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A review of pediatric pulmonary hypertension with new guidelines

Serdar KULA[1,*], Ayhan PEKTAŞ[2]
[1]Department of Pediatric Cardiology, Faculty of Medicine, Gazi University, Ankara, Turkey
[2]Department of Pediatric Cardiology, Faculty of Medicine, Afyon Kocatepe University, Afyon, Turkey

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Abstract: This study aims to review pediatric pulmonary hypertension (PH) by comparing the guidelines of the European Society of Cardiology (ESC)/European Respiratory Society (ERS), the American Heart Association (AHA)/American Thoracic Society (ATS), and the European Pediatric Pulmonary Vascular Disease Network (EPPVDN). All three sets of guidelines define PH as having a mean pulmonary artery pressure of ≥25 mmHg and accept the validity of the World Health Organization (WHO) classification system. Every child with a high index of suspicion for PH should undergo an initial work-up of chest X-rays, electrocardiography, and echocardiography. The AHA/ATS guidelines emphasize the necessity of cardiac catheterization and hemodynamic studies. As mentioned in the AHA/ATS guidelines, the symptoms and tests that can detect PH include right ventricle failure, WHO functional class, syncope, echocardiography findings, hemodynamic data, brain natriuretic peptide (BNP)/N-terminal pro-BNP, the 6-min walk test, and cardiopulmonary exercise tests. The EPPVDN guidelines refer to positive acute vasoreactivity test results and growth as risk factors. All three guidelines highlight the importance of treating and following affected children in specialized centers and recommend calcium channel blockers as a first-line treatment in children (aged >12 months) who have a positive acute vasoreactivity test. Children with PH have distinct clinical features. In order to overcome the controversies related to the optimal management of pediatric PH, well-designed clinical studies should be carried out on a large cohort of affected children.

Key words: Child, classification, guideline, pulmonary hypertension, risk, treatment

1. Introduction

Pulmonary hypertension (PH) has traditionally been considered within the context of adult diseases. Because of this, the study of pediatric disease has been limited and complicated by many unanswered questions throughout the long history of PH.

The literature consists of many randomized controlled studies that have been conducted on adults with PH, but pediatric patients have either been the participants of small-scale studies or they have constituted an insignificant component of the cohort of large-scale studies. Other problems are the inadequacy of monitorization parameters and the lack of clinical studies focusing on treatment regimens. Moreover, the pediatric doses of drugs prescribed for PH are unspecified, and they are usually extrapolated from adult studies (1–4).

The Panama Pediatric Pulmonary Vascular Disease Group was the first to consider the clinical differences between affected children and adults and, therefore, to assess pediatric PH in detail (5). The guidelines from this group included recommendations about the etiological and functional classification of pediatric PH.

Later, the guidelines of the European Society of Cardiology (ESC)/European Respiratory Society (ERS) underlined the necessity for specific schedules for the diagnosis, follow-up, and treatment of affected children (6). Similarly, the American Heart Association (AHA) and the American Thoracic Society (ATS) published new joint guidelines that can be considered the first companion guides for pediatric PH (7). As these joint guidelines were based on expert opinion, the European Pediatric Pulmonary Vascular Disease Network (EPPVDN) created a new set of guidelines that aim to better observe the requirements of pediatric patients (8). This study aims to review pediatric PH by comparing the ESC/ERS, AHA/ATS, and EPPVDN guidelines.

2. Definition

The most widely accepted definition of PH is one based on a mean pulmonary artery pressure (mPAP) of ≥25 mmHg. However, the Pulmonary Vascular Research Institute observed that the definition of pediatric PH should be differentiated from that of adult PH because children and adults have different physiological characteristics. Thus,

* Correspondence: kula@gazi.edu.tr

the concept of pediatric pulmonary hypertensive vascular disease (PPHVD) was developed (5).

According to the guidelines of the ESC/ERS, precapillary PH is defined as the combination of mPAP of ≥25 mmHg, end-expiratory pulmonary artery wedge pressure (PAWP) of >15 mmHg, and pulmonary vascular resistance (PVR) of >3 Wood units (WU). However, this definition is invalid for newborns. Moreover, children with some cardiac pathologies and single ventricle physiology could develop pulmonary vascular disease in the absence of the aforementioned criteria.

The AHA/ATS guidelines provide a more detailed definition based on mPAP of >25 mmHg in infants over the age of 3 months at sea level. The combination of mPAP of >25 mmHg, PAWP of <15 mmHg, and PVR index of >3 $WU.m^2$ is required to describe pulmonary arterial hypertension (PAH). It should be emphasized that the $WU.m^2$ unit has been previously used to define pediatric PH. The necessity of using the $WU.m^2$ unit in the description of pediatric PH has been assessed recently (9). Additionally, the AHA and ATS described pulmonary hypertensive vascular disease as having a transpulmonary gradient of >6 mmHg or a high PVR index in patients with cavopulmonary anastomoses and normal mPAP values.

In May 2016, the EPPVDN revised its definition of PH as having an mPAP of ≥25 mmHg and a PVR index of >3 $WU.m^2$ for biventricular circulation, a mean transpulmonary gradient of >6 mmHg, or a PVR index of >3 $WU.m^2$ for cavopulmonary anastomosis (e.g., Fontan physiology).

3. Classification

The ESC/ERS, AHA/ATS, and EPPVDN guidelines accept the validity of the classification system for pediatric PH put forward by the World Health Organization (WHO) and most recently revised at the Fifth World Symposium for Pulmonary Hypertension, held in Nice, France (Table) (10). Both the AHA/ATS and EPPVDN guidelines stress that more research is needed to approve the validity of the Panama Classification System.

4. Diagnosis

All three guidelines agree with the recommendation that children with PH should be followed and treated in specialized centers as this disease has a complicated pathophysiology. Generally, there is no marked difference between the three guidelines with respect to diagnostic tests and algorithms.

Each patient with a high index of suspicion for PH should undergo an initial workup of chest X-rays, electrocardiography, and echocardiography. The AHA/ATS guidelines expressly emphasize the necessity of cardiac catheterization and hemodynamic studies in clinical diagnosis and monitorization (Figure). The EPPVDN guidelines further analyze cardiac-computed tomography and magnetic resonance imaging (11), transthoracic echocardiography, (12) and cardiac catheterization–hemodynamic studies (13) under separate headings. Different from the AHA/ATS guidelines, the EPPVDN guidelines include different recommendation tables for each of these diagnostic and monitorization methods.

The AHA/ATS guidelines accept the WHO system for functional classification but also indicate that this system has limited value in patients under 8 years of age. On the other hand, the EPPVDN guidelines state that the functional classification system proposed by the Pulmonary Vascular Research Institute requires external validation and correlation with clinical outcomes in children (14).

In accordance with the sophisticated pathogenesis of pediatric PH, both the AHA/ATS and EPPVDN guidelines specifically address genetic defects, congenital heart diseases, acute or chronic pulmonary diseases, and intensive care as underlying causes. What is noteworthy here is that the EPPVDN guidelines consider these underlying causes as independent articles and offer different recommendation tables for each one. That is, the diagnostic and therapeutic algorithms for children with congenital heart disease differ from those established for children with parenchymal lung disease (15–18).

5. Risk evaluation

The ESC/ERS guidelines determine that children with PH should be evaluated differently than adults. This recommendation is based on the findings of Ivy et al. (19) about pediatric PH. In contrast with the ESC/ERS guidelines, the AHA/ATS guidelines do not delineate an "intermediate risk" group. The risk factors identified by the AHA/ATS guidelines consist of right ventricle failure, WHO functional class, syncope, echocardiography findings, hemodynamic data, brain natriuretic peptide (BNP)/N-terminal pro-BNP, the 6-min walk test distance, and cardiopulmonary exercise test results. In addition, the AHA/ATS guidelines use the term "significant increase/worsening" instead of referring to specific values for echocardiographic findings and BNP/N-terminal pro-BNP concentrations.

The AHA/ATS guidelines can be distinguished from the ESC/ERS guidelines in the way they feature the PVR index and PVR/systemic vascular resistance (SVR) among hemodynamic parameters. The EPPVDN guidelines also cite PVR index of >15 $WU.m^2$, mean right atrium pressure (mRAP) of >15 mmHg, and the mPAP/mRAP ratio (rather than the PVR/SVR ratio) as the hemodynamic factors for high risk (mPAP/sPAP > 0.75). The major disparity of the EPPVDN guidelines is the inclusion of an

Table. Classification of pulmonary hypertension (PH).

1. Pulmonary arterial hypertension	
1.1. Idiopathic	
1.2. Heritable	1.2.1. BMPR2 mutation 1.2.2. Other mutations
1.3. Drugs and toxins induced	
1.4. Associated with	1.4.1. Connective tissue diseases 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 and/or pulmonary capillary hemangiomatosis	
1" Persistent pulmonary hypertension of the newborn	
2. Pulmonary hypertension due to 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 2.5. Other	
3. Pulmonary hypertension caused by lung disease or hypoxemia	
3.1. Chronic obstructive pulmonary disease 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 syndromes 3.6. Long-term exposure to high altitudes 3.7. Developmental lung diseases	
4. Chronic thromboembolic disease	
4.1. Chronic thromboembolic pulmonary hypertension 4.2. Other pulmonary artery obstructions	
5. Pulmonary hypertension with unclear or multifactorial mechanisms	
5.1. Hematological disorders	5.1.1. Chronic hemolytic anemia 5.1.2. Myeloproliferative disorders 5.1.3. Splenectomy
5.2. Systemic disorders	5.2.1. Sarcoidosis 5.2.2. Pulmonary histiocytosis 5.2.3. Lymphangioleiomyomatosis
5.3. Metabolic disorders	5.3.1. Glycogen storage diseases 5.3.2. Gaucher disease 5.3.3. Thyroid disorders
5.4. Others	5.4.1. Tumor obstruction 5.4.2. Fibrosing mediastinitis 5.4.3. Chronic renal failure 5.4.4. Segmental pulmonary hypertension

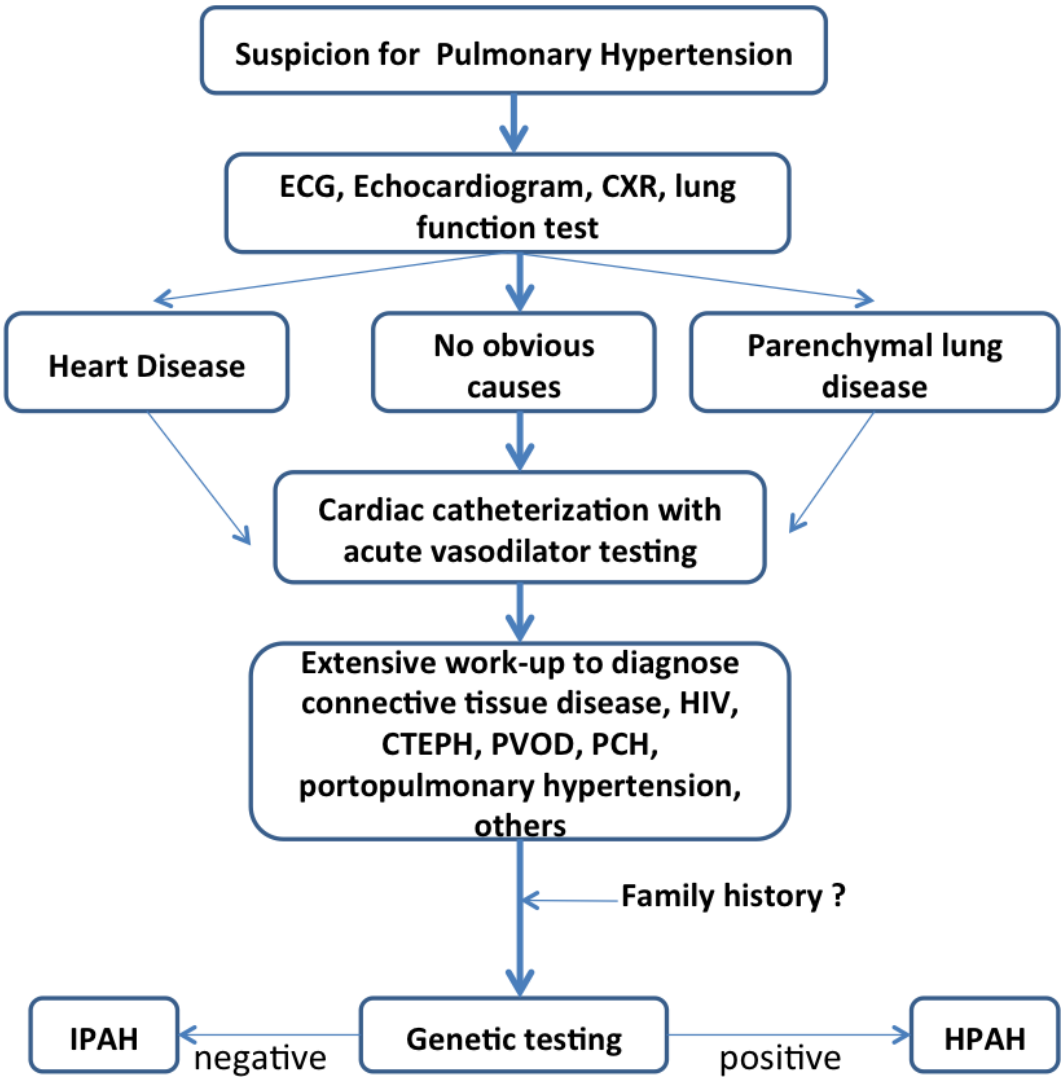

Figure. Generalized diagnostic algorithm for pediatric pulmonary hypertension (PH).
ECG: electrocardiogram; CXR: chest X-ray; CTEPH: chronic thromboembolic pulmonary hypertension; PVOD: pulmonary veno-occlusive disease; PCH: pulmonary capillary hemangiomatosis; IPAH: idiopathic pulmonary arterial hypertension; HPAH: hereditary pulmonary arterial hypertension.

acute vasoreactivity test as a factor for low risk. It can be concluded that the PVR/SVR or mPAP/mRAP ratios have more significance than that of a designated PVR index or mRAP values. The reason is that utilization of such ratios would narrow the margin of error because of the limitations of the Fick principle.

Another point to be taken into account is the utilization of the 6-min walk test in the AHA/ATS guidelines (lower risk vs. higher risk: >500 m vs. <300 m). The 6-min walk test is usually regarded as an independent factor for the morbidity and mortality of children over the age of 7 (20). The values designated for the 6-min walk test vary with respect to age and anthropometric measurements. This is why it would be more appropriate to evaluate each pediatric patient individually by using 6-min walk test percentiles (21). On the contrary, the EPPVDN guidelines refer to growth as a risk factor. Because PH is a chronic and progressive disease, it would be prudent to expect its hazardous effects on growth and development. Therefore, listing growth as a risk factor would be a rational approach.

6. Treatment

All three guidelines have similar recommendations for the treatment of PH. The guidelines indicate calcium channel blockers as the first-line treatment in children (aged over 12 months) with a positive acute vasoreactivity test. As for the management of children with a negative acute vasoreactivity test, the EPPVDN guidelines differ

from the AHA/ATS guidelines in two ways. First, the EPPVDN guidelines mention that combination treatment is preferred in the early management of low risk patients in the WHO functional class II and III categories. Second, the EPPVDN guidelines qualify the Potts shunt and atrial septostomy as decompression procedures before lung transplantation.

The AHA/ATS and EPPVDN guidelines have different recommendations for the management of children who have congenital heart disease-associated PH. Both sets of guidelines recommend that children with a PVR index of <6 WU.m^2 and a PVR/SVR ratio of <0.3 can undergo surgery after a thorough preoperative examination.

The AHA/ATS guidelines point out that an acute vasoreactivity test should be performed in all children with congenital heart diseases who have a PVR index of >6 WU.m^2 and a PVR/SVR ratio of >0.3. The guidelines also indicate that surgery can be undertaken in children with a positive acute vasoreactivity test after careful assessment (fenestration if needed) is made. In the event that the acute vasoreactivity test has a negative result, these children should be reassessed after initiation of specific treatment for PH.

The EPPVDN guidelines categorize children with congenital heart diseases who show a PVR index of >6 WU.m^2 and a PVR/SVR ratio of >0.3 into two groups: children with a PVR index range of 6–8 WU.m^2 and a PVR/SVR ratio of 0.3–0.5 (gray zone), and children with a PVR index of >8 WU.m^2 and a PVR/SVR ratio of >0.5. Since the EPPVDN guidelines do not offer different therapeutic options for these two groups, it is uncertain why such a categorization is mentioned.

Both the AHA/ATS and EPPVDN guidelines define the management of intensive care-associated PH as a distinct clinical entity. Moreover, the EPPVDN guidelines offer differential treatment algorithms for persistent PH in newborns and bronchopulmonary dysplasia or neonatal chronic lung disease-related PH (14).

7. General approach

The ESC/ERS, AHS/ATS, and EPPVDN guidelines have undertaken similar measures for the vaccination, physical training, transportation, and support of affected children.

8. Conclusion

In 2011, the Panama Pediatric Pulmonary Vascular Disease Group was the first to specifically investigate issues surrounding children with PH. Since then, there has been pronounced progress in the field of pediatric PH in several ways. First, it has been well established that children with PH have distinct clinical features. Second, the ESC/ERS, AHA/ATS, and EPPVDN guidelines focusing on pediatric PH were published within a 1-year period. All three sets of guidelines have highlighted the importance of performing the management and follow-up of affected children in specialized centers. Third, the recommendations of the aforementioned guidelines are usually based on expert opinions rather than valid scientific data. In order to overcome controversies surrounding the optimal management of pediatric pulmonary hypertension, well-designed clinical studies should be carried out on a large cohort of affected children.

References

1. Badesch DB, Raskob GE, Elliott CG, Krichman AM, Farber HW, Frost AE, Barst RJ, Benza RL, Liou TG, Turner M et al. Pulmonary arterial hypertension: baseline characteristics from the REVEAL Registry. Chest 2010; 137: 376-387.
2. Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, Yaici A, Weitzenblum E, Cordier JF, Chabot F et al. Pulmonary arterial hypertension in France: results from a national registry. Am J Respir Crit Care Med 2006; 173: 1023-1030.
3. Abman SH, Raj U. Towards improving the care of children with pulmonary hypertension: The rationale for developing a Pediatric Pulmonary Hypertension Network. Prog Pediatr Cardiol 2009; 27: 3-6.
4. Barst RJ, Ertel SI, Beghetti M, Ivy DD. Pulmonary arterial hypertension: a comparison between children and adults. Eur Respir J 2011; 37: 665-677.
5. Cerro MJ, Abman S, Diaz G, Freudenthal AH, Freudenthal F, Harikrishnan S, Haworth SG, Ivy D, Lopes AA, Raj JU et al. A consensus approach to the classification of pediatric pulmonary hypertensive vascular disease: Report from the PVRI Pediatric Taskforce, Panama 2011. Pulm Circ 2011; 1: 286-298.
6. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Respir J 2015; 46: 903-975.

7. Abman SH, Hansmann G, Archer SL, Ivy DD, Adatia I, Chung WK, Hanna BD, Rosenzweig EB, Raj JU, Cornfield D et al. Pediatric pulmonary hypertension: Guidelines from the American Heart Association and American Thoracic Society. Circulation 2015; 132: 2037-2099.

8. Hansmann G, Apitz C, Abdul-Khaliq H, Alastalo TP, Beerbaum P, Bonnet D, Dubowy KO, Gorenflo M, Hager A, Hilgendorff A et al. Executive summary. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. Heart 2016; 102 (Suppl. 2): ii86-ii100.

9. Kula S, Göktaş T. Wood units · m2 or Wood units/m2: does it matter? Anatol J Cardiol 2016; 16: 360.

10. Simonneau G, Robbins IM, Beghetti M, Channick RN, Delcroix M, Denton CP, Elliott CG, Gaine SP, Gladwin MT, Jing ZC et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2009; 54 (Suppl.): S43-S54.

11. Latus H, Kuehne T, Beerbaum P, Apitz C, Hansmann G, Muthurangu V, Moledina S. Cardiac MR and CT imaging in children with suspected or confirmed pulmonary hypertension/pulmonary hypertensive vascular disease. Expert consensus statement on the diagnosis and treatment of pediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. Heart 2016; 102 (Suppl. 2): ii30-ii35.

12. Koestenberger M, Apitz C, Abdul-Khaliq H, Hansmann G. Transthoracic echocardiography for the evaluation of children and adolescents with suspected or confirmed pulmonary hypertension. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and D6PK. Heart 2016; 102 (Suppl. 2): ii14-ii22.

13. Apitz C, Hansmann G, Schranz D. Hemodynamic assessment and acute pulmonary vasoreactivity testing in the evaluation of children with pulmonary vascular disease. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. Heart 2016; 102 (Suppl. 2): ii23-ii29.

14. Lammers AE, Adatia I, Cerro MJ, Diaz G, Freudenthal AH, Freudenthal F, Harikrishnan S, Ivy D, Lopes AA, Raj JU et al. Functional classification of pulmonary hypertension in children: Report from the PVRI pediatric taskforce, Panama 2011. Pulm Circ 2011; 1: 280-285.

15. Pattathu J, Gorenflo M, Hilgendorff A, Koskenvuo JW, Apitz C, Hansmann G, Alastalo TP. Genetic testing and blood biomarkers in paediatric pulmonary hypertension. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. Heart 2016; 102 (Suppl. 2): ii36-ii41.

16. Hilgendorff A, Apitz C, Bonnet D, Hansmann G. Pulmonary hypertension associated with acute or chronic lung diseases in the preterm and term neonate and infant. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. Heart 2016; 102 (Suppl. 2): ii49-ii56.

17. Kaestner M, Schranz D, Warnecke G, Apitz C, Hansmann G, Miera O. Pulmonary hypertension in the intensive care unit. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. Heart 2016; 102 (Suppl. 2): ii57-ii66.

18. Kozlik-Feldmann R, Hansmann G, Bonnet D, Schranz D, Apitz C, Michel-Behnke I. Pulmonary hypertension in children with congenital heart disease (PAH-CHD, PPHVD-CHD). Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. Heart 2016; 102 (Suppl. 2): ii42-ii48.

19. Ivy DD, Abman SH, Barst RJ, Berger RM, Bonnet D, Fleming TR, Haworth SG, Raj JU, Rosenzweig EB, Schulze Neick I et al. Pediatric pulmonary hypertension. J Am Coll Cardiol 2013; 62: 117-126.

20. Benza RL, Miller DP, Gomberg-Maitland M, Frantz RP, Foreman AJ, Coffey CS, Frost A, Barst RJ, Badesch DB, Elliott CG et al. Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). Circulation 2010; 122: 164-172.

21. Kanburoglu MK, Ozdemir FM, Ozkan S, Tunaoglu FS. Reference values of the 6-minute walk test in healthy Turkish children and adolescents between 11 and 18 years of age. Respir Care 2014; 59: 1369-1375.