Comprehensive Evaluation and Ongoing Approach to Children With Down Syndrome Who Have Pulmonary Hypertension or Are at Risk of Developing Pulmonary Hypertension

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Children with Down syndrome and pulmonary hypertension (PH) are a unique and challenging group of patients. Down syndrome, or Trisomy 21, affects approximately one in every 600 to 800 live births. PH, currently defined as a resting mean pulmonary artery pressure of ≥25 mm Hg, is known to increase morbidity and mortality significantly in this group of patients and has been identified in as many as 28% of all patients with Down syndrome. Furthermore, specific risk factors and comorbidities have been shown to increase the chance of developing PH in this population. Careful screening and proper treatment is imperative in children with Down syndrome to prevent the development, recurrence, or progression of PH in this population.

Recent findings from Bush et al demonstrate clear clinical characteristics and risk factors for development of PH in children with Down syndrome. Prior to this study, data regarding the incidence of PH throughout the Down syndrome lifespan, associations with comorbidities, exacerbating factors, and overall impact of PH in the Down syndrome population were lacking. Most notably, perhaps, was their finding that a vast majority (87%) of patients who suffered from recurrent PH after a previous resolution were classified as World Health Organization (WHO) Group 3 or associated with lung disease. The study also demonstrated that obstructive sleep apnea (OSA), recurrent hypoxia, and aspiration are clear risk factors for development or recurrence of PH. Given these findings, we as providers must take an organized approach in screening for potentially preventable lung insults that contribute to the development and further progression of PH.

CLASSIFICATION AND INCIDENCE
It is well known that PH in children with Down syndrome is most frequently classified as Group 1 PH (PAH, pulmonary arterial hypertension) associated with congenital heart disease (CHD) or persistent pulmonary hypertension of the newborn (PPHN), and oftentimes a combination of the two. For one cohort of children with Down syndrome followed prospectively in the Netherlands, 5.2% had PPHN, which is significantly higher than the reported 0.1% in the general population. In the large group of children followed in the Down Syndrome Clinic at Denver Children’s Hospital (n=1252), of the 28% identified as having PH, 82% had associated CHD and 45% had PPHN. The most common cardiac congenital malformations associated with Down syndrome include atrioventricular canal, patent ductus arteriosus, atrial septal defect, and ventricular septal defect, all of which include cardiac shunts that can lead to PH due pulmonary over circulation. The American Academy of Pediatrics (AAP) recommends an echocardiogram in the first month of life for all babies with Down syndrome; therefore, most are diagnosed and repaired in infancy.

While cardiopulmonary abnormalities including CHD and PPHN are the most common etiology of PH onset in infancy, lung disease is the more common etiology seen after infancy or with recurrent disease. It appears that PH develops more readily from hypoxia in the Down syndrome population, and that children with a prior diagnosis of PH are more likely to develop a recurrence of disease in the context of a respiratory comorbidity such as OSA, intermittent hypoxia, recurrent pneumonia, and chronic aspiration. Given the high rate of respiratory comorbidities in these children, it is not surprising that 87% of children experiencing a second episode of PH after a previous resolution were classified as WHO Group 3. For any patient with Down syndrome and PH (or history of PH), a primary pediatric pulmonologist should be identified and follow the patient along with the PH team indefinitely.

For those Down syndrome patients who have resolution of their PH, it is imperative they have regular screening for comorbid respiratory conditions despite the presence or absence of symptoms.
Given what we know about this population, we are empowered to prevent the recurrence of PH in this high-risk population by continuing to regularly screen for respiratory comorbidities, rather than screening only after echocardiogram evidence of PH becomes apparent.

FREQUENT COMORBID CONDITIONS

Aspiration
A frequently overlooked cause of PH and other respiratory symptoms in Down syndrome is unrecognized aspiration. Children with Down syndrome are at significant risk for chronic aspiration due to delayed oral development, structural abnormalities, and hypotonia. One study of patients with Down syndrome followed in a sleep clinic in the United Kingdom showed 16/17 computerized tomography (CT) scans done on this population revealed findings suggestive of aspiration. In the Denver cohort, 35% of all patients with Down syndrome with PH were reported to have chronic aspiration. That number increased to 48% of patients with recurrent PH, highlighting the significant role chronic aspiration can play in chronic PH, emphasizing the need for ongoing OSA screening. While adenotonsillectomy can improve sleep-disordered breathing in this population, underlying airway structure or dynamics may cause significant residual OSA. Because of this, reassessment after surgery is also imperative.

Parenchymal and Structural Airway Disease
Children with Down syndrome are known to have an increased incidence of pulmonary abnormalities when compared to the general population. Common airway abnormalities include anomalies such as macroglossia, tonsil and adenoid hypertrophy, laryngomalacia, tracheobronchomalacia, subglottic stenosis, and tracheal stenosis. These airway abnormalities predispose patients to intermittent hypoxia, which can lead to the development of PH in this at-risk population. In one review, approximately 50% of patients with upper airway obstruction had PH documented by echocardiogram or cardiac catheterization, with 91% resolution of PH following surgery. While we know patients with Down syndrome can also have primary parenchymal lung disease (such as pulmonary hypoplasia, pulmonary lymphangioleiomyomatosis, lymphoid interstitial pneumonitis, and other interstitial lung disease), they are more likely to have diffuse parenchymal disease from secondary causes such as postinfectious changes, chronic lung disease of prematurity, and chronic aspiration. Interestingly, there are significantly lower rates of asthma in the Down syndrome population, which should prompt the provider to screen for alternative causes of coughing and wheezing.

These well recognized comorbidities highlight the importance of proper screening for pulmonary abnormalities, including advanced imaging with high-resolution chest CT at the time of PH diagnosis or recurrence, and need for good, ongoing pulmonary specialty care. Furthermore, it is has been shown that patients with Down syndrome may not respond to pulmonary vasodilators in the same way as patients without Down syndrome, potentially indicating that ongoing pulmonary (or other) insults have not been properly identified or treated correctly prior to initiation of PH-specific
therapy. The Pediatric PH Guidelines from the American Heart Association and American Thoracic Society also highlight the importance of identifying and treating primary or secondary respiratory disease prior to the initiation of long-term pulmonary vasodilator therapy.

**CONCLUSION**

Given what we currently know about Down syndrome and PH, our PH center at Seattle Children’s Hospital has developed guidelines and standards of care for the patient with Down syndrome throughout their lifespan (Table 1). Both inpatient and outpatient PH referrals too often come after months to years of unrecognized pulmonary insults. With proper education and reinforcement of proposed guidelines for screening, our hope is that comorbidities are recognized and treated prior to the development of or worsening of PH, ideally prior to referral to the PH center, but certainly as part of the ongoing, comprehensive care of the child with Down syndrome and PH.

**References**


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<thead>
<tr>
<th>Table 1. Seattle Children’s Hospital screening guidelines for children with Down syndrome and PH or at risk of developing PH</th>
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<tbody>
<tr>
<td><strong>AAP standard of care for all patients with Down syndrome</strong></td>
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<td><strong>Echocardiogram</strong></td>
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<td><strong>Pulmonology consult</strong></td>
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<td><strong>VFSS</strong></td>
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<td><strong>Sleep study</strong></td>
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<td><strong>Chest CT</strong></td>
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<tr>
<td><strong>Lab surveillance:</strong></td>
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Dry mouth or aspiration may be considered for ongoing evidence of aspiration, other parenchymal disease, or pulmonary venous obstruction.

No improvement in PH / worsening

As frequent as PH team suggests

As frequent as PH team suggests

Continue to follow regularly until lung disease r/o as contributing factor

At least annually (more frequent if unexplained worsening)

Annually repeat after any surgical airway management

Consider repeating at intervals decided with primary pulmonologist to screen for ongoing evidence of aspiration, other parenchymal disease, or pulmonary venous obstruction

At least annually. BNP more frequently to trend response to treatment

**References**