria for PAH are the same in adults and children, some question the use of a mean PAP > 25 mm Hg in infants or young children, whose systemic BP is significantly lower than that of an adult. Many pediatric practitioners use indexed PVR > 3 units $\times$ m^2 as well as a ratio of PVR to systemic vascular resistance > 0.5 in determining the presence of pediatric PAH.[3,7]

TABLE 1] Nice Classification of PH

1. Pulmonary arterial hypertension
1.1 Idiopathic
1.2 Heritable (1.2.1 BMPR2, 1.2.2 ALK-1, ENG, SMAD9, CAV1, KCNK3, 1.2.3 unknown)
1.3 Drug- and toxin-induced
1.4 Associated (1.4.1 Connective tissue disease, 1.4.2 HIV infection, 1.4.3 Portal hypertension, 1.4.4 Congenital heart diseases, 1.4.5 Schistosomiasis)
1′ Pulmonary veno-occlusive disease/pulmonary capillary hemangiomatosis
1″ Persistent PH of the newborn
2. PH from left heart disease
2.1 Left ventricular systolic dysfunction
2.2 Left ventricular diastolic dysfunction
2.3 Valvular disease
2.4 **Congenital/acquired left heart inflow/ outflow tract obstruction, congenital cardiomyopathies**
3. PH from lung disease and/or hypoxia
3.1 COPD
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental lung diseases
4. Chronic thromboembolic PH
5. PH from unclear multifactorial mechanisms
5.1 Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Other: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, **segmental PH**

Pediatric-related revisions to the WHO classification system are highlighted in boldface type. PH = pulmonary hypertension. (From Simonneau et al.[5])

Classification

Classification of pediatric PH is challenging because of the many diseases associated with PH across the life span, ranging from the fetus to the onset of adulthood. The World Health Organization (WHO)/World Symposium and Panama classifications have been applied to children with PH; however, controversies persist regarding the relative utility of each system.[6,7] The WHO Symposium in 1998 at Evian originally established a classification schema that described five