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REVIEW

Pulmonary Hypertension in the Population with Down Syndrome

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ABSTRACT

Persons with Down syndrome (DS) have an increased reported incidence of pulmonary hypertension (PH). A majority of those with PH have associations with congenital heart disease (CHD) or persistent pulmonary hypertension of the newborn (PPHN); however, there are likely multifactorial contributions that include respiratory comorbidities. PH appears to be most commonly identified early in life, although respiratory challenges may contribute to a later diagnosis or even a recurrence of previously resolved PH in this population. Currently there are few large-scale, prospective, lifetime cohort studies detailing the impact PH has on the population with DS. This review will attempt to summarize the epidemiology and characteristics of PH in this population. This article will additionally review current known and probable risk factors for developing PH, review pathophysiologic mechanisms of disease in the population with DS, and evaluate current screening and management recommendations while suggesting areas for additional or ongoing clinical, translational, and basic science research.

Keywords: Down syndrome; Trisomy 21; Pulmonary hypertension; Pulmonary arterial hypertension; Congenital heart disease

Key Summary Points

Pulmonary hypertension is a common comorbidity in the population with Down syndrome, frequently with multifactorial etiologies including congenital heart disease, developmental lung disease, and other respiratory pathologies.

Screening for pulmonary hypertension in the population with DS remains challenging, but novel biomarkers are currently being investigated.

Understanding the etiology of pulmonary hypertension in the population with Down syndrome can help guide treatment strategies.

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INTRODUCTION

Pulmonary hypertension (PH) is frequently identified in individuals with Down syndrome (DS). The high frequency of PH in this population has probable genetic (Table 1), congenital, and environmental contributions [1]. While the lifetime prevalence remains unknown, reports of PH incidence in childhood may be as high as 28% in this population [2]. The etiology of PH in persons with DS varies; however, there is a strong association with congenital heart disease (CHD), which is present in 38–58% of this population [3–6]. Those without CHD also appear to be at higher risk of developing PH when compared to the general population, and there are likely additional respiratory and cardiovascular reasons for this increase [1].

The World Symposium on Pulmonary Hypertension (WSPH) classifies PH into five major groups including pulmonary arterial hypertension (PAH; Group 1); PH due to left-sided heart disease (Group 2); PH due to lung disease or hypoxia (Group 3); chronic thromboembolic PH (CTEPH; Group 4) and PH due to multifactorial, mixed or unclear mechanisms (Group 5) [7]. Many reports of PH in persons with DS attribute the PH to Group 1 PAH; however, there are likely underreported contributions from left heart disease, disorders of the

Table 1 Possible genetic contributions to the development of pulmonary hypertension in Down syndrome

Contribution to PH	Gene	Protein
Hemodynamic stress		
Congenital heart disease		
(AVSD)	*CRELD1*	Cysteine-rich with EGF-like domain protein 1
(VSD)	*HEY2*	Hairy/enhancer-of-split related with YRPW motif protein 2
	GATA3	(Transcription factor)
	KCNH2	Kv11.1
	ENG	Endoglin
	FLNA	Filamin A
	GUSB	Beta-glucuronidase
Pulmonary hypoplasia		
Antiangiogenesis		
	RCAN1	Regulator of calcineurin-1
	COL18a1	Endostatin
	APP	Amyloid beta protein
Endothelial dysfunction		
Proinflammatory	*IFNAR1*	Interferon-alpha/beta receptor 1
	IFNAR2	Interferon-alpha/beta receptor 2
	IFNGR2	Interferon-gamma receptor 2
	IL10RB	Interleukin-10 receptor subunit beta

AVSD atrioventricular septal defect, *VSD* ventricular septal defect

lung, and complex CHD (Group 5—category that includes segmental pulmonary hypertension, single ventricle disorders, and Scimitar syndrome) [8]. As such, a better understanding of the etiology of PH in the population with DS is necessary to help determine appropriate screening and interventions. This review will serve as a critical evaluation of the current literature, will provide ideas for interim strategies to help manage cardiopulmonary challenges in persons with DS and will offer suggestions for future research. This manuscript is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

EPIDEMIOLOGY

A recent meta-analysis reported that the average life expectancy for individuals with DS is approximately 30 years less than individuals without DS. In this analysis, cardiovascular disorders accounted for 1.5–24%, cardiac failure 18.8–33%, and CHD accounting for 3–50% of deaths in this population [9]. A large population study using data from the US Centers for Disease Control and Prevention National Center for Health Statistics reported increased odds of death (odds ratio 3.83 with 95% CI 3.60–4.07) from pulmonary vascular disease in persons with DS between 1983 and 1997 [10]. These findings suggest the burden of pulmonary vascular disease is higher in the population with DS.

There are few large cohort studies evaluating the lifetime incidence of PH in individuals with DS from all causes. One moderate-sized (n = 1242), single-institution, retrospective study suggested that childhood incidence of PH is as high as 28%, increasing to 45% in the presence of CHD [2]. The vast majority of studies have evaluated the incidence of PH classified as Group 1, primarily PAH associated with CHD or persistent pulmonary hypertension of the newborn (PPHN; Group 1.7). PPHN has been reported to occur at a rate of 1.2–9.7% in the population with DS (0.1% in the general population), perhaps suggesting an innate abnormality in vasoactive regulation or airway structure associated with the overexpression of human chromosome 21-related genes [2, 11].

The timing of PH onset appears to most commonly occur in the first year of life, particularly with PPHN and in the presence of CHD [2, 12]. In one moderate-sized retrospective study, 70% of children with PH experienced transient disease with resolution following interventions, a small portion (15%) experienced persistent PH, and a similar amount (15%) developed recurrence of PH, frequently as a result of respiratory comorbidities [2]. The average age of recurrence was 1.7 years in this study, suggesting that PH may be most challenging early in life in the population with DS. In another small (n = 102) prospective study, the prevalence of PH in DS was 5.9% at 1 year and 15% at 10 years, although the study appears to have been evaluating older children (mean age 16.4 ± 12 years) without surgically corrected CHD, complicating our understanding of the condition [3].

The need for specialty providers and expensive invasive (cardiac catheterization) or non-invasive (echocardiography) testing to identify PH may have historically hindered a thorough understanding of the incidence of PH in this population. Further, pulmonary hypertension is not always symptomatic, and early recognition of the disease may be limited in more sedentary populations or those who are unable to comply with clinical assessments (e.g., exercise testing or 6-minute walk distance testing), underestimating the population prevalence of PH. There may even be bias against evaluating for the condition in specialty practices without echocardiography (e.g., pulmonology) or failure to recognize the condition in the setting of other CHD (e.g., left heart disease or complex cardiac disease) and thus an underreporting of disease prevalence. Further, in 2018, the Pediatric Task Force of the 6th World Symposium on Pulmonary Hypertension (WSPH; Nice, France, 2018) revised the definition of PH, reducing the diagnostic threshold of mean pulmonary arterial pressure (mPAP) from 25 to 20 mmHg, as studies placed this more than two standard deviations above the population mean [13]. Prior studies have used the higher mPAP

threshold, likely reducing the reported incidence of PH. Thus, a better understanding of PH disease incidence and prevalence in the population with DS is needed.

CLASSIFICATION, ETIOLOGY, AND RISK FACTORS

Pulmonary hypertension develops when pulmonary arterial pressure increases in order to maintain blood flow in the presence of the increased pulmonary vascular resistance that occurs due to vascular remodeling (Ohm's law). The etiology of pulmonary hypertension in individuals with Down syndrome is not always straightforward and can often be attributed to multiple underlying challenges to the pulmonary vascular system including increases in hemodynamic stress, abnormalities in lung development, intrinsic endothelial dysfunction, increases in pulmonary vascular resistance, and post-capillary disease (Fig. 1). Large prospective studies evaluating etiologies of PH in the population with DS are lacking; however, a thorough literature review has revealed known and likely risk factors for developing PH (Table 2).

Individuals with Down syndrome very often fit into multiple PH classification categories (Table 3). The most common classification is Group 1, PAH associated with either CHD or PPHN; however, there are frequent contributions from left heart inflow or outflow disease (Group 2), respiratory challenges from chronic or intermittent hypoxia (Group 3), and occasionally complex cardiac disease (Group 5) or metabolic derangements such as hypothyroidism (Group 5). Given the complexity of classifying PH in DS, the WSPH has recommended that in the absence of CHD, individuals with DS who have PH should be categorized as Group 3 disease due to the high frequency of associated respiratory challenges [13].

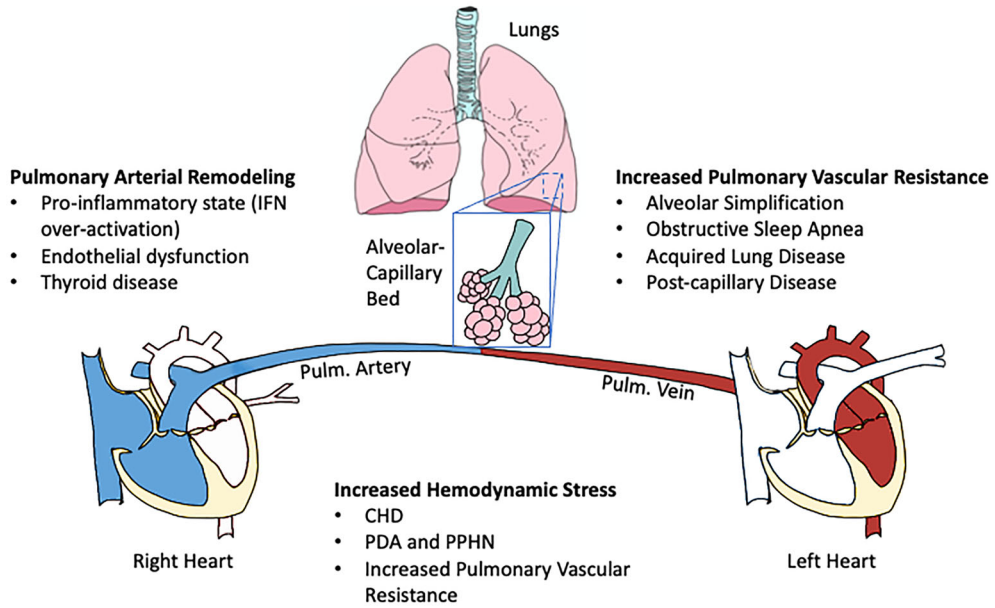

Fig. 1 Pathophysiology and etiologies of development of pulmonary hypertension in Down syndrome. Early pulmonary arterial remodeling may occur due to an innate interferonopathy, intrinsic endothelial dysfunction or other metabolic conditions. Increases in hemodynamic stress can occur from congenital heart disease (CHD) or patent ductus arteriosus (PDA) causing persistent pulmonary hypertension of the newborn (PPHN) in developmentally immature lungs with high pulmonary vascular resistance. Increased pulmonary vascular resistance can occur from acquired lung disease and capillary or post-capillary disorders

Table 2 Comorbid conditions and reported frequencies in the population with DS (modified from Bush et al. Ped Pulm, 2019) [57]

	% in DS	% in DS with PH [2]	Relative risk for PH (95% CI) [2]
Cardiac conditions			
CHD	40–75	94.2	5.3 (3.5–8.2)
CHD with L-to- R shunt	35.1	59.8	2.1 (1.7–2.5)
AVSD	9–49	19.9	1.6 (1.3–1.9)
VSD	26–35	32	1.8 (1.5–2.1)
ASD	2–38	46.2	1.9 (1.6–2.3)
PDA	3–47	59.8	1.6 (1.3–1.9)
CHD without L-to-R shunt	7.2	4.6	1.4 (1.3–1.9)
Pulmonary conditions			
Pulmonary hypoplasia	*	N/A	N/A
OSA	45–79	77.5	N/A
Intermittent or chronic hypoxia	*	55.5	N/A
Recurrent pneumonia	*	43.1	N/A
Aspiration	35–39	35.5	N/A
Asthma	32–36	20.5	N/A
Chronic lung disease/BPD	*	19.9	N/A
Tracheobronchomalacia	3–33	15.9	N/A
Tracheal bronchus	3–5		
Subglottic stenosis	4–6	8.4	N/A
Laryngomalacia	*	7.8	N/A
Metabolic conditions			
Thyroid abnormalities	27	32.1	N/A
Gastrointestinal conditions			
GER	9	34.4	N/A

CHD congenital heart disease, *AVSD* atrioventricular septal defects, *VSD* ventricular septal defect, *ASD* atrial septal defect, *PDA* patent ductus arteriosus, *OSA* obstructive sleep apnea, *BPD* bronchopulmonary dysplasia, *GER* gastroesophageal reflux
N/A not available
L-to- R: systemic to pulmonary
*Case reports/case series

Increased Hemodynamic Stress

Congenital heart disease is present in 38–58% of individuals with DS, with likely genetic contributions (Table 1) [3–6, 14–16]. Children with DS are more likely to experience PH in the presence of CHD (38–80%) than those with CHD who do not have DS (4–15%)

Table 3 Classification of pulmonary hypertension in individuals with Down syndrome [2]

WHO classification group			% (*n* = 346)
1	Pulmonary arterial hypertension		
	1.4.4	CHD-associated PAH	44.8
	1.7	PPHN	35.3
2	PH due to left-sided heart disease		1.2
3	PH caused by lung disease or hypoxemia		
	3.4	Sleep-disordered breathing	17.9
	3.5	Developmental lung disease	^
4	PH due to pulmonary arterial obstructions		0
5	PH with unclear or multifactorial mechanisms		
	5.3	Thyroid disorders	0
	5.4	Complex CHD	*

CHD congenital heart disease, *PPHN* persistent pulmonary hypertension of the newborn
*Referenced study precedes WSPH updates
^Biopsies not obtained

[2, 3, 12, 17, 18]. A left-to-right intracardiac shunt, in particular, increases the risk of developing PH in individuals with DS, with a relative risk of 2.1 (95% CI 1.7–2.5; Table 2) [2]. Increases in pulmonary arterial blood flow through an intracardiac shunt can increase pulmonary arterial pressures, create shear stress, and contribute to endothelial dysfunction, vascular remodeling, and altered vasoactive mediator expression [19]. Left uncorrected, ventricular septal defects (VSD) and atrioventricular septal defects (AVSD) frequently progress to Eisenmenger syndrome, an end-stage reversal of the intracardiac shunt [17].

Pulmonary Hypoplasia

Several small case series have reported evidence of abnormal lung development or pulmonary hypoplasia in individuals with DS [20–22]. These autopsy reports have revealed evidence of increased pulmonary blood flow through dilated or congested pulmonary vasculature, and have revealed evidence of pulmonary arterial remodeling and noted disturbances in microvascular development. The overexpression of the human chromosome 21 (Hsa21)-encoded antiangiogenic genes for endostatin (*COL18a1*), amyloid beta protein (*APP*), and regulator of calcineurin-1 (*RCAN1*) may contribute to impaired pulmonary vascular development [23]. Increased pulmonary blood flow to a pulmonary vascular bed with reduced capacitance may increase the risk of developing PH, as it contributes to hemodynamic stress to the arterial endothelium and exacerbates hypoxia through impairments in diffusion and ventilation-to-perfusion matching.

Intrinsic Endothelial Dysfunction

The increased prevalence of PPHN and the existence of possible intrapulmonary bronchopulmonary anastomoses (IBA) in the population with DS may suggest an innate abnormality in endothelial function or vasomotor tone in the pulmonary circulation [11, 22]. Reports of elevated endothelin-1 (ET-1; a potent vasoconstrictor) in children with DS who have CHD and reduced endothelial

Table 4 Screening guidelines for children with Down syndrome and PH or at risk of developing PH (modified from Seattle Children's Hospital proposed guidelines) [41]

	AAP standard of care for all patients with Down Syndrome	Any child with chronic respiratory symptoms or conditions	New PH diagnosis or recurrent episode	PH resolved or well controlled	No improvement in PH/worsening
Echo	First month of life	Consider screening for PH every year	With initial evaluation	Annually until school age for resolved PH (CHD, PPHN, or other cause of PH) At least annually indefinitely for well-controlled PH	As frequently as PH team suggests
Pulmonology consult	N/A	Annual pediatric pulmonology evaluation	With initial evaluation if not previously established	Continue to follow regularly until lung disease ruled out as contributing factor	Continue to follow regularly until lung disease ruled out as contributing factor
VFSS	In first year of life only if symptoms present	As soon as respiratory symptoms become apparent	With initial evaluation	Annual evaluation by speech–language pathologist and VFSS until age 6 years; consider annual screening thereafter for those with history of diagnosed aspiration	At least annually (more frequent if unexplained worsening)
Sleep study	By age 4 years	Per primary pulmonologist	With initial evaluation	Consider annual sleep clinic evaluation	Annually, repeat after any surgical airway management
Chest CT with and without IV contrast	N/A	Encouraged if signs of lower airway or pulmonary vascular disease	With initial evaluation	N/A	Consider repeating at intervals decided with primary pulmonologist to screen for ongoing evidence of aspiration, other parenchymal lung disease, or pulmonary venous obstruction

Table 4 continued

	AAP standard of care for all patients with Down Syndrome	Any child with chronic respiratory symptoms or conditions	New PH diagnosis or recurrent episode	PH resolved or well controlled	No improvement in PH/worsening
Lab surveillance: BNP, thyroid, BMP, autoimmune	Thyroid: NB, 6 months, 12 months, annually	Consider BNP with echo screening, BMP for hypoventilation	With initial evaluation	At least annually	At least annually, BNP more frequently to trend response to treatment

AAP American Academy of Pediatrics, *Echo* echocardiogram, *CHD* congenital heart disease, *VFSS* video fluoroscopic swallow study, *CT* computed tomography, *BNP* brain-type natriuretic peptide, *BMP* basic metabolic panel, *NB* newborn, *PPHN* persistent pulmonary hypertension of the newborn

production of nitric oxide (NO; a potent vasodilator) may be secondary to the overexpression and increased activity of four Hsa21-encoded interferon receptors [24–27]. Interferon has negative modulatory effects on NO expression and can lead to upregulation of ET-1 [28]. The therapeutic use of interferon in the non-DS population has led to the development of PAH, a frequent finding in disorders of genetic overexpression of interferon unrelated to DS [29–31].

Increased Pulmonary Vascular Resistance

Individuals with DS have a high incidence of respiratory comorbidities including obstructive sleep apnea (OSA), intermittent or sustained hypoxia, recurrent pneumonia, and chronic aspiration (Table 2) [2, 32]. Intermittent or chronic respiratory insults lead to regional or global hypoxic pulmonary vasoconstriction and may contribute to increases in pulmonary vascular resistance. Of particular interest, OSA has been reported in 45–79% of individuals with DS and has been implicated as a cause of PH in this population [33–37].

Congenital airway disorders are frequently reported in this population, particularly in those with chronic cough or recurrent respiratory infections. In children with DS undergoing endoscopic airway evaluations for these symptoms, airway abnormalities were identified in 14–75% of patients (Table 2) [38–40]. Commonly reported findings include tracheobronchomalacia and subglottic stenosis (acquired and congenital). A high incidence of tracheal bronchus (3–5%) and laryngeal cleft (1%) has also been reported in the population with DS, suggesting more obvious etiologies of recurrent pneumonia and aspiration, respectively [38, 40]. Consequential airway compression from cardiovascular abnormalities (e.g., cardiomegaly, vascular abnormalities) may be a complicating factor in those with CHD [39, 40]. Airway disorders can contribute to intermittent hypoxia and impair one's ability to mobilize lower airway secretions, directly contributing to the increased risk of acquiring lower respiratory tract infections. These insults lead to transient or sustained increases in pulmonary vascular resistance and likely contribute to the higher incidence of PH observed in the population with DS. While direct evidence linking airway disease to the onset of PH is lacking in the population with DS, associations have been described, as the authors have previously

Table 5 Managing conditions contributing to PH in individuals with DS

Condition	Specialty	Evaluations	Possible interventions
CHD	Cardiology	Echocardiogram, cardiac catheterization	Pre-load reduction, surgical correction, targeted vasodilator therapy
PPHN	Neonatology, cardiology, pulmonology	Echocardiogram	Oxygen and ventilation support, targeted vasodilator therapy
OSA	Pulmonology, sleep provider	Polysomnography, laryngoscopy, bronchoscopy	Surgical intervention, noninvasive ventilation
Pulmonary hypoplasia	Pulmonology	CT chest, lung biopsy	Limit inflammatory insults, promote growth
Hypoxia	Pulmonology, sleep provider	Polysomnography, CT chest, echocardiogram, cardiac catheterization	Supplemental oxygen, improve pulmonary toilet, ventilatory support, surgical correction
Recurrent pneumonia/ aspiration	Pulmonology	CT chest, bronchoscopy, swallow evaluation	Improve pulmonary toilet, treat cause of aspiration
Airway disorders (e.g., tracheomalacia)	Pulmonology	CT chest, bronchoscopy	Improve pulmonary toilet, ventilatory support
Thyroid disorders	Endocrinology	Serum TSH, free T4	Levothyroxine

CHD congenital heart disease, *PPHN* persistent pulmonary hypertension of the newborn, *OSA* obstructive sleep apnea, *CT* computed tomography, *TSH* thyroid stimulating hormone

reported new diagnoses of OSA in 21% and recurrent pneumonia in 17% of children with DS prior to identifying a recurrence of their previously resolved PH [2]. Notably, large prospective studies evaluating respiratory comorbidities and risk for developing PH in the population with DS are lacking.

Post-Capillary Disease

Pulmonary vein stenosis has been reported to occur with increased frequency in the population with DS; however, the exact incidence is unknown [41–44]. Additionally, with the high frequency of CHD, there is likely an increase in disorders of left heart outflow, which can increase pulmonary vascular resistance and can contribute to the onset of PH. Certain forms of AVSD, such as single papillary muscle with deficient mural leaflet, frequently lead to increased left-sided AV valve stenosis or insufficiency causing or exacerbating pulmonary hypertension. Prospective, large-scale studies are necessary to identify the true incidence of left-sided heart disease and its contribution to PH onset (PH Group 2) in the population with DS.

Screening

There are currently no accepted screening guidelines for pulmonary hypertension in individuals with DS; however, a recent publication by the Pulmonary Hypertension Association has suggested a comprehensive approach (Table 4) [45]. Generally accepted guidelines

remain limited to the screening of comorbid conditions including CHD (within the first month of life), valvular disease (between 13–-21 years), sleep-disordered breathing (by age 4 years), and swallowing disorders (if ever symptomatic) [46]. When diagnosis is uncertain or targeted therapy is being considered, a cardiac catheterization is recommended by the American Heart Association and American Thoracic Society (AHA/ATS) [7]. Understandably, this is not always possible, and clinicians are encouraged to use their best clinical judgment when initiating therapies.

Recent work has identified possible biomarkers of PH specific to the population with DS including evidence of increased circulating inflammatory cells (immunomodulatory myeloid-derived suppressor cells and fibrocytes) [47] and dysregulated angiogenesis favoring antiangiogenesis (high serum levels of endostatin coupled with low levels of angiogenin) [48], although a subsequent study challenged endostatin's role as a biomarker in favor of the cardiac markers N-terminal prohormone of brain natriuretic peptide and galectin-3 [49]. These small studies were largely specific to the population with PAH (Group 1), and additional, more thorough investigations are needed.

Given the high frequency of disease in the population with DS, new biomarkers of early disease are needed. Echocardiography is an expensive test and identifies late evidence of pulmonary vascular disease (e.g., right ventricular hypertension) while cardiac catheterization is expensive, invasive, and not always feasible. Ongoing work should focus on risk stratification tools, evaluating hemodynamic stress in the vasculature, early or predictive protein signatures, or other biomarkers of early disease.

Management

The multiple underlying causes and risk factors for developing PH in the population with DS requires a multidisciplinary treatment approach. At a minimum, this should include pediatric cardiology, pediatric pulmonology, and relevant surgical subspecialties [45, 50]. Interventions should target the underlying cause of the disease both medically and surgically where appropriate (Table 5). Notably, addressing upper airway obstruction has been reported to improve mPAP on cardiac catheterization [37, 50]. Additionally, given the complexity of the disorder, pre-anesthesia risk stratification specific to the population with DS may help guide safe surgical interventions [51].

In those patients with chronic respiratory symptoms, early referral to a comprehensive aerodigestive team may provide useful diagnostic insight or therapeutic opportunities to address underlying airway or digestive disorders that may contribute to the development of PH. Following American Academy of Pediatrics (AAP) screening recommendations for polysomnography may identify pathology and suggest referral to sleep or pulmonary specialists; however, a low threshold for referral to pulmonary specialists may provide additional benefit [45].

Early surgical correction is often necessary to prevent the development or progression of PH in individuals with DS who have CHD with systemic-to-pulmonary intracardiac shunts, including atrial septal defect (ASD) [52, 53]. Generally, surgical correction of CHD in individuals with DS is recommended by 2 years of age; however, preoperative hemodynamic assessment can aid in risk stratification of patients. In many centers, surgery is performed even earlier. A pulmonary vascular resistance index (PVRi) of < 6 Wood units (WU) m^{-2} or ≥ 6 WU m^{-2} but with adequate reversibility (vasoreactivity with supplemental oxygen and inhaled NO with a reduction in PVRi < 6 WU m^{-2} and pulmonary vascular resistance/systemic vascular resistance [PVR/SVR] < 0.3) response is associated with favorable outcomes [7]. Of note, there have been reports of increases in postoperative PH in children with DS undergoing surgical repair for both ASD (1.7% vs. 0.2%) and VSD (2.2% vs. 0.7%) compared to non-DS controls [54].

For individuals with DS who have intrinsic disease of the pulmonary arteries such as PAH associated with CHD or PPHN, targeted PH pharmacotherapies can be considered. There are very few studies evaluating pharmacotherapies specifically in the population with DS; however,

the studies available and sub-analyses of general PAH population studies have suggested that endothelin receptor antagonists (ERA) can improve quality of life, exercise capacity, and functional classification, and have been generally well tolerated [55–59]. The phosphodiesterase-5 inhibitor sildenafil may not be as efficacious as ERA, as a suboptimal improvement in pulmonary vascular resistance index and mPAP was reported in a DS-specific subanalysis of the STARTS-1 trial [60]. This study did report that the drug was well tolerated in this population, but did not evaluate for confounding comorbidities or causes of PH in the population with DS involved. Dosing for pediatric [7] and adult [61] targeted therapies can be found elsewhere. Of note, as of the writing of this manuscript, in the United States, the only Food and Drug Administration-approved medication for PAH in children is the ERA bosentan.

Future Areas of Research

With updated classifications and a more inclusive definition for pulmonary hypertension, it stands to reason that more people with DS will be diagnosed with PH. Large prospective cohort studies are required to better understand the prevalence and risk factors contributing to the development of PH in individuals with DS. Screening for the condition may be improving, as novel biomarkers have been identified and are currently under investigation [47, 62]. Ongoing PH registries are improving our understanding of how individuals with DS respond to targeted therapies; however, therapeutic studies specific to the population with DS are needed, including those that evaluate the response to treating cardiac and respiratory comorbidities.

Preclinical mouse models of lung disease in the population with DS may prove valuable in studying mechanisms of disease and isolating genetic contributions to the onset of PH [63]. While the mouse orthologues for human chromosome 21 are distributed across three murine chromosomes (Mm10, Mm16, and Mm17), complicating preclinical studies, a trisomic Mm16 (Dp16) mouse, when raised in hypoxic conditions, develops the hypoplastic pulmonary phenotype and has evidence of pulmonary hypertension (data presented in the form of n platform presentation by Bush et al. at the American Thoracic Society International Conference, 2017).

CONCLUSIONS

PH in the population with DS appears to be more common than that in the population without DS. There are multifactorial reasons for the higher prevalence of PH in this population including abnormal pulmonary development, increased hemodynamic stress in the pulmonary vasculature, capillary and post-capillary obstructive disorders, and inflammatory and possibly metabolic contributions [64]. Additional large-scale epidemiologic and clinical investigations are needed to understand the impact of this disease on this vulnerable population, and ongoing basic and translational science is required to identify biomarkers of early pulmonary vascular disease, understand genetic and molecular pathways, and evaluate effective targeted therapies.

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REFERENCES

1. Naumburg E, Soderstrom L, Huber D, Axelsson I. Risk factors for pulmonary arterial hypertension in children and young adults. Pediatr Pulmonol. 2017;52:636–41.

2. Bush D, Galambos C, Ivy DD, Abman SH, Wolter-Warmerdam K, Hickey F. Clinical characteristics and risk factors for developing pulmonary hypertension in children with Down syndrome. J Pediatr. 2018;202:212–9.

3. Espinola-Zavaleta N, Soto ME, Romero-Gonzalez A, Gomez-Puente Ldel C, Munoz-Castellanos L, Gopal AS, et al. Prevalence of congenital heart disease and pulmonary hypertension in Down's syndrome: an echocardiographic study. J Cardiovasc Ultrasound. 2015;23:72–7.

4. Weijerman ME, van Furth AM, van der Mooren MD, van Weissenbruch MM, Rammeloo L, Broers CJ, et al. Prevalence of congenital heart defects and persistent pulmonary hypertension of the neonate with Down syndrome. Eur J Pediatr. 2010;169:1195–9.

5. Cullum L, Liebman J. The association of congenital heart disease with Down's syndrome (mongolism). Am J Cardiol. 1969;24:354–7.

6. Freeman SB, Bean LH, Allen EG, Tinker SW, Locke AE, Druschel C, et al. Ethnicity, sex, and the incidence of congenital heart defects: a report from the National Down Syndrome Project. Genetics Med. 2008;10:173–80.

7. Abman SH, Hansmann G, Archer SL, Ivy DD, Adatia I, Chung WK, et al. Pediatric Pulmonary Hypertension: Guidelines From the American Heart Association and American Thoracic Society. Circulation. 2015;132:2037–99.

8. Colquitt JL, Morris SA, Denfield SW, Fraser CD, Wang Y, Kyle WB. Survival in children with Down syndrome undergoing single-ventricle palliation. Ann Thorac Surg. 2016;101:1834–41.

9. O'Leary L, Hughes-McCormack L, Dunn K, Cooper SA. Early death and causes of death of people with Down syndrome: a systematic review. J Appl Res Intellect Disabil. 2018;31:687–708.

10. Yang Q, Rasmussen SA, Friedman JM. Mortality associated with Down's syndrome in the USA from 1983 to 1997: a population-based study. Lancet. 2002;359:1019–25.

11. Cua CL, Blankenship A, North AL, Hayes J, Nelin LD. Increased incidence of idiopathic persistent pulmonary hypertension in Down syndrome neonates. Pediatr Cardiol. 2007;28:250–4.

12. Mourato FA, Villachan LR, Mattos SS. Prevalence and profile of congenital heart disease and pulmonary hypertension in Down syndrome in a pediatric cardiology service. Rev Paul Pediatr. 2014;32:159–63.

13. Rosenzweig EB, Abman SH, Adatia I, Beghetti M, Bonnet D, Haworth S, et al. Paediatric pulmonary arterial hypertension: updates on definition, classification, diagnostics and management. Eur Respir J. 2018;53:1801916.

14. de Rubens FJ, del Pozzo MB, Pablos Hach JL, Calderon Jimenez C. Castrejon Urbina R [Heart malformations in children with Down syndrome]. Rev Esp Cardiol. 2003;56:894–9.

15. Li H, Cherry S, Klinedinst D, DeLeon V, Redig J, Reshey B, et al. Genetic modifiers predisposing to congenital heart disease in the sensitized Down syndrome population. Circ Cardiovasc Genet. 2012;5:301–8.

16. Alharbi KM, Al-Mazroea AH, Abdallah AM, Almohammadi Y, Carlus SJ, Basit S. Targeted next-generation sequencing of 406 genes identified genetic defects underlying congenital heart disease in Down syndrome patients. Pediatr Cardiol. 2018;39:1676–80.

17. Duffels MG, Engelfriet PM, Berger RM, van Loon RL, Hoendermis E, Vriend JW, et al. Pulmonary arterial hypertension in congenital heart disease: an epidemiologic perspective from a Dutch registry. Int J Cardiol. 2007;120:198–204.

18. Greenwood RD, Nadas AS. The clinical course of cardiac disease in Down's syndrome. Pediatrics. 1976;58:893–7.

19. Adatia I, Kothari SS, Feinstein JA. Pulmonary hypertension associated with congenital heart disease: pulmonary vascular disease: the global perspective. Chest. 2010;137:52S-61S.

20. Cooney TP, Thurlbeck WM. Pulmonary hypoplasia in Down's syndrome. N Engl J Med. 1982;307:1170–3.

21. Betsy L, Schloo M, Gordon F, Vawter M, Lynn M, Reid M. Down syndrome: patterns of disturbed lung growth. Human Pathol. 1990;22:919–23.

22. Bush D, Abman SH, Galambos C. Prominent intrapulmonary bronchopulmonary anastomoses and abnormal lung development in infants and children with Down syndrome. J Pediatr. 2017;180:156-62e1.

23. Galambos C, Minic AD, Bush D, Nguyen D, Dodson B, Seedorf G, et al. Increased lung expression of anti-angiogenic factors in Down syndrome: potential role in abnormal lung vascular growth and the risk for pulmonary hypertension. PLoS ONE. 2016;11:0159005.

24. Kageyama K, Hashimoto S, Nakajima Y, Shime N, Hashimoto S. The change of plasma endothelin-1 levels before and after surgery with or without Down syndrome. Paediatr Anaesth. 2007;17:1071–7.

25. Aoki M, Hirono K, Higuma T, Suzuki Y, Nakayama K, Yamashita A, et al. Pulmonary vascular disease in a failed Fontan patient with Down's syndrome. Gen Thorac Cardiovasc Surg. 2018;66:299–302.

26. Cappelli-Bigazzi M, Santoro G, Battaglia C, Palladino MT, Carrozza M, Russo MG, et al. Endothelial cell function in patients with Down's syndrome. Am J Cardiol. 2004;94:392–5.

27. Sullivan KD, Lewis HC, Hill AA, Pandey A, Jackson LP, Cabral JM, et al. Trisomy 21 consistently activates the interferon response. Elife. 2016;5.

28. Buie JJ, Renaud LL, Muise-Helmericks R, Oates JC. IFN-alpha negatively regulates the expression of endothelial nitric oxide synthase and nitric oxide production: implications for systemic lupus erythematosus. J Immunol. 2017;199:1979–88.

29. George PM, Oliver E, Dorfmuller P, Dubois OD, Reed DM, Kirkby NS, et al. Evidence for the involvement of type I interferon in pulmonary arterial hypertension. Circ Res. 2014;114:677–88.

30. Papani R, Duarte AG, Lin YL, Kuo YF, Sharma G. Pulmonary arterial hypertension associated with interferon therapy: a population-based study. Multidiscip Respir Med. 2017;12:1.

31. Adang LA, Frank DB, Gilani A, Takanohashi A, Ulrick N, Collins A, et al. Aicardi goutieres syndrome is associated with pulmonary hypertension. Mol Genet Metab. 2018;125:351–8.

32. McDowell KM, Craven DI. Pulmonary complications of Down syndrome during childhood. J Pediatr. 2011;158:319–25.

33. Marcus CL, Keens TG, Bautista DB, von Pechmann WS, Ward SL. Obstructive sleep apnea in children with Down syndrome. Pediatrics. 1991;88:132–9.

34. Maris M, Verhulst S, Wojciechowski M, Van de Heyning P, Boudewyns A. Prevalence of Obstructive Sleep Apnea in Children with Down Syndrome. Sleep. 2016;39:699–704.

35. Dyken ME, Lin-Dyken DC, Poulton S, Zimmerman MB, Sedars E. Prospective polysomnographic analysis of obstructive sleep apnea in Down syndrome. Arch Pediatr Adolesc Med. 2003;157:655–60.

36. Ayeni TI, Roper HP. Pulmonary hypertension resulting from upper airways obstruction in Down's syndrome. J R Soc Med. 1998;91:321–2.

37. Loughlin GM, Wynne JW, Victorica BE. Sleep apnea as a possible cause of pulmonary hypertension in Down syndrome. J Pediatr. 1981;98:435–7.

38. De Lausnay M, Verhulst S, Boel L, Wojciechowski M, Boudewyns A, Van Hoorenbeeck K. The prevalence of lower airway anomalies in children with Down syndrome compared to controls. Pediatr Pulmonol. 2020;55:1259–63.

39. Bertrand P, Navarro H, Caussade S, Holmgren N, Sanchez I. Airway anomalies in children with Down syndrome: endoscopic findings. Pediatr Pulmonol. 2003;36:137–41.

40. Hamilton J, Yaneza MM, Clement WA, Kubba H. The prevalence of airway problems in children with Down's syndrome. Int J Pediatr Otorhinolaryngol. 2016;81:1–4.

41. Gowda S, Bhat D, Feng Z, Chang CH, Ross RD. Pulmonary vein stenosis with Down syndrome: a rare and frequently fatal cause of pulmonary hypertension in infants and children. Congenit Heart Dis. 2014;9:E90–7.

42. Ooi YK, Sinha P, Gierdalski M, Harahsheh A. High-risk single ventricle palliation in children with Down syndrome: single institution experience. Cardiol Young. 2015;25:539–43.

43. Nasr VG, Callahan R, Wichner Z, Odegard KC, DiNardo JA. Intraluminal Pulmonary Vein Stenosis in Children: A "New" Lesion. Anesth Analg. 2019;129:27–40.

44. Seale AN, Webber SA, Uemura H, Partridge J, Roughton M, Ho SY, et al. Pulmonary vein stenosis: the UK, Ireland and Sweden collaborative study. Heart. 2009;95:1944–9.

45. Jackson EO, Davis A. PH Professional Network: Comprehensive evaluation and ongoing approach to children with Down syndrome who have pulmonary hypertension or are at risk of developing pulmonary hypertension. Adv Pulm Hypertens. 2019;18:37–9.

46. Bull MJ. Committee on G. Health supervision for children with Down syndrome. Pediatrics. 2011;128:393–406.

47. Colvin KL, Ivy DD, Yeager ME. Altered Peripheral Blood Myeloid Cell Subpopulations in Children With Down Syndrome and Pulmonary Hypertension. J Pediatr Hematol Oncol. 2017;39:158–9.

48. Bush D, Wolter-Warmerdam K, Wagner BD, Galambos C, Ivy DD, Abman S, et al. EXPRESS: Angiogenic Profile Identifies Pulmonary Hypertension in Children with Down Syndrome. Pulmonary circulation. 2019:2045894019866549.

49. Griffiths M, Yang J, Vaidya D, Nies M, Brandal S, Ivy DD, et al. Biomarkers of Pulmonary Hypertension Are Altered in Children with Down Syndrome and Pulmonary Hypertension. J of Pediatr. 2021.

50. Hawkins A, Langton-Hewer S, Henderson J, Tulloh RM. Management of pulmonary hypertension in Down syndrome. Eur J Pediatr. 2011;170:915–21.

51. Lewanda AF, Matisoff A, Revenis M, Harahsheh A, Futterman C, Nino G, et al. Preoperative evaluation and comprehensive risk assessment for children with Down syndrome. Paediatr Anaesth. 2016;26:356–62.

52. Balint OH, Samman A, Haberer K, Tobe L, McLaughlin P, Siu SC, et al. Outcomes in patients with pulmonary hypertension undergoing percutaneous atrial septal defect closure. Heart. 2008;94:1189–93.

53. Iwaya Y, Muneuchi J, Inoue Y, Watanabe M, Okada S, Ochiai Y. Relationship between pulmonary arterial resistance and compliance in patients with Down syndrome. Pediatr Cardiol. 2019;40:841–7.

54. Fudge JC Jr, Li S, Jaggers J, O'Brien SM, Peterson ED, Jacobs JP, et al. Congenital heart surgery outcomes in Down syndrome: analysis of a national clinical database. Pediatrics. 2010;126:315–22.

55. Duffels MG, Vis JC, van Loon RL, Berger RM, Hoendermis ES, van Dijk AP, et al. Down patients with Eisenmenger syndrome: is bosentan treatment an option? Int J Cardiol. 2009;134:378–83.

56. Serino G, Guazzi M, Micheletti A, Lombardi C, Danesi R, Negura D, et al. Effect of bosentan on exercise capacity and clinical worsening in patients with dual Down and Eisenmenger syndrome. Clin Med Insights Cardiol. 2013;7:29–34.

57. Duffels MG, Vis JC, van Loon RL, Nieuwkerk PT, van Dijk AP, Hoendermis ES, et al. Effect of bosentan on exercise capacity and quality of life in adults with pulmonary arterial hypertension associated with congenital heart disease with and without Down's syndrome. Am J Cardiol. 2009;103:1309–15.

58. Kermeen FD, Franks C, O'Brien K, Seale H, Hall K, McNeil K, et al. Endothelin receptor antagonists are an effective long term treatment option in pulmonary arterial hypertension associated with congenital heart disease with or without trisomy 21. Heart Lung Circ. 2010;19:595–600.

59. D'Alto M, Romeo E, Argiento P, D'Andrea A, Sarubbi B, Correra A, et al. Therapy for pulmonary arterial hypertension due to congenital heart disease and Down's syndrome. Int J Cardiol. 2013;164:323–6.

60. Beghetti M, Rudzinski A, Zhang M. Efficacy and safety of oral sildenafil in children with Down syndrome and pulmonary hypertension. BMC Cardiovasc Disord. 2017;17:177.

61. Klinger JR, Elliott CG, Levine DJ, Bossone E, Duvall L, Fagan K, et al. Therapy for pulmonary arterial hypertension in adults: update of the CHEST guideline and expert panel report. Chest. 2019;155:565–86.

62. Bush D, Wolter-Warmerdam K, Wagner BD, Galambos C, Ivy DD, Abman S, et al. EXPRESS: Angiogenic Profile Identifies Pulmonary Hypertension in Children with Down Syndrome.0:2045894019866549.

63. Gupta M, Dhanasekaran AR, Gardiner KJ. Mouse models of Down syndrome: gene content and consequences. Mamm Genome. 2016;27:538–55.

64. Bush D, Galambos C, Dunbar Ivy D. Pulmonary hypertension in children with Down syndrome. Pediatric pulmonology. 2020.