



Respiratory disorders in Down's syndrome: overview with diagnostic and treatment options

Summary of a presentation by Dr Iolo Doull
Consultant Respiratory Paediatrician, Respiratory/Cystic Fibrosis Unit,
University Hospital of Wales, Cardiff

This overview mainly covers the portion of the respiratory tract distal to the epiglottis. Problems related to the upper airway are covered in this series in the overview on sleep-related upper airway obstruction (srUAO).

Respiratory problems are a primary cause of morbidity and/or hospital admission particularly in young children with Down's syndrome. Most textbooks do not make reference to this and there is a lack of published research. There is an increased prevalence of sleep-related upper airway obstruction and lower airway disease, but the significance of symptoms is often under-recognised. Therefore, specialist investigation and treatment are often necessary but not often sought.

Studies suggest that up to 88% of children with Down's syndrome will be hospitalised at some stage before their 16th birthday, and about 16% of these will have more than four hospitalisations. In a teaching hospital in Australia, a retrospective chart review of 232 admissions of children with Down's syndrome over a 6.5-year period gave over half the causes for admission as respiratory problems. Of the total admissions, 10% were ultimately admitted to the Paediatric Intensive Care Unit. Half of these PIC admissions were attributed to respiratory conditions.

Many factors contribute to the excess of lower respiratory airway problems seen in children with Down's syndrome (Panel 1). There is rarely one single causative factor – the underlying pathology is often multifactorial. Furthermore, the lower airway cannot be looked at in isolation; a lot of what appear to be lower airway symptoms relate to upper airway problems. Panel 2 lists features associated with Down's syndrome which predispose to upper airway disease. Determining the significance of different factors is critically important for appropriate management.

Panel 1: Factors contributing to lower airway problems in Down's syndrome

- Hypotonia
- Relative obesity
- Immune dysfunction
- Cardiac disease
- Large airway compression
- Small lower airway volume
- Tracheobronchomalacia
- Pulmonary hypoplasia
- Subpleural cysts
- Gastro-oesophageal reflux

Panel 2: Features associated with Down's syndrome which predispose to upper airway disease

- Hypotonia
- Obesity
- Mid-face hypoplasia
- Relative glossoptosis
- Small upper airway volume
- Increased secretions
- Nasal congestion
- Tonsils and adenoids

Lower airway problems

Congenital abnormalities

In the general population, 7.5–20% of all congenital anomalies are of the respiratory tract, and these are strongly associated with cardiovascular anomalies. They can be divided broadly into stenotic or malacic (airway collapse) anomalies, tracheo-oesophageal fistula and branching anomalies. It appears that congenital lower airway problems are significantly more common in children with Down's syndrome, particularly if there are associated cardiac defects. Unfortunately, there is a lack of published data.



Vascular compression of the large airways

The heart can cause vascular compression of the large airways, either due to the heart chamber itself, or to aberrant or distended vessels. The left atrium is particularly important, but vascular slings or rings and aberrant pulmonary or innominate arteries can cause respiratory problems.

In the absence of cardiac failure, it is easy to dismiss the heart and abnormalities of the blood vessels as causes of lower airway symptoms, but these must always be considered.

Tracheobronchomalacia

In most groups of children prone to respiratory problems, tracheobronchomalacia and bronchomalacia are most probably underdiagnosed. Part of the problem of diagnosis is that the presentation can be non-specific and unless tracheobronchomalacia is specifically considered it probably will not be diagnosed. Panel 3 lists presenting features. Tracheobronchomalacia can be diagnosed both by bronchoscopy and bronchography which may show dramatic narrowing during expiration. Management options are summarised in Panel 4.

Panel 3: Presenting features of tracheobronchomalacia

- Recurrent chest infections
- Monophonic wheeze (a single note)
- Stridor (with or without cough)
- Failure to extubate
- Sudden collapse (death attacks) – children with tracheobronchomalacia may experience breathing difficulties as their airway can become very floppy. If the child begins to panic they increase their intrathoracic pressure, compressing the airway and exacerbating respiratory distress. A vicious cycle develops which can lead to collapse
- Disproportionate ventilatory requirement relative to lung disease
- Corticosteroid/ β_2 -agonist-resistant lung disease

Immune dysfunction

Children with Down's syndrome have an increased risk of infection, autoimmune diseases and malignancy as a result of immune dysfunction. Immune problems are subtle and their contribution to the increased rate of infection is as yet unclear.

Children with Down's syndrome possess small cortical thymocytes, have altered intrathymic maturation and decreased numbers of leucocytes and lymphocytes, which affect both cellular and humoral immunity.

Immunoglobulin levels are normal until the age of about 5 years, but, thereafter, have increased levels of IgA, IgM, IgG₁ and IgG₃ and decreased levels of IgG₂ and IgG₄.

Panel 4: Tracheobronchomalacia management options

- Observation – many children grow out of this condition
- Oxygen – a common approach for children with Down's syndrome; may be adequate as sole therapy
- Continuous positive airway pressure (CPAP) – quite high pressures may be needed (20 cm H₂O)
- Negative pressure ventilation
- Surgery – aortopexy or, very rarely, a tracheal reconstruction

There are normal numbers of CD4 cells but, on average, decreased numbers of CD4/CD45RA cells (memory cells) and increased numbers of CD8 cells (killer cells). However, despite normal CD4 and increased CD8 there is decreased responsiveness on stimulation with phytohaemagglutinin (PHA) or concanavalin A. Therefore, even though the numbers of immune cells are increased, they are unable to function normally. There is also decreased production of interleukin 2, interferon gamma and tumour necrosis factor alpha. (For more information, see Nespoli et al, 1993.)

Airway size

In Down's syndrome, there is good evidence that the lower airway and lungs are smaller than normal. There are documented problems with intubation and the risk of subluxation, and a number of reports that children with Down's syndrome require a smaller endotracheal tube than expected – even correcting for age and height. A significant decrease in both the coronal and sagittal diameter of the trachea in adults with Down's syndrome has also been reported.

Pulmonary hypoplasia

In children with Down's syndrome there is an increased risk of abnormalities of lung development. In a post-mortem study of children with heart disease, six out of seven children with Down's syndrome had hypoplastic lungs. All showed a decreased number of terminal lung units, the acini contained decreased number of alveoli, the alveolar ducts were spacious and distended and there was a decreased number of large alveoli.

Pulmonary vascular disease

It has been recognised for a number of years that the risk of pulmonary hypertension and the development of Eisenmenger heart disease in children with Down's syndrome is greater compared with children without Down's syndrome. This could be explained by pulmonary hypoplasia. The capillary bed in the lungs parallels the alveolar surface area; with a decreased number of alveoli the pulmonary vascular size is decreased, increasing the risk of pulmonary problems. In association with sleep-related upper airway obstruction, this is what is now perceived to be the cause of accelerated pulmonary vascular disease in children with Down's syndrome.

Subpleural cysts

Subpleural cysts are almost specific to Down's syndrome, where they have been well documented, and may be related to the increased risk of pulmonary hypoplasia. The subpleural cysts can be detected by computed tomography but not by standard radiography.

Gastro-oesophageal reflux

Gastro-oesophageal reflux disease (GORD) is a very important problem in Down's syndrome. In many children with Down's syndrome, GORD is misdiagnosed as asthma and remains untreated.

Common presenting symptoms are:

- vomiting, which may cause failure to thrive
- oesophagitis, which may or may not be associated with chest pain, anaemia and irritability
- respiratory symptoms – apnoea, coughing, wheeze and aspiration pneumonia.

A simplistic view of GORD is that the gastric contents rise up the oesophagus and spill into the trachea and cause aspiration pneumonia. There is now substantial evidence that spilling of gastric contents into the lungs is not the only cause of respiratory symptoms.

A study in rabbits looked at the effects on respiratory conductance of intra-oesophageal acid and oesophageal distension. Both decreased conductance compared with baselines, making it harder for the rabbit to breathe. In both situations, this was reversed by vagotomy. This is only part of an increasing body of evidence that in humans simply having acid in the oesophagus may affect respiratory status, whether or not it spills over into the lungs.

Investigation of children with Down's syndrome and lower airway symptoms

A child with Down's syndrome and lower airway symptoms should be investigated systematically (Panel 5). The first step is to refer the child to a cardiologist to eliminate the possibility of the lower airway symptoms being cardiac-related. The child should then be formally assessed for upper airway obstruction, as some lower airway symptoms in children with Down's syndrome are a reflection of upper airway problems.

Panel 5: A recommended investigation strategy for children with Down's syndrome and lower airway symptoms

1. Review cardiac status
2. Assess for upper airway obstruction
3. Check immune status
4. Upper GI contrast series
5. 24-hour pH probe
6. Flexible bronchoscopy
7. Repeat steps 1 and 2

The next step is gastrointestinal imaging to exclude vascular slings and rings and compression of the trachea, as well as to detect GORD. A 24-hour pH probe can be also be performed to check for GORD. If necessary, a flexible bronchoscopy can investigate upper and lower airway compression. Immune dysfunction can be examined by a full blood count and immunoglobulin check, but this rarely affects management.

If no underlying cause is found following these investigations, it is worth reviewing the cardiac status and the possibility of upper airway obstruction again as these are the two major contributors to lower airway problems in children with Down's syndrome.

As already mentioned it is important to remember that asthma is over-diagnosed in children with Down's syndrome. It should be, therefore, a diagnosis of exclusion.

Approaches to treatment and management of lower airway symptoms

- Treat cardiac disease aggressively
 - If there is no evidence of respiratory failure secondary to tissue fluid, investigate further to ensure that the heart size is normal and not compressing large airways.



- Treat GORD aggressively
 - For the treatment of **mild** cases of GORD, positioning is of limited use. Antacids and milk thickeners can help in mild to moderate cases. A cow's-milk-free diet may be considered if there are symptoms suggesting cow's milk protein intolerance. Prokinetics are useful – cisapride seems to be more effective than domperidone, although it is currently unavailable in the UK.
 - In **moderate** GORD, H₂-receptor antagonists have limited success. Omeprazole has been shown to be a more effective treatment.
 - **Severe** GORD with significant symptoms is an indication for fundoplication.

Note: It may be months before any respiratory benefit is seen following commencement of treatment, but thereafter improvement tends to be progressive.

- Treat upper airway disease aggressively
- Treat lower airway disease
 - The mainstays of management are continuous prophylactic antibiotics and regular inhaled glucocorticosteroids.
 - A once-daily regimen of **prophylactic antibiotics** is very useful for children with Down's syndrome and lower airway problems. The choice of antibiotic is influenced by a number of factors:
 - Whether a particular respiratory pathogen is identified from cough, swab or sputum samples
 - Septrin (co-trimazole) is often used, unless there are abnormal blood counts. Alternatives include Augmentin (amoxycillin with clavulanic acid) or cefixime.
 - Patient preference is very important.
 - Ideally, a metered dose inhaler with a large volume spacer should be used to administer **inhaled glucocorticosteroids**, with a mask for younger children. Compliance, especially in children, is an important issue and, although the guidelines do not recommend it, nebulised corticosteroids can be useful.
- Physiotherapy
 - Regular physiotherapy is not popular with children, especially those with lower airway problems. However, it may be useful to teach parents how to perform physiotherapy so that it can be used when their child is unwell, and so may tolerate it better.

Summary of treatment and management approaches

- Treat cardiac disease aggressively
 - Treat GORD aggressively
 - Treat upper airway disease aggressively
 - Treat lower airway disease
 - Consider physiotherapy during relapse
 - Consider supplementary oxygen
 - Non-invasive ventilation rarely needed
- Non-invasive ventilation
 - A large number of children may simply require oxygen, even if they have large airway problems. Non-invasive ventilation is relatively uncommon.

Summary

- Children with Down's syndrome have significant respiratory morbidity which is under-recognised and accounts for a large number of hospitalisations.
- Contributory factors include hypotonia and obesity, both of which can affect the other contributory factors. Other factors include cardiac disease, both failure and the compression effect on airways and lungs, immune dysfunction and GORD.
- The causes are often multifactorial. Treating one factor alone is often unsuccessful. It is therefore important that treatment aims to optimise all the contributory factors.

Further reading

Nespoli L, Burgio GR, Ugazio AG, Maccario R. Immunological features of Down's syndrome: a review. *J Intellect Disabil Res* 1993;**37**:543–51.

A complete transcript of this presentation, together with references, is available at www.dsmig.org.uk.