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## Development of pulmonary hypertension remains a major hurdle to corrective surgery in Down syndrome

Akash Batta, Juniali Hatwal

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### Abstract

Down syndrome is the most common chromosomal abnormality encountered in clinical practice with 50% of them having associated congenital heart disease (CHD). Shunt lesions account for around 75% of all CHDs in Down syndrome. Down syndrome patients, especially with large shunts are particularly predisposed to early development of severe pulmonary hypertension (PH) compared with shunt lesions in general population. This necessitates timely surgical correction which remains the only viable option to prevent long term morbidity and mortality. However, despite clear recommendations, there is wide gap between actual practice and fear of underlying PH which often leads to surgical refusals in Down syndrome even when the shunt is reversible. Another peculiarity is that Down syndrome patients can develop PH even after successful correction of shunt. It is not uncommon to come across Down syndrome patients with uncorrected shunts in adulthood with irreversible PH at which stage intracardiac repair is contraindicated and the only option available is a combined heart-lung transplant. However, despite the guidelines laid by authorities, the rates of cardiac transplant in adult Down syndrome remain dismal largely attributable to the high prevalence of intellectual disability in them. The index case presents a real-world scenario highlighting the impact of severe PH on treatment strategies and discrimination driven by the fear of worse outcomes in these patients.

**Key Words:** Down syndrome; Congenital heart disease; Pulmonary hypertension; Cardiac transplantation; Pulmonary vascular resistance; Surgical correction

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**Core Tip:** Down syndrome is the most common chromosomal abnormality with roughly half of them having associated congenital heart disease (CHD). People with Down syndrome are especially predisposed to early development of severe pulmonary hypertension (PH) compared with CHDs in general population. It is not uncommon to come across Down syndrome patients with uncorrected shunts in adulthood with irreversible PH at which stage the only option available is a combined heart-lung transplant. However, despite the guidelines laid by authorities, the rates of cardiac transplant in adults with Down syndrome remain dismal largely attributable to the high prevalence of intellectual disability in them.

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## INTRODUCTION

Down syndrome is the most common chromosomal abnormality encountered in clinical practice[1]. Congenital heart disease (CHD) is present in roughly half of all people with Down syndrome and remains the leading cause of mortality in this population[2]. Amongst the wide variety of CHDs seen in Down syndrome, shunt lesions in particular atrio-ventricular septal defects and ventricular septal defects are the most frequent accounting for 3/4<sup>th</sup> of all CHDs in this population[3]. People with Down syndrome especially with large shunts are particularly predisposed to early development of severe pulmonary hypertension (PH) compared with CHDs in general population (10 times higher risk) [4,5]. In patients with Down syndrome and large post-tricuspid shunts, PH is present in up to 1/3<sup>rd</sup> of them within the first year itself[6,7]. The reason for earlier development of significant PH is attributable to genetic predisposition and associated comorbidities (most notably lung developmental disorders). Another peculiarity is the development of PH even after timely corrective repair of the shunt lesions in some patients with Down syndrome[6]. Thus, screening for PH is an essential component of life-long care in Down syndrome.

Therefore, in Down syndrome early surgical repair is critical in preventing the development of PH which once established significantly increases the procedural risks and prohibits surgical repair. Development of severe and irreversible PH (Eisenmenger syndrome) due to structural changes and fibroses in pulmonary vasculature is associated with high morbidity and mortality in these patients. Guidelines recommend management of shunt lesions in Down syndrome similar to general population, however, early development of severe PH often leads to reluctance on the part of surgeon to go ahead with corrective repair. The reluctance is largely driven by the fear of adverse hemodynamic consequences of severe PH in these patients. Further, limited representation of Down syndrome patients in trials of PH reducing therapies (endothelin antagonists and prostacyclin analogues) makes choice of optimal medical therapy difficult which further contributes to poorer outcomes[8,9].

## SURGICAL INTERVENTION IN DOWN SYNDROME WITH CHD

Despite, the high-risk nature of intracardiac repair in Down syndrome, there has been progress over the last few decades and now intracardiac repair is increasingly being offered to this subset of patients[10]. In general, patients with Down syndrome are much younger and have lower body weight at the time of intracardiac repair compared to general population[11]. Overall, the increased perioperative risk and high prevalence of non-cardiac developmental diseases has resulted in lack of enthusiasm amongst pediatric cardiac surgeons to take these patients up for intracardiac repair despite the evidence supporting comparable outcomes of cardiac surgery in these patients[12]. As such, presentation at a later stage with severe PH and shunt reversal is not uncommon[4,5]. At this stage given the pulmonary vascular resistance and irreversible nature of PH, intracardiac repair is contraindicated and the only option available is a combined heart-lung transplant. However, this is easier said than done with dismal rates of transplant procedures being performed in these patients. Since the first report of heart-lung transplant in Down syndrome in 1996 after a national wide anti-discrimination campaign, only a handful of Down syndrome patients have undergone cardiac transplant rendering the assessment of outcomes difficult[13,14]. A major reason for low rates of cardiac transplant in adult Down syndrome remains the high prevalence of intellectual disability in them[7]. Another major concern remains the predisposition of Down syndrome to develop oncological disorders which is further aggravated because of the immunosuppressive agents post-transplant and Epstein-Barr virus infection[15]. Nonetheless, the international society for heart-lung transplant and the committee on bioethics has made clear stance that patients with Down syndrome should be given equal right to transplant listings and that discrimination on the basis of intellectual disability or syndrome is unjustified[13,16].

The recent paper by Kong *et al*[17], appropriately reflects the current practice in regards to the management of Down syndrome with CHD. In the index paper, a 13-year-old boy having a large atrial septal defect and patent ductus arteriosus (PDA), underwent PDA closure in childhood. Despite, this he developed severe PH many years later. This in fact highlights the genetic predisposition to develop that these patients have which is not the case in shunt lesions with normal chromosomal structure. Given the high pulmonary vascular resistance, the boy was denied definitive a procedure (heart-lung transplant) at multiple hospitals possibly due to the fear of worse outcome. This is a reflection of the wide gap

between recommendations and actual clinical practice. As mentioned earlier the governing authorities should provide Down syndrome patients with equal opportunities for heart transplantation, which is in fact is hardly ever the case in real world setting [13,16,18]. The authors deserve credit for their decision to offer heart-lung transplant to the index child albeit it did not materialize on this occasion.

## CONCLUSION

Down syndrome with CHD is particularly predisposed to develop severe PH early in the course. Hence, timely surgical correction is crucial to improve long term outcomes. Another oddity in these patients is the development of PH even after successful closure of the shunt lesions which highlights the predisposition to develop pulmonary remodeling and fibroses de novo. The index case highlights the same and also raises concern for the discrimination faced by this group of individuals and preferential exclusion from advanced intervention in the form of heart-lung transplantation despite the opposition to the same by the governing bodies.

## FOOTNOTES

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