

## Treatment of Pulmonary Hypertension in Down's Syndrome

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### Abstract

Down's Syndrome (DS) is the most common chromosomal abnormality associated with multiple comorbidities including congenital heart disease and respiratory disease typically with airway obstruction. These comorbidities have been documented to contribute to pulmonary arterial hypertension (PAH) within months if left untreated. It is therefore of paramount importance to identify congenital abnormalities to prevent the progression of PAH in such people. Since people with DS have a higher risk of developing PAH in comparison to the normal population, they must be both monitored for symptoms of disease as categorized by WHO functional class and be actively treated in order to halt or slow the disease process.

**Keywords:** Pulmonary hypertension; Chromosomal abnormality; Trisomy 21

### Background

Down's syndrome (trisomy 21) is the most common chromosomal abnormality with incidence ranging from 1 in 319 to 1 in 1000 live births. It is well known that DS is associated with multiple comorbidities, 50% of children having congenital heart disease (CHD) [1]. The Atlanta Down's syndrome project documented structural abnormalities ranging from Ventricular septal defect (VSD) to Tetralogy of Fallot [2]. The most common CHD was atrioventricular septal defect (AVSD) with 45% prevalence. Other potential structural abnormalities in DS patients include airway obstruction with adenotonsillar hypertrophy and malacic airways [3]. CHD, obstructed airways and Gastro-oesophageal reflux (GOR) are comorbidities that predispose DS patients to pulmonary arterial hypertension (PAH) which is amplified by DS patients having a higher risk of PAH in comparison to those without DS [4,5]. Other causes of PAH are outlined in Table 1.

### Pathogenesis

PAH is defined as a raised mean pulmonary arterial pressure greater than 25mmHg at rest with no evidence of left atrial hypertension (left atrial mean pressure <15 mmHg). PAH may occur secondary to increased blood flow in the pulmonary arteries, which are commonly in association with CHD, for example a left to right shunt. The abnormal circulation causes stress on the pulmonary vasculature allowing remodelling to take place by a combination of proliferation, hypertrophy and impaired growth [6]. This can lead to arterial obstruction resulting in high pulmonary vascular resistance [3].

PAH is typically associated with non-specific symptoms but if left untreated then Eisenmenger's syndrome can develop [7]. This is an

irreversible, obstructive pulmonary vascular disease with a reversal of shunt due to the resistance in the pulmonary circulation exceeding that of the systemic. This is the most severe form of PH, and patients will suffer with central cyanosis and chronic hypoxaemia [8].

### Diagnosis

Pulmonary vasculature irreversible changes can take place within 6 months in DS patients with CHD, with the most common and severe shunts (AVSD) causing problems at the earliest age [3]. Therefore it is important to establish diagnosis and initiate treatment for these patients without delay.

DS is screened antenatally in the first trimester with combined screening tests, including nuchal translucency, beta-human chorionic gonadotrophin and pregnancy associated plasma protein A and definitive diagnostic tests of amniocentesis and chorionic villus sampling. Once the diagnosis of DS has been made, fetal echocardiography is performed to assess for CHD. We know that PAH development has numerous contributing factors and therefore a full respiratory screen and echocardiography is repeated as soon as possible postnatally, treatment can then be targeted at the underlying problem. A normal echocardiogram is often repeated at 3 weeks to eliminate the masking of CHD left to right shunts by respiratory inefficiency and the high pulmonary vascular resistance seen in all babies at the time of birth. Evidence of CHD manifests as high or low pulmonary blood flow. Heart failure, wet lungs and poor weight gain indicate high flow, whereas low flow (with right to left shunt) is indicated by cyanosis without heart failure [9]. Abnormal respiratory screen includes adenotonsillar hypertrophy which may appear over the next few years and which, after further investigation by bronchoscopy and polysomnography, can be corrected by adenotonsillectomy and malacic airways are usually investigated and managed with night oxygen or even non-invasive ventilation. Prophylactic antibiotics and anti-reflux medication are frequently prescribed to prevent airway disease progressing to PAH.

Neonatal	Persistent pulmonary hypertension, respiratory distress syndrome, chronic lung disease
Cardiac	Left to right shunt (ASD, VSD, AVSD, PA), Transposition of the great arteries, obstructive lesions (TAPVC, MS, HLHS, HOCM, DCM)
Acquired	Chronic hypoxia (Cystic fibrosis, high altitude), scoliosis, airway obstruction (OSA, tonsillar hypertrophy, tracheal stenosis), vasculitis (uncommon- connective tissue disease, sickle cell)
Idiopathic	Sporadic, familial
ASD, atrial septal defect; AVSD atrioventricular septal defect; DCM, dilated cardiomyopathy; HLHS, hypoplastic left heart syndrome; HOCM, hypertrophic obstructed cardiomyopathy; MS, mitral stenosis; OSA, obstructive sleep apnoea; PA, pulmonary arterial; TAPVC, total anomalous pulmonary venous connection; VSD, ventricular septal defect	

**Table 1:** Causes of PAH in paediatrics. Adapted from Tulloh, 2005 [5].

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## Management

Management of PAH in DS is with a multidisciplinary team approach with PH specialist involvement to obtain maximum benefit for the patient. Cardiac abnormalities are quickly recognized by echocardiography. High pulmonary blood flow is treated surgically to correct the CHD, usually at 3-6 months of age. Low blood flow (for example tetralogy of Fallot) is managed according to the degree of obstruction to the pulmonary circuit but will end with a surgical intervention usually around 6 months of age. In those where the cardiac anatomy is normal, further investigations will be needed to determine the cause of the PAH. Cardiac catheterisation to evaluate the degree of pulmonary vascular resistance (PVR) is undertaken and a series of investigations including ECG, and blood tests to rule out clotting abnormalities, infections, autoimmune disease, and other respiratory disease for example  $\alpha 1$  antitrypsin deficiency. It is important to note that babies require general anaesthetic for cardiac catheterization, and even in the older child, this is distressing. However, people with DS are a high-risk group for general anaesthetic and therefore cardiac catheterisation needs to be performed in a Centre with all the skills and support mechanisms in place. Vaso-reactivity studies use oxygen and nitric oxide to determine pulmonary dilator response as a means to determine prognosis and to guide therapy. In the case of Eisenmenger's syndrome, children are usually much older, diagnosis is clear-cut and cardiac catheterisation is not necessary and can be dangerous with hypoxia from anaesthesia causing a profound rise in pulmonary vascular resistance. At the same time as the anaesthetic for pulmonary vascular resistance measurement, it is simple to perform bronchoscopy. This avoids the risk of further anaesthesia and can lead to a diagnosis of malacic airways. Sometimes, floppy upper airways require surgical intervention, such as aryepiglottoplasty, which strengthens the upper airway and can reduce the obstructive sleep apnoea that could otherwise ensue.

In cases where cardiac catheterisation is inappropriate, echocardiography can be used to estimate PA pressure. The peak velocity of tricuspid regurgitation jet,  $>2.7\text{m/s}$ , in the absence of high pulmonary blood flow or right ventricular outflow tract obstruction, is indicative of a diagnosis of PAH and will be present in all children and young adults with Eisenmenger syndrome. Other factors should be assessed if there is a diagnosis of PAH including quality of life measures, assessment of right ventricular function on echocardiography (Tricuspid annular plane systolic excursion [TAPSE] and tissue Doppler interrogation [S wave velocity], and six-minute walk test [7]). However, the walk test is difficult to perform in children with DS since they can struggle to comply in a reliable manner that is needed to make the test meaningful.

New York Health Association (NYHA) functional classification is used alongside other clinical tests to describe the severity of activity limitation due to PAH, taking into consideration severity of symptoms and quality of life [10]. WHO functional class can be assigned without clinical tests, just by taking a history from the patient or the patient's family. WHO functional class, modified for pulmonary hypertension, adds specific clinical value when deciding on treatment for an individual (Table 2).

## Treatment

Once surgery and correction of underlying factors contributing to PAH have been resolved, the next step is drug therapy, which is based on WHO functional class. Therapy is in keeping with British cardiovascular society guidelines. Old fashioned therapy includes diuretics, digoxin, warfarin and calcium channel blockers. These are rarely used now, except in the occasion where there is a specific indication (for example in

WHO functional class	Clinical description
Class I	Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain or near 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:** WHO functional class. Adapted from Hawkins et al, 2009 [7].

the small proportion of people when they are responders to pulmonary vasodilators during the right heart catheter study).

First line treatment is recommended with the phosphodiesterase Va inhibitor, sildenafil. This is now very inexpensive if used generically and has been shown to have minimum side effects. The dose should be limited in small children to 1mg/kg (maximum 10mg) three times a day and side effects can be stuffy nose, acid gastro-oesophageal reflux and nose bleeds.

Additional therapy includes the endothelin receptor antagonists such as Bosentan, Macitentan and Ambrisentan. As a newer class of drug, these have proven benefit in congenital heart disease and DS. They are expensive and require monitoring of the liver function and blood count [3]. They are, like other PAH disease-modifying therapy, only to be prescribed and managed by specialists in pulmonary hypertension. A third class of drug – the prostanoids - is also available to treat PAH. Epoprostenol, a synthetic prostacyclin agonist is the most effective, but requires the use of an indwelling central line, management of which is not straightforward in young children, especially those with DS. In addition, this therapy is extremely expensive and is only used on rare occasions. Other medications are constantly being developed and may find their way into the pharmacopoeia for children and young adults with PAH, in order to help manage this difficult condition and to improve the life expectancy. A recent meta-analysis of studies found that overall current guidelines for active treatment resulted in reduction of mortality [7]. Dual therapy is of use in patients with more severe PAH.

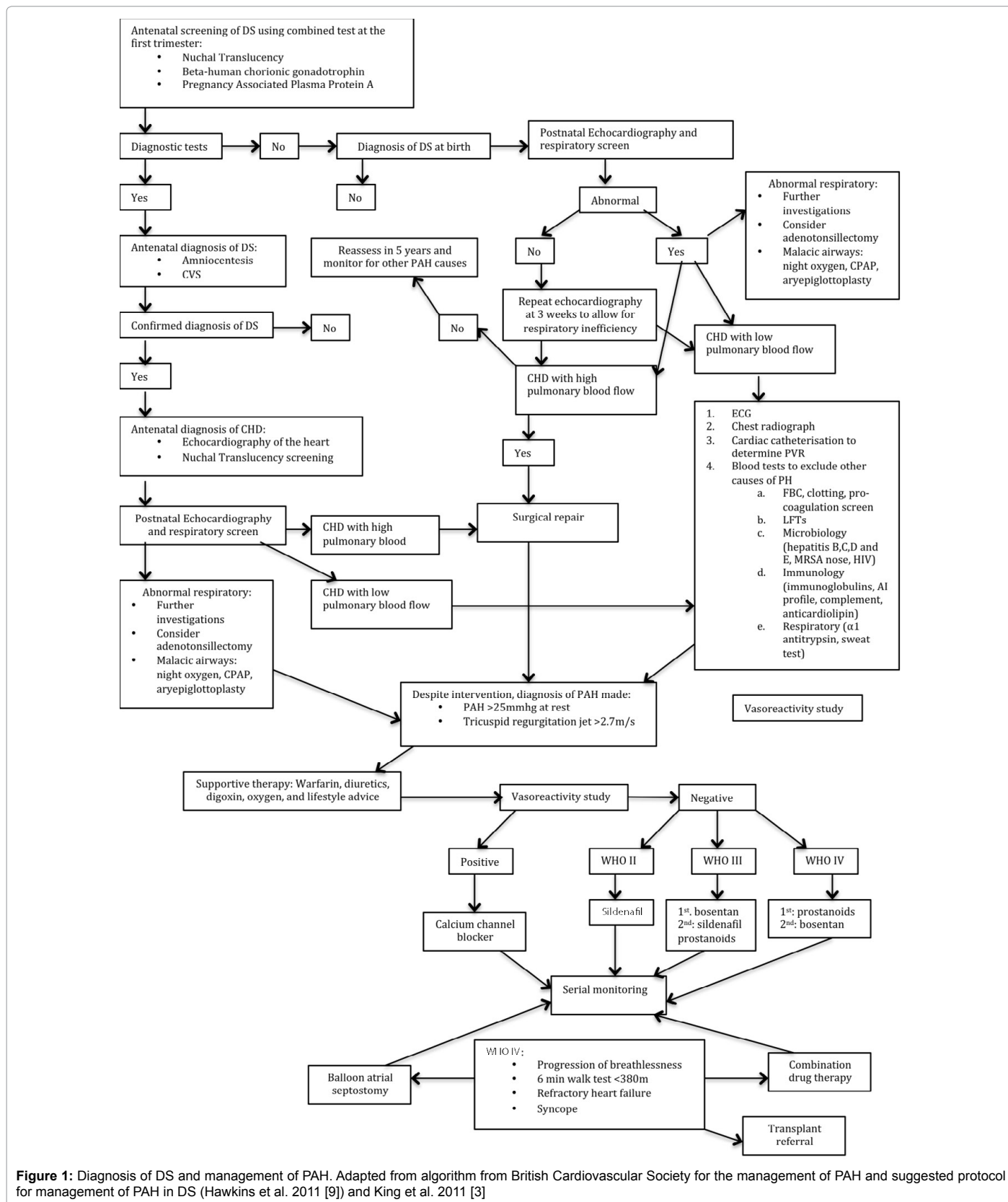
The decision to start oral therapy for PAH is a joint decision by the MDT, the families and patient. The obvious undesirable side effects for Sildenafil (priapism) make it unpopular with the families of male DS patients. In practice, Epoprostenol is also rarely used because of the need for indwelling central lines and there are safety issues surrounding people with DS undergoing general anaesthetic. Bosentan is therefore often used and although it does not prevent progression of the disease, it has been shown to slow down its course with an improvement of quality of life as reported by the patients and family.

The current British Cardiovascular Society guidelines focus on PAH treatment in all patients and are not specific to DS. There is debate on whether the effects of medication are the same as in people without DS and further research needs to be undertaken to resolve these questions.

Transplant is the final stage of treatment for PAH but is frequently not a simple undertaking in people with DS. As compliance with anti-rejection medication and the number of monitoring tests that have to be completed, are important for transplant success, this is thought to have

a serious impact on quality of life. The decision to undertake transplant is again an MDT decision and is made after with full explanation and

discussion with the patient's family to understand whether this is the most appropriate treatment (Figure 1).



**Figure 1:** Diagnosis of DS and management of PAH. Adapted from algorithm from British Cardiovascular Society for the management of PAH and suggested protocol for management of PAH in DS (Hawkins et al. 2011 [9]) and King et al. 2011 [3]

## Summary

PAH can progress very quickly in DS patients with a number of contributing factors affecting the development of the disease. These include upper airway obstruction, tracheobronchomalacia, hypoplastic lung volume, gastro-oesophageal reflux and congenital heart disease (CHD). Screening for CHD is important, but it is equally vital to screen for other causes of PAH common in DS such as obstructed airways and to manage contributing factors for example gastroesophageal disease.

Early intervention with surgery for CHD and management of obstructed airways can help to prevent PAH progression. Large ventricular and atrio-ventricular septal defects and also large persistent arterial ducts need to be closed in the first few months of life (3-6 months) in order to reduce the risk of pulmonary vascular disease. It is important to eliminate as many contributing factors to PAH to minimise disease process. Despite this, some DS patients still require vasodilator therapy emphasizing the importance of MDT approach and following up these patients into adult life.

Current methods of assessing PAH are clinically useful since multiple factors are considered together. This includes clinical symptom assessment and quality of life determine the patient's WHO functional class, which is important before prescribing therapy. Also, the use of echocardiography and differential oxygen saturations will detect significant CHD at an early stage, preferably in the first month of life.

The current life expectancy for PAH and DS patients is into the fourth or fifth decade of life it is known that the comorbidities can have a significant impact on their quality of life, so more research needs to be done to better understand the future for DS and PAH patients.

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