

## Lower Respiratory Conditions in Down Syndrome: Review Article

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### ABSTRACT

**Background:** Down syndrome (DS) is by far the most common chromosomal abnormality, manifested clinically with distinctive dysmorphism, functional and anatomical defects compromising multiple body systems with greater impact on respiratory system. **Objective:** This review aim to review and summarize reported lower respiratory conditions that exceeded the general population prevalence and their clinical outcomes in DS.

**Methods:** The databases were searched for articles published on 2 databases [PubMed and Google scholar] and Boolean operators (and, or, not) had been used such as [Down syndrome, trismomy21, respiratory, pulmonary] and in peer-reviewed articles between January 2005 and June 2022.

**Conclusion:** The spectrum of lower respiratory conditions in Down syndrome is wide. Multiple conditions confirmed to be higher in individuals with DS compared to normal population. In this article we reviewed the prevalence and outcomes of lower respiratory infections, recurrent wheezing, airways anomalies, pulmonary artery hypertension (PHN), Morgagni hernia and subpleural cysts. The rarity and the non-specific clinical presentation of some conditions lead to delayed diagnosis and intervention, warranting a need for awareness efforts targeting general practitioners and general pediatricians.

**Keyword:** Congenital anomalies, Down syndrome, Pneumonia, Pulmonary hypertension, Wheezing.

### INTRODUCTION

Down syndrome (DS) is the most common chromosomal abnormality in the general population with an incidence around 1 in 700 live birth <sup>[1]</sup>. It was first described by **John Langdon Down** in 1866 <sup>[2]</sup>. In most cases it is caused by an additional partial or complete copy of human chromosome 21 <sup>[3]</sup>.

This chromosomal anomaly is characterized by distinctive dysmorphic features, anatomical anomalies and functional defects. Variable body systems can be involved, including but not limited to respiratory system <sup>[1]</sup>.

People with Down syndrome have a life expectancy about 3 decades lower than the general population. Congenital heart disease and respiratory illnesses are the most common causes of early death <sup>[4]</sup>. Respiratory conditions account for one third of deaths of children with DS <sup>[5]</sup>.

Lower respiratory illnesses spectrum includes but not limited to increased risks of lower respiratory tract infections, recurrent wheezing, airways anomalies, interstitial lung disease, pulmonary artery hypertension (PHT), and Morgagni hernia <sup>[1,6-8]</sup>.

Although there has been a noticeable improvement in Down syndrome care, awareness of lower respiratory illnesses in DS is necessary <sup>[1,4]</sup>. In this article we will review lower respiratory conditions that could be encountered in DS.

### Lower respiratory tract infections

Individuals with Down syndrome has increased risk of contracting respiratory infections because of their

structural abnormalities, inability to control respiratory secretions and immune impairment involving both humoral and cellular arms of the immune system <sup>[4,9]</sup>.

Pneumonia is more common in DS than general population <sup>[9]</sup>. Individual with DS are prescribed with antibiotics for pneumonia more often than general population <sup>[10]</sup>. They have higher risk for respiratory tract related hospitalization with longer hospital stay <sup>[4,9,11]</sup>. Pneumonia was also a lot more common cause of death amongst people with Down syndrome than in the general population <sup>[4]</sup>.

Aspiration pneumonia is higher in individual with Down syndrome compared to normal population <sup>[4]</sup>.

**Day et al.** <sup>[12]</sup> reported standardized mortality ratios of 140.4 for aspiration pneumonia as a cause of death among individuals with Down syndrome compared with the general population.

**Stanley et al.** <sup>[8]</sup> reported that 39% of screened Down syndrome had dysphagia severe enough to warrant formula consistency change or nonoral feeds in particular individual with functional airway/respiratory abnormalities. Infants with desaturation with feedings and respiratory/airway anomalies had a significant risk for feeding and swallowing disorders. DS who are premature or underweight had an increased risk of dysphagia.

Bronchiolitis, especially that caused by respiratory syncytial virus (RSV) is a common cause of hospitalization in the general population, up to 3% of children are hospitalized because of RSV bronchiolitis <sup>[13,14]</sup>. The percentage of DS children who are hospitalized with RSV-Bronchiolitis varying from 9.6% to 19.5% <sup>[15]</sup>.

<sup>[19]</sup>. DS have higher severity score, longer hospital stay, more pediatric intensive care unit (PICU) admissions and more need for respiratory support compared to general population <sup>[16,20,21]</sup>. Down syndrome alone is an independent risk factor for severe RSV bronchiolitis and may benefit from RSV prophylaxis <sup>[22]</sup>.

The negative impact of recurrent attacks of respiratory infection on motor and mental development was reported <sup>[23,24]</sup>.

**Van Trotsenburg *et al.*** <sup>[24]</sup> reported that DS with recurrent pulmonary disease had greater motor development delay at the age of 2 years. Similarly, **Verstegen *et al.*** <sup>[23]</sup> reported that recurrent respiratory tract infections in DS correlated with mental and motor delay.

During COVID-19 pandemic, DS reported having 4 folds COVID-19 related hospitalizations and 10 folds COVID-19 related deaths compared to matched general population <sup>[25]</sup>.

### Wheezing and asthma

Recurrent wheezing is more common in DS than non-DS. **Bloemers *et al.*** <sup>[26]</sup> reported that DS previously hospitalized with RSV-bronchiolitis had a prevalence of physician-diagnosed wheeze compared to DS children without previous RSV hospitalization (36% vs 30%, respectively). Conversely, the prevalence of recurrent wheezing in non-DS children previously hospitalized with RSV-bronchiolitis compared to non-DS without previous RSV hospitalization is (31% vs 8%, respectively). Meaning that previous RSV-bronchiolitis is not a contributing factor of recurrent wheezing in DS.

**Weijerman *et al.*** <sup>[27]</sup> reported that the parents of DS individuals reported significantly higher wheezing episodes in the past 12 months compared to matched non-DS control. However, physicians' diagnosis of asthma was significantly less in DS compared to control (3.1% vs 6.7, respectively,  $p=0.04$ ). Researchers found no sensitization inhalation allergens in DS group ( $n=24$ ).

In summary, recurrent wheezing is a common presentation in DS but neither asthma nor previous RSV-bronchiolitis are contributing factors in these recurrent wheezing episodes <sup>[26,27]</sup>.

### Airway anomalies

Down syndromes population have higher prevalence of airways anomalies compared to the normal population <sup>[28,29]</sup>. Airway endoscopy showed that 75.8% of those who underwent the procedure had airways anomalies <sup>[30]</sup>. The indications of endoscopic procedures are difficult extubation, stridor, atelectasis, recurrent chest infections and chronic cough <sup>[28-30]</sup>.

The commonest airways anomalies were airway malacia in 44% (mainly tracheomalacia followed by laryngomalacia and bronchomalacia). Tracheal bronchus

in 3.1%, subglottic stenosis in 3.1% and combined anomalies in 20%. Tracheomalacia was significantly higher in DS compared to control (33% in DS vs. 7.4%, respectively) <sup>[30]</sup>.

**Moreno *et al.*** <sup>[31]</sup> reported that 8.3% of patients with tracheal bronchus had DS. Other form of tracheal anomalies were reported to be higher in DS than non-DS, like congenital and acquired tracheal stenosis and compression of trachea by vascular anomalies like vascular ring or sling.

### Pulmonary artery hypertension

Pulmonary artery hypertension (PHN) needs to be considered in DS individuals once clinically suspected, as it can lead to unwanted irreversible complications <sup>[1]</sup>.

In one large retrospective cohort PHN findings were suggested in 28% of 1252 cases of DS. However, most of the cases were discovered early in life reflecting a high incidence of persistent pulmonary artery hypertension (PPHN). in DS, around 70% will had a transient PHN and the remaining will had persistent PHN or recurrent PHN <sup>[32]</sup>. Identified risk factors to develop PHN in DS are: Congenital heart disease (CHD), obstructive sleep apnea (OSA), intermittent hypoxia, recurrent attacks of pneumonia, bronchopulmonary dysplasia and interstitial lung disease <sup>[32,33]</sup>.

### Morgagni hernia

Morgagni hernia is a rare form of diaphragmatic hernia, characterized by herniation of abdominal contents thorough retrosternal diaphragmatic defects <sup>[34]</sup>. The main presentation is a nonspecific recurrent attacks of chest infection. Since the incidence of Morgagni hernia is rare and the symptoms are nonspecific, delayed diagnosis is expected <sup>[34,35]</sup>.

A correlation between DS and Morgagni hernia was reported. Out of all Morgagni hernia 30% to 50% had Down syndrome <sup>[34,35]</sup>. All DS individuals with recurrent attacks of chest infections need to be screened for Morgagni hernia <sup>[34]</sup>. Once Morgagni hernia is diagnosed, surgery is indicated. Recurrence may happen <sup>[34,35]</sup>.

### Subpleural cysts

Subpleural cysts are a unique finding in Down syndrome and a common finding in chest CT scan. **Biko *et al.*** <sup>[8]</sup> reported a prevalence of subpleural cysts among DS as high as 36%. It is poorly understood but linked to underlying lung hypoplasia <sup>[8]</sup>.

Previous observation of early death of DS children with subpleural cyst was reported. It is very important not to confuse these cysts with other similar radiological findings like honeycomb or bronchiectasis <sup>[8]</sup>.

**Table (1):** Summary of lower respiratory conditions that were more prevalent in DS

Recurrent attacks of Pneumonia
Recurrent attacks of wheezing*
RSV-related hospitalizations
COVID19 related hospitalizations
Swallowing incoordination
Pulmonary artery hypertension
Tracheomalacia
Bronchomalacia
Laryngomalacia
Airways vascular compression (Like vascular ring and sling)
Tracheal bronchus
Tracheal stenosis (congenital and acquired)
Morgagni hernia
Subpleural cysts
Lung hypoplasia
Recurrent attacks of Pneumonia

\*Note: Asthma, post RSV-bronchiolitis recurrent wheezing and allergens sensitization were less than normal population.

## CONCLUSION

Down syndrome is a predisposing factor for multiple lower respiratory conditions. It increases the burden on families and on healthcare providers. The spectrum of these conditions is wide, including recurrent lower respiratory tract infections, recurrent wheezing episodes, pulmonary artery hypertension, swallowing incoordination, airway congenital anomalies Morgagni hernia, subpleural cysts and lung hypoplasia. The overlap of the clinical presentations and the rarity of some conditions is challenging and needs awareness efforts targeting frontline physicians.

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