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Decreased Mortality of Pulmonary Arterial Hypertension in Duchenne Muscular Dystrophy and Down Syndrome

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Decreased Mortality of Pulmonary Arterial Hypertension in Duchenne Muscular
Dystrophy and Down Syndrome

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ABSTRACT

The genetic cause of significant disorders like Down syndrome (DS) and Duchenne muscular dystrophy (DMD) is well documented. Pulmonary arterial hypertension (PAH), a co-morbid condition, is tied to mortality among these groups. If undetected or untreated, in DS, this condition can lead to complications with coronary and lung disease later in life. If undetected or untreated in DMD it can hasten the inevitable prognosis of the disease. Individuals with the ability to communicate their symptoms and actively participate in treatment are at an advantage with subsequent benefit. DS and DMD significantly decrease physical ability and communication capacity.

Genetic research has allowed for earlier identification of, or predisposition for, the development of PAH. Work has also progressed toward manipulation at the genetic level to decrease the severity and even eradicate the cardiopulmonary disorder. This information is beginning to be applied in treatment for individuals with PAH. The purpose of this scholarly project is to identify the research, prediction methods and treatment of PAH in individuals with Duchenne muscular dystrophy (DMD) and Down syndrome (DS) as it relates to decreased mortality or increased life expectancy among those groups. The results showed significant gains in the understanding of PAH, DS and DMD individually. There was little evidence of research focusing on PAH as it pertains particularly to DS or DMD. Original studies were sought as a priority in the development of this work. Some meta-analysis studies were included to further develop the expert opinion recommendations for treatment. Keyword searches and sub-heading searches were performed within the PUBMED and CLINAHL databases.

Keywords: Pulmonary Arterial Hypertension, Duchenne muscular dystrophy, Down syndrome, Congenital Heart Defects, Pulmonary Hypertension.

Introduction

The exchange of carbon dioxide and oxygen at the alveolar level is an intricate process. An exacting balance is struck within the cardiopulmonary circuit to maintain pH, temperature and pressure. The human body's ability to buffer such imbalance is extraordinary. Most problems that arise can be corrected with minor physiologic changes to the system. Unfortunately, some imbalances result in workload discrepancies for constituents of the system. One such discrepancy leads to increased pressure in the pulmonary arteries.

Pulmonary arterial hypertension (PAH) is one of five forms of pulmonary hypertension (Tonelli et al., 2013). PAH can take on one of several forms. The 5th World Symposium on Pulmonary Hypertension, that was held in Nice, France, February 27 to March 1, 2013, identifies four specific types of PAH: Idiopathic, Familial, Drug or Toxin Induced and Associated. Idiopathic PAH (IPAH) causes are unknown (Saji, 2014). Familial PAH (FPAH) has a genetic cause (Chew, Loyd & Austin, 2017). Drug or Toxin Induced PAH is a growing concern (Peacock, Murphy, McMurray, Baballero & Stewart, 2007). The most common type of PAH, associated (APAH), and occurs along with or by other medical conditions (Chew et al., 2017)

Recent studies have provided insight in the diagnosis and screening for both familial and associated pulmonary arterial hypertension. Research has led to earlier diagnosis of and screening for PAH (Tonelli et al., 2013). Unfortunately, co-morbid and/or exacerbating conditions often dictate patient outcome (Tonelli et al., 2013). Many disorders of the body cause APAH. Two genetic conditions that have co-morbid

occurrence of APAH are Down syndrome and Duchenne muscular dystrophy. Both of these disorders have high mortality rates.

Statement of the Problem

Identifying the specific underlying pathophysiology and etiology of PAH when associated with DMD and DS is vitally important to treatment. It is also important to understand the options with proven, evidenced-based modalities particular to co-morbid conditions can have positive influence on patient outcomes from increased life expectancy to improved quality of life. Reviewing what research has been completed helps deepen the understanding of the direction future investigation in PAH is taking.

Statement of the Research Questions

What is the correlation between genetic disorders like DMD and DS with increased incidence of PAH? What has current and existing research shown in the understanding of pulmonary arterial hypertension? What is the recommended, evidence based treatment modality for PAH specific to DMD and DS? Among individuals with Duchenne muscular dystrophy and Down syndrome with co-morbid pulmonary arterial hypertension (PAH) has early recognition and treatment through genetic discovery, lead to a statistically significant increase in life expectancy versus previously undiagnosed or unrecognized PAH?

REVIEW OF LITERATURE

Research Methods

In finding sources for the topic three medical research databases were used. PubMed, Medscape and CINAHL provided for ease of search term manipulation and consistent operation. Of the three, PubMed and CINAHL resulted in the majority of

found sources. The search for sources began with an article entitled “Cardiopulmonary Support in Duchene Muscular Dystrophy,” by J. Finsterer, 2006, *Lung*, 184(4), p. 205-215. With the exception of this article, all sources were published within the last ten years. Initial keyword searches helped develop more focused subject headings later on. The initial keyword searches included terms like: pulmonary hypertension and Duchene muscular dystrophy, pulmonary hypertension and Down syndrome, Duchenne muscular dystrophy and cause of death, Down syndrome and cause of death. From the keyword search 4-5 articles were chosen and the subject headings were scrutinized to develop a more specific search. The subject heading search used terms like: BMPR2 and Duchene and congenital heart disease, pulmonary arterial hypertension and congenital heart disease, advanced therapy and Duchenne, therapies and Down syndrome, Down syndrome and nitric oxide and pulmonary hypertension, trisomy 21 and congenital heart defect, epigenetic and pulmonary arterial hypertension, pulmonary hypertension and DNA methylation, Down syndrome and congenital heart disease, pulmonary hypertension and BMPR2. From these searches, 68 articles were found. Articles were scrutinized for reputation of publication and pertinence to topic. Of the 68, 20 were chosen. 26 articles were excluded based on sample sizes less than 20 participants. 31 articles were excluded as they were meta-analysis involving information from greater than 30 years ago. Eleven studies on pulmonary hypertension related to genetic disorders were excluded as they were not specific to PAH. The remaining 20 articles provide credence and deeper understanding toward the research topic. Three additional resources were added that included information that is greater than ten years old, as they provide insight into the foundation of understanding as well as perspective toward the advances

that have occurred.

Pathophysiology of Pulmonary Arterial Hypertension (PAH):

In the normal cardiopulmonary cycle, de-oxygenated blood is pumped by the right ventricle of the heart to the lungs through the pulmonary arteries. Pressure in the pulmonary arteries is maintained at an average of 25 mmHg (Elliott, 2013). This force is necessary to support gas exchange between the capillaries and alveoli of the lungs. The pressure in the pulmonary arteries will rise in order to overcome any force working against it. When pressure chronically exceeds this average, undue stress is placed on the heart often resulting in right-sided heart failure (Tonelli et al., 2013).

PAH is a disease of vascular tissue of the pulmonary system. The disease progresses rapidly. It is defined hemodynamically as a mean arterial pressure (mPAP) \geq 25 mmHg and pulmonary capillary wedge pressure (PCWP) of \leq 15 mm Hg. PAH is characterized by destructive vascular changes that include: inflammation, vasoconstriction, cell proliferation, hypertrophy and (in severely symptomatic patients) formation of plexiform lesions (Archer, Weir & Wilkins, 2010). Progression of these structural changes eventually leads to right ventricular strain and dysfunction.

Within the pulmonary vasculature, three pathways that are known to be involved in pulmonary arterial hypertension include: endothelin, nitric oxide and prostacyclin. These pathways play instrumental roles in the regulation of vascular tone.

Endothelin, a signaling peptide, is an important component in the progression of PAH (Archer et al., 2010). In normal physiology, circulating endothelin helps maintain normal vascular tone. In PAH, levels are elevated in the blood stream and the capacity to clear endothelin from the circulation is reduced. Endothelin exerts its effects by

activating two distinct receptors, endothelin A (ETA) and endothelin B (ETB) (Archer et al., 2010). These receptors mediate the pathophysiologic role of endothelin in PAH. In normal physiology, endothelial cells express only the ETB receptor and smooth muscle cells express both receptors. ETA receptors on smooth muscle cells primarily mediate vasoconstriction and cellular proliferation. In PAH, excessive stimulation of ETA receptors is thought to cause vasoconstriction, cell proliferation and hypertrophy (Archer et al., 2010). ETB receptors, located on the endothelial cells, mediate endothelin dependent vasodilation. On smooth muscle cells these receptors mediate vasoconstriction. It is hypothesized that under pathologic conditions, smooth muscle cell vasoconstriction predominates due to down regulation of ETB on endothelial cells and up regulation on smooth muscle cells and the vasodilating response decreases and the vasoconstrictive response prevails.

Nitric oxide (NO) is a diatomic gas that plays an important role in cell signaling which stimulates enzyme activity in the vasculature. Nitric oxide is a vasodilator that also inhibits platelet aggregation, thrombosis and inflammation. Under normal conditions, nitric oxide is produced continuously in the vascular endothelium. Nitric oxide diffuses into vascular smooth muscle cells where it binds to and activates guanylate cyclase stimulating the synthesis of cGMP, a second messenger for signaling smooth muscle relaxation and inhibiting cellular proliferation (Archer et al., 2010). Rising levels of cGMP mediate the effects of nitric oxide. In PAH, levels of nitric oxide synthase are decreased, promoting vasoconstriction and cellular proliferation in vascular smooth muscle cells (Pietra et al., 1989). The availability of nitric oxide is also affected by the phosphodiesterase type-5 (PDE-5) enzyme, which degrades cGMP in vascular smooth

muscle cells and counteracts the vasodilator effects set in motion by nitric oxide.

Inhibition of PDE-5 can block this break down of cGMP (Pietra et al., 1989).

Prostacyclin is the main arachadonic acid metabolite of vascular endothelial and smooth muscle cells (Archer et al., 2010). This potent vasodilator plays a key role in maintaining vascular tone. Prostacyclin is produced in endothelial cells through the action of prostacyclin synthase. Prostacyclin binds to prostaglandin receptors located on endothelial and smooth muscle cells leading to a cascade that signals adenylate cyclase to produce cAMP. The second messenger, cAMP inhibits unnecessary platelet aggregation and also leads to relaxation of the underlying vascular smooth muscle cells (Archer et al., 2010). In PAH, prostacyclins are reduced. Reduced levels of prostacyclin lead to deficient dilatory and anti-proliferative effects. The addition of prostacyclin has been shown to play a pivotal role in the management of PAH (Archer et al., 2010).

PAH may be heritable or idiopathic, but people with a wide range of conditions including those with connective tissue diseases or congenital heart disease are at greater risk of developing PAH (Pietra et al., 1989). As PAH progresses pulmonary vasculature resistance increases and cardiac output decreases, which may develop into a severe limitation of a patient to perform their daily activity. Patients with PAH should be carefully monitored at regular intervals. The mean time from symptom onset to diagnosis is 2.8 years and left untreated patients with this frequently misdiagnosed rapidly progressing have an estimated median survival rate of only 2.8 years (Peacock et al., 2007). Prompt intervention in PAH is critical.

FPAH and APAH (inclusive of Down syndrome and Duchenne muscular dystrophy) have specific causes for the increase of arterial pressure. FPAH results from

tightening and/or hardening of the walls of the pulmonary arteries due to inherited genetic traits (Vis et al., 2009). In the case of Down syndrome congenital heart defects and the structure of the pulmonary vascular wall increase the pressure (Kim, Ryan, Marsboom & Archer, 2011). APAH related to Duchenne muscular dystrophy results from wasting of striated muscle leading to frequent pneumonia and pulmonary edema (Saji, 2014).

From May of 2007 to December of 2008, 704 patients with congenital heart defects were studied to identify independent risk factors of PAH in CHD. The study included 319 males and 385 females with a median age of 5 years. The causes included atrial septal defect (n = 185), ventricular septal defect (VSD, n = 452), patent ductus arteriosus (PDA, n = 48) and a combinations of the above lesions (n = 19) and 280 (39.8%) CHD patients had PAH. Logistic regression analysis revealed that age, systemic artery systolic blood pressure, VSD, PDA and combined lesions were independent risk factors of PAH in CHD (Li et al., 2014).

Cause of Familial Pulmonary Arterial Hypertension (FPAH):

Also known as heritable pulmonary hypertension (HPAH), FPAH is an example of gene mutation with reduced (Ma et al., 2013), (Elliott, 2013) or incomplete (Vis et al., 2009) penetrance. Early studies found that the expression of the autosomal dominant gene mutation resulted in approximately 20% of individuals developing PAH (Vis et al., 2009). The mutation of the gene in question, bone morphogenetic receptor type 2 (BMP2), was present in all individuals that developed PAH across studies (Elliott, 2013). Among the test groups females were twice as likely to develop PAH suggesting sex influence of the disorder (Vis et al., 2009). Research published as recently as 2013

suggest an epistatic effect of BMPR2 mutation on potassium channel subfamily K, member 3 (KCNK3) (Ma et al., 2013) and TGF-Beta (single pass serine/threonine kinase) receptors (Vis et al., 2009). The result would be potassium and calcium channelopathy of smooth muscle respectively (Ma et al., 2013), (Vis et al., 2009). Inotropic, *squeezing*, of the smooth muscle lining the arteries increases as a result of intracellular and extracellular ion imbalance.

Additional research has focused on epigenetic mechanisms that influence FPAH. Modification of gene function or phenotypic expression without mutation in DNA is the definition of epigenetics (Kim et al., 2011). Two areas of study focus on epigenetic consequence of enzyme production. The first effect centers on the formation of superoxide dismutase. This enzyme changes radicals created during cellular respiration to be broken into molecular oxygen or hydrogen peroxide (Xu, Cheng & Du, 2011). Without appropriate function of superoxide dismutase cellular respiration byproducts result in significant cell damage particular to smooth muscle cells of arteries (Xu et al., 2011). The second epigenetic effect involves the formation of nitric oxide synthase (Huang, Liang, Zhao, Wu & Zhang, 2013). Production of nitric oxide from the catalyst of L-arginine allows for appropriate control of vascular control and airway tone (Xu et al., 2011).

Cause of Associated Pulmonary Arterial Hypertension (APAH) related to Down syndrome and Duchenne muscular dystrophy:

Down syndrome, also known as Trisomy 21, results in a wide range of physical and physiological abnormalities. Affected individuals do not always develop cardiovascular problems. In fact only 45-50% of individuals presenting with Down syndrome have subsequent congenital heart defects (CHD) (Kim et al., 2011). Of those

affected, congenital heart defects are predominantly of the septal wall or of the atrioventricular valve (Li et al., 2012). Neonatal surgery to correct CHD is often necessary (Li et al., 2012). Individuals that do and do not receive surgery for CHD are at high risk of developing PAH (Sailani et al., 2013) as decreased contractile force of the right ventricle affects the pressure in the pulmonary arteries. Septal wall and atrioventricular defects have been related to the expression of two genes. The CRELD1 cysteine-rich with EGF-like domains 1 (CRELD1) gene encodes a protein that may function as a cell adhesion molecule (Xu et al., 2011). Additional studies have reported that the HEY2 (Hes-Related Family BHLH Transcription 2) gene may have an epistatic effect on cardiovascular development (Huang et al., 2013). A study involving twenty individuals with complete AVSD associated with pulmonary hypertension was reported in 2009. Nitric Oxide (NO) and endothelin-1 levels were monitored and compared between twelve patients, at 4 to 8 months of age, with Down syndrome and eight patients, at 4 to 12 months of age, without Down syndrome. The study concluded that when compared to each other individuals with AVSD associated with pulmonary hypertension had no difference in NO or endothelin-1 levels (Saji, 2014). However, individuals with DS did show significant increase in pulmonary vascular resistance and pulmonary artery pressure compared to individuals without DS in the comparison (Saji, 2014). When the individuals with DS and individuals without DS both with ASVD related to pulmonary hypertension were compared to individuals without ASVD related to pulmonary hypertension nitrate and ET-1 levels were significantly higher in the former group (Saji, 2014).

Duchenne muscular dystrophy is a fatal, X-linked disorder (Saji, 2014). Individuals affected by the disease suffer from the loss of striated (skeletal and cardiac) muscle tissue. Resultant inability to move and loss of respiratory muscle effort due to the progression of the disease can cause frequent pneumonia and pulmonary edema. In order to maintain homeostasis the body increases the pressure in the pulmonary arteries. In DMD, gene mutation results in the production of non-functioning dystrophin (López-Hernández et al., 2015). This dystrophin protein is responsible for connecting the muscle fiber skeleton to the surrounding structures within the muscle cell (Finsterer, 2006). A study published in 2004 showed strong evidence that NO production was significantly decreased in individuals with DMD. In the study, thirty-one DMD patients with an average age of 21.87 years, were compared with twenty-nine patients with other neuromuscular disorders average age 40.35 years, along with eleven healthy controls average age 30.64 years (Kasai et al., 2004). Specifically excluding patients taking nitrate based medications and patients with active infections the study measured nitrite/nitrate levels in the blood. The results showed significantly lower NO levels in individuals with DMD than healthy individuals (2.771 ± 2.621 versus 10.405 ± 4.240 gmol/L respectively, $p \leq 0.0001$) (Kasai et al., 2004).

DISCUSSION

Pulmonary arterial hypertension is a complex disorder. Those affected by PAH have high rates of mortality directly connected to the disorder. It is widely accepted that the treatment for PAH is largely supportive of cardiopulmonary symptoms (D'Alto et al., 2013), (Favilli et al., 2015), (Archer et al., 2018). Advances in medical care and treatment have resulted in increased life expectancy for all affected by PAH. Life

expectancy for individuals with co-morbid Down syndrome and PAH has increased over time (Saji, 2014), (Vis et al., 2009), (Weijerman et al., 2008). Quality of life and end stage comfort has improved for individuals with Duchenne muscular dystrophy (Finsterer, 2006), (Yotsukura, 1988), (Lopez-Hernandez et al., 2015). Increases in life expectancy for this chronic yet still fatal condition, increase the need for critical care in hospice and other residential facilities.

What is the correlation between genetic disorders like DMD and DS with increased incidence of PAH?

Pulmonary arterial hypertension is a relatively rare disorder with a prevalence of between 15-50 cases per million (Peacock et al., 2007). As previously noted, pulmonary hypertension takes on one of five groups. The first listed group is pulmonary arterial hypertension (PAH). PAH is further divided into four different sub-types. All too often the true cause of PAH in individuals is unfortunately unknown. When patients present with co-morbid conditions such as Down syndrome and Duchenne muscular dystrophy, one could draw correlations between the common concomitant pathophysiologic processes and the increased likelihood of PAH. Among the four divisions of PAH, associated pulmonary arterial hypertension (APAH) involves the following co-morbidities: connective tissue disease, HIV infection, portal hypertension, congenital heart disease and schistosomiasis (Saji, 2014).

The physical and physiologic changes associated with Down syndrome vary widely. Sadly, congenital heart defects result in an overwhelming number of deaths in individuals diagnosed with Down syndrome. In a 2003 study of 182 children diagnosed with Down syndrome in the Netherlands, 12.2% of subjects died within 12 hours of birth

and an additional 3.67% died within 10 days of birth due to complications of congenital heart defects (Weijerman et al., 2008). Not all individuals with Down syndrome experience congenital heart defects, in fact, 45-50% of the diagnosed population are free from CHD (Kim et al., 2011). A reverse analysis of that statistic would suggest that 50-55% of individuals with Down syndrome do suffer from a form of CHD. The majority of CHD in Down syndrome are related to septal wall and atrioventricular valve defects (Li et al., 2012). The inborn defects of the heart most associated with PAH are coincidentally those of a ventricular septal defect (VSD) or patent ductus arteriosus (PDA) are identified as independent risk factors in PAH. From May of 2007 to December of 2008, 704 patients with congenital heart defects were studied to identify independent risk factors of PAH in CHD. Logistic regression analysis revealed that age, systemic artery systolic blood pressure, VSD, PDA and combined lesions were independent risk factors of PAH in CHD (Li et al., 2014). Although individuals with Down syndrome were not identified in the study, one could draw a correlation between its population and the incidence of specific CHD in Down syndrome.

PAH is the result of pathogenesis in one of three or a combination of three pathways: endothelin, nitric oxide and prostacyclin. Duchenne muscular dystrophy progresses with muscle wasting and connective tissue disorders. These processes result in eventual dystrophy of the diaphragm and pneumonia. Evidence has been presented that would suggest that DMD would show decreased levels of nitric oxide and prostacyclin with increased levels of endothelin. A study comparing thirty-one individuals with DMD and eleven healthy individuals a significant correlation ($r = -0.384$, $p = 0.0391$) between plasma nitric oxide levels and ejection fraction measured by

echocardiogram in the DMD group (Kasai et al., 2004). The finding suggests that there is a significant decrease in production of nitric oxide as part of the disease process of DMD. As described earlier, decreased levels of nitric oxide have a direct effect on prostacyclin and a converse effect on endothelin. As the genetic disorder progresses, seemingly all individuals affected by DMD develop pulmonary hypertension. Specifically, a study of eight individuals with advanced development of DMD were evaluated by right heart catheterization. A mPAP of > 20 mmHg was noted in all subjects while five of the eight had a mean pulmonary arterial pressure of > 40 mmHg (Yotsukura, Miyagawa, Tsuya, Ishihara & Ishikawa, 1988). Although the study was very limited it does suggest that pulmonary hypertension is inevitable in DMD and that PAH is highly likely.

What has current and existing research shown in the understanding of pulmonary arterial hypertension?

PAH encompasses a number of disorders with somewhat varied epidemiology, depending on the particular PAH subgroup referenced. Pulmonary hypertension is actually relatively common; however, most patients with pulmonary hypertension do not have PAH. PAH is a rare disorder with overall prevalence of 15-50 cases per million (Peacock et al., 2007). In certain high risk populations, the prevalence of PAH is much higher: systemic sclerosis 12%, sickle cell disease/hemolytic anemia 4% and HIV infection 0.5% (Archer et al., 2010). Overall PAH is two to four-fold more common in women vs. men (Peacock et al., 2007). Though symptoms can occur at any age, the disease most commonly begins showing symptoms in the fourth or fifth decade of life. Idiopathic PAH makes up nearly 50% of the cases of PAH with associated PAH accounting for the remainder.

Although the exact molecular basis of the PAH remains to be elucidated, several molecular pathways have been implicated in the pathophysiology of PAH (Archer et al., 2010). The initial inciting event in PAH is felt to be pulmonary endothelial cell injury. This in turn triggers a molecular cascade which eventually results in a distal small vessel arteriopathy characterized by medial hypertrophy, intimal proliferation and thickening, microthrombi formation, and ultimately plexiform lesions (Pietra et al., 1989).

The Pulmonary Hypertension Association summarized the pathophysiologic pathways of PAH at its 2017 symposium:

- **Nitric oxide (NO):** endogenous pulmonary vasodilator which also possesses anti-proliferative properties and a relative deficiency of endothelial NO in the pulmonary vasculature may be one mechanism which contributes to the development of PAH.
- **Endogenous prostacyclins:** systemic and pulmonary vasodilators, anti-proliferative agents and also have antithrombotic/antiplatelet effects. Relative deficiency or down-regulation of endogenous prostacyclin may contribute to the development of PAH.
- **Endothelin-1:** an endogenous vasoconstrictor and up-regulation of endogenous endothelin-1 may also contribute to the pathogenesis of PAH. (paragraph 9, PHA Online University Diagnosis and Treatment)

The small vessel arteriopathy in PAH leads to a progressive rise in RV afterload and pulmonary vascular resistance (PVR). As a result, the RV undergoes remodeling changes including right ventricular hypertrophy, dilatation and finally dysfunction. If PAH is left

untreated, right ventricular failure will ultimately result in patients experiencing syncope, angina, edema and abdominal distention (Favilli et al., 2015). Right ventricular failure is the most common cause of death in patients with PAH (Sitbon and Morrell, 2012).

Most recently, there have been studies identifying a specific protein that is linked to the development of PAH. PDLIM5 protein is produced in the smooth muscle cells of the pulmonary artery (Zhou, Chen and Raj, 2015). Within the past year the American Lung Association has begun investigating the effect hypoxia has on the PDLIM5 expression. Of particular note is the suppressive effect PDLIM5 plays on the activation of a downstream protein SMAD2/3 which are responsible for cell signaling in smooth muscle (Ousterout et al., 2015). This study is scheduled to conclude in 2019.

What is the recommended, evidence based treatment modality for PAH specific to DMD and DS?

There are no specific plans for the treatment of PAH in DMD or DS. Care for pulmonary hypertension in general involves volume maintenance, appropriate immunization and oxygen therapy (Favilli et al., 2015). There are specific treatment plans written for each type of pulmonary hypertension, however, the plan for APAH, under which DMD and DS fall, is largely reserved for the advanced stages of the disease. As there is currently no way to treat the underlying genetic disorders, the care remains supportive. Surgical correction of congenital heart defects is a necessity prior to further treatment (Saji, 2014). At this time medical treatment is based by and large on the opinion of experts rather than clinical trial or study. Again, the 5th World Symposium on

Pulmonary Hypertension, Nice, France, February 27 to March 1, 2013 developed the algorithm shown in Figure 1.

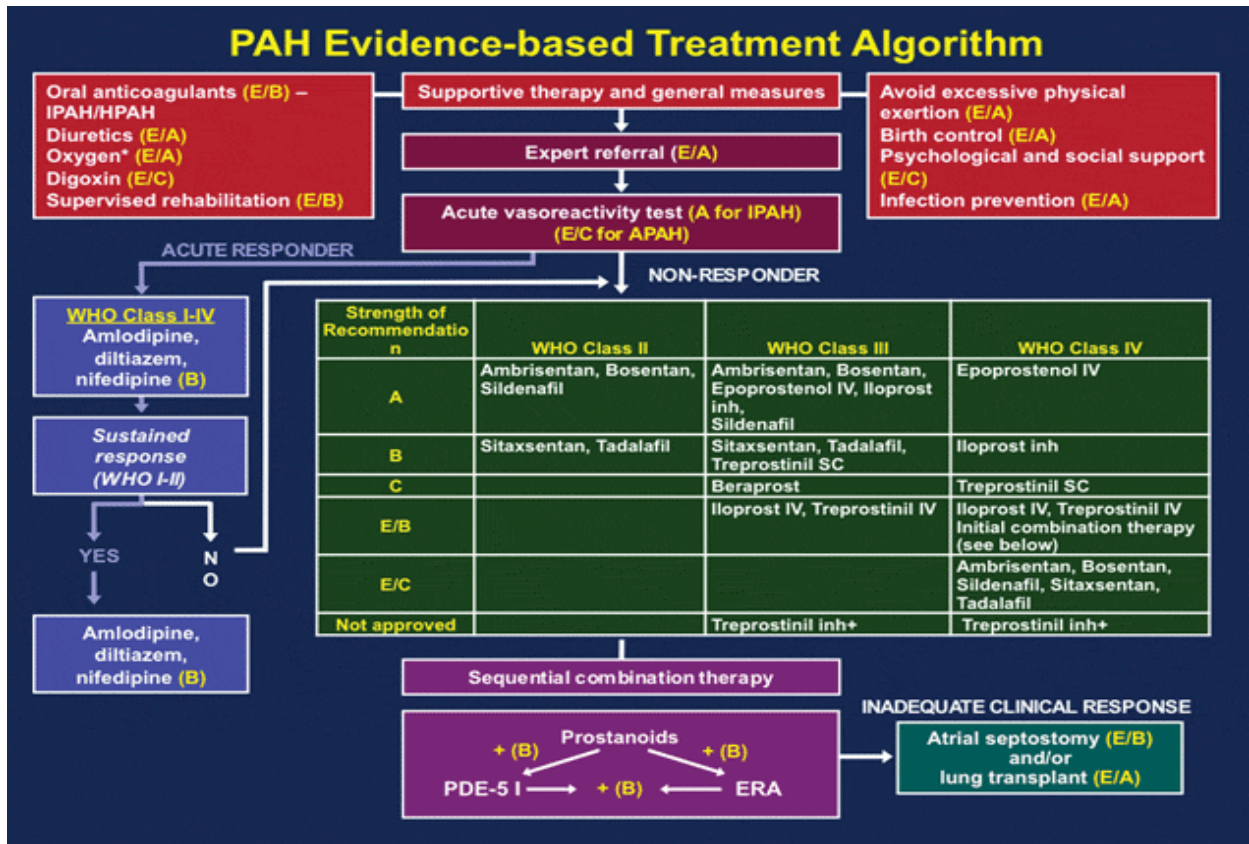


Figure 1. Flow Chart of PAH Evidence-based Treatment Algorithm: Journal of the American College of Cardiology by AMERICAN COLLEGE OF CARDIOLOGY Reproduced with permission of ELSEVIER INC. in the format Thesis/Dissertation via Copyright Clearance Center.

Differentiation into class I-IV is based off of patient diagnosis with pulmonary hypertension by right heart catheterization and by ability to carry out physical activity (Favilli et al., 2015).

The World Health Organization (WHO) functional classification for pulmonary hypertension is as follows:

- **Class I-** Patients with pulmonary hypertension but without resulting limitations of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or syncope.
- **Class II-** Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.
- **Class III-** Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.
- **Class IV-** Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right-heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity. (table 2, p. 1791)

Critical weight is placed on the individual patient's ability to be involved in their care. In the case of patients with DMD or DS concomitant PAH treatment become problematic. As classification is based, in part, on physical activity level, emphasis is placed on the patient's ability to communicate effectively. This may be a limiting factor as PAH presents as a late stage of development in DMD. Activity level will be significantly lowered at this point due to the progressively degenerative nature of the disorder. Furthermore, the ability of to communicate symptoms and activity level may be

diminished within the population of individuals with Down syndrome as well.

Successful recognition and treatment of PAH in DMD and DS would require concerted effort by care providers including: the patient, family members, healthcare workers, community integration personnel, teachers, etc...

Among individuals with Duchenne muscular dystrophy and Down syndrome with co-morbid pulmonary arterial hypertension (PAH) has early recognition and treatment through genetic discovery lead to a statistically significant increase in life expectancy versus previously undiagnosed or unrecognized PAH?

There is no direct evidence to suggest that there has been an increase in life expectancy with early recognition and treatment of PAH through genetic discovery amongst individuals with DMD and DS. Pulmonary arterial hypertension remains a complex disease process. Those affected by PAH have high rates of mortality directly connected to the disorder. As it stands, the treatment for PAH is largely supportive of cardiopulmonary symptoms and is largely carried out by cardiologists and pulmonologists with significant training and experience. Advances in medical care and treatment have resulted in increased life expectancy for all affected by PAH. Likewise, life expectancy for individuals with co-morbid Down syndrome and PAH alone has increased from 12 to 60 years of age since the 1940's (Vis et al., 2009). The application of clinical practices would seem to benefit all groups diagnosed with the disorder. Increases in life expectancy for this chronic yet still fatal condition increase the need for critical care in hospice and other residential facilities.

Research finding the genetic cause of specific types of PAH is necessary in locating the cure for the spectrum disorder. Identification of gene mutation and

epigenetic influence has provided strong foundations for continued research. New research should be based on treatment of existing illness, screening for prevention and cure in order to improve quality of life.

CLINICAL APPLICATION

The incidence of pulmonary arterial hypertension is increased among populations of individuals with Duchenne muscular dystrophy and Down syndrome. Having an understanding of the pathophysiology of the disease will help patients and families understand its progression. A primary care provider in a rural area could be called upon to act as the intermediary between a cardiologist or pulmonologist in the treatment of such individuals. Furthermore, the PCP is instrumental in providing screening and wellness services to this specific population. Developing a thorough familiarity with individual patients will help tease out or recognize changes in activities of daily living. Advances in research prove the need to continually develop knowledge and skill.

DMD is a progressive, fatal disease. The disease affects the cardiopulmonary circuit as a late stage. 53-90% of the mortality associated with DMD is from respiratory failure (Finsterer, 2006). Although the prognosis is an inevitability measures can be applied to improve quality of life. The PCP can help guide the patient and family through these practices. Advice concerning surgery to correct associated scoliosis, noninvasive ventilatory management, nutritional support, and expiratory muscle training could prove instrumental in maintaining cardiopulmonary function for longer periods of time (Finsterer, 2006). Management of medications like corticosteroids, PDE-5

inhibitors and endothelin receptor antagonists will help reduce precapillary pulmonary hypertension (Yotsukura et al., 1988).

The effects of DS do not necessarily lead to the untimely prognosis of DMD. Because of its pathogenesis the effects of PAH are recorded much earlier in the disorder particularly in the case of congenital heart defects associated with DS. The vasculature of individuals with DS is markedly decreased in caliber compared to individuals without. This is particularly noted in the capillaries of the pulmonary circuit resulting in the increase in pulmonary arterial pressure (Saji, 2014). Understanding the need for early correction of CHD in individuals with DS will hopefully be recognized before delivery or soon thereafter, a PCP could easily be part of that conversation. Moreover, knowing that the vasculature narrows with time regardless of surgical CHD correction will help an individual understand the importance of medication management.

Developing a health and wellness routine for individuals who are likely to develop or currently afflicted by PAH would be under the purview of the PCP. The need to keep immunizations up to date in fragile populations should be nothing new. The understanding of profound effect influenza or pneumonia would have on an individual with PAH should increase the investment in prophylactic measures. Beyond having a deeper insight for vaccination schedules, the PCP would need to have an intuitive appreciation for the decreases in activities of daily living (ADLs) for this specific population. Teasing out the nature or cause of decrease in ADLs can help differentiate progression of PAH from progression of DMD or DS. This familiarity is much more likely in the primary care setting rather than the specialty. Indeed, the personal

relationship that is developed in the primary care setting creates a situation that allows for better medication and interventional therapies.

The primary care provider needs to be involved in the coordination of care of the individual with DMD or DS with concomitant PAH. Input from family, friends, teachers, care providers, case managers, social workers, physical/occupational and respiratory therapists is invaluable. Working to share ideas and observations is a vital step in the cohesive plan management of patient care. Attendance at multi-disciplinary team meetings would seem obvious.

Finally, the ever changing nature of this topic further solidifies the need to continue growth and development of knowledge and skill. In the course of researching this topic there have been two studies that have caused changes in what was known about PAH. As discussed, a pivotal study is underway and scheduled to be completed in 2019. The knowledge that clinical practice generally lags behind research by ten years may sound discouraging, however, personal devotion to improvement can change that.

Research to help find the genetic cause of specific types of PAH is necessary in locating the cure for the spectrum disorder. Identification of gene mutation and epigenetic influence has provided strong foundations for continued research. New research should be based on: treatment of existing illness, screening for prevention and the possibility of a cure in order to improve quality of life.

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