Dr. Aine Lynch and Prof. Paul McNally

Department of Respiratory Medicine

A Guideline for the Management of Respiratory Complications of Down Syndrome in Children in Ireland

Link to Summary

Aim

The aim of this document is to provide a guideline for the appropriate investigation and management of respiratory morbidity in infants and children with Down Syndrome, and to establish criteria for referral to tertiary respiratory services.

Target Patient Population

This guideline applies to infants and children with a diagnosis of Down Syndrome presenting to general physicians or paediatric services.

Target Users

This guideline is directed at health-care professionals engaged in the care of infants and children in with a diagnosis of Down Syndrome. Although many aspects of this guideline may be extrapolated for use across all healthcare settings involved in the care of infants and children with Down Syndrome, this guideline is written specifically with paediatric physicians.

Available Evidence

At the time of creating this guideline, we found no existing clinical guideline for the management of Respiratory Complications of Down Syndrome. Two recent review articles provided some information on respiratory morbidities in Down Syndrome, however they did not include guidelines for management or referral. The majority of evidence referenced in this guideline therefore came from focused searches relating to specific respiratory complications.

Introduction

Down Syndrome is the commonest chromosomal disorder in humans with an incidence of 1 in 546 live births in Ireland, the highest in Europe. (1)
Children with Down Syndrome present with typical phenotypic features and can have congenital anomalies and/or dysfunction in multiple organ systems including cardiac, respiratory, gastro-intestinal, haematological, immunological, musculoskeletal, endocrine, neurological and problems with hearing and vision.
Respiratory issues are extremely common, often significantly under-recognised and are a significant cause of morbidity and mortality in Down Syndrome. Respiratory disease is the second most common cause of death in children with Down Syndrome and the most common cause of hospital admission in children under 3 years of age(2,3,4). In addition to this, respiratory issues causing chronic hypoxaemia and sleep disturbance can have significant effects on growth and development.

Appropriate management of respiratory disorders in Down Syndrome is therefore essential to optimise quality of life, growth and development. (5)

There are several key issues relating to the respiratory system which will be dealt with in greater detail:

- Proximal airway abnormalities
- Obstructive Sleep Apnoea
- Recurrent respiratory infection
- Pulmonary aspiration
- Pulmonary Hypertension

General Recommendations

- *Parents should be counselled early in the child's life regarding the common respiratory manifestations of Down Syndrome.*
- *Medical and health and social care team members looking after children with Down Syndrome should receive ongoing education in relation to respiratory complications. A focused respiratory history should be taken at every general consultation.*
- *Children with significant morbidity as a result of respiratory manifestations should be referred to a consultant in paediatric respiratory medicine*

Proximal airway abnormalities

Children with Down Syndrome have multiple risk factors for upper airway obstruction. These include phenotypic facial features, structural abnormalities of the larynx and trachea, and other factors such as hypotonia. (6, 7) (See table 1)

Table 1: Common airway problems in Down Syndrome (7)

Upper airway problems related to phenotypic features	Hypotonia of the lip and tongue Small oral cavity Midface Hypoplasia
Associated conditions affecting the upper airway	Adenotonsillar hypertrophy Choanal stenosis
Structural problems of the larynx and trachea	Laryngomalacia Narrow trachea Tracheomalacia Subglottic stenosis
Other contributing factors	Obesity Hypotonia

There is a higher prevalence of laryngomalacia (up to 50%), tracheomalacia (up to 33%) and subglottic stenosis in children with Down Syndrome (6, 7). Children with Down Syndrome are also predisposed to tracheal bronchus and abnormal segmental bronchial branching (6). Laryngomalacia is the most common cause of diurnal airway obstruction in children with Down Syndrome under 2 years of age (8). It commonly presents with inspiratory stridor. Fixed proximal airway obstruction including sub-glottic stenosis and tracheal rings are more likely to present with biphasic (inspiratory and expiratory) stridor.

Subglottic stenosis is more common in children with Down Syndrome due to narrower airway dimensions and increased rates of intubation for surgery (9). It is unclear whether subglottic stenosis in these patients

is congenital or acquired, however the incidence of post-extubation stridor is significantly higher in patients with Down Syndrome than in the general population at 24% (9).

Tracheomalacia and bronchomalacia are more common in children with Down Syndrome than in the general population (6). These disorders may be idiopathic or may be due to extrinsic compression (from vascular rings or cardiac compression). Airway malacia may present with stridor, increased work of breathing, feeding difficulty, recurrent wheeze or recurrent respiratory tract infections. The diagnosis of tracheo-bronchomalacia is made at flexible bronchoscopy which may be required in some cases. In some instances airway malacia may need to be further investigated with a contrast CT thorax (inspiratory and expiratory phases) to outrule additional vascular anomalies or anatomical variants. (4) (8)

Recurrent right upper lobe pneumonia or persistent right upper lobe atelectasis in children with Down Syndrome raises the possibility of tracheal bronchus. The abnormality occurs in approximately 2% of children with Down Syndrome. In some instances, surgical resection may be necessary (6, 7).

Proximal Airway Disorders: Recommendations

- A history of stridor should be elicited at clinic visits. Children with stridor who have poor feeding or recurrent respiratory infection should be referred to respiratory and ENT services

Obstructive Sleep Apnoea

Children with Down Syndrome are at increased risk of obstructive sleep apnoea. The overall prevalence is thought to be approximately 50% (7,9), however various studies have reported prevalence rates up to 80% (9).

OSA in children with Down Syndrome usually relates to the characteristic midface hypoplasia, crowded pharynx and hypotonia, although adenotonsillar hypertrophy may contribute in some children. Children will usually present with snoring and observed apnoeic episodes, however presentation can be very variable, and a high index of suspicion is required. Reliance on **history alone is insufficient** in terms of establishing a diagnosis and will often result in under-diagnosis of OSA (9). OSA and other pulmonary manifestations of Down Syndrome (such as pulmonary aspiration and recurrent respiratory infection) can frequently co-exist, have additive negative interactions and make assessment of individual disorders difficult.

Table 2: The typical symptoms of OSA in children with Down Syndrome:

Night -time symptoms	**Daytime symptoms**
Snoring	Fatigue/Somnolence
Increased work of breathing	Faltering developmental progress
Observed apnoea	Poor concentration
Restlessness, frequent position changes	Inattention
Sleeping sitting up or forward	Hyperactivity
Frequent arousals	Poor weight gain
	Lower than expected tone

OSA can lead to very significant **impairment in quality of life and developmental gains** in children with Down Syndrome. In children with congenital heart disease in particular, OSA can cause significant, but potentially reversible, pulmonary hypertension to the point where it can affect surgical outcomes (5).

Treatment of OSA in children with Down Syndrome can lead to significant improvements in health related quality of life. OSA in children with Down Syndrome has been historically under-recognised and under-treated (7). Children who have symptoms of OSA should be referred to a consultant in paediatric respiratory/sleep medicine given the complex presentation of OSA in this group of children and the interaction between co-morbid conditions. Clinicians should maintain a high index of suspicion for OSA in children with Down Syndrome.

Overnight oximetry is usually the first line diagnostic test for children suspected of having OSA. Oximetry has a good positive predictive value overall, however a normal or non-diagnostic study has a poor negative predictive value and cannot exclude OSA (10). Caution should be exercised in interpreting oximetry in children with Down Syndrome as there are many conditions and co-morbidities other than OSA that can produce a similar oximetry picture. Clinical judgement should be used if there is a discrepancy between the oximetry findings and the clinical picture.

Children in whom there is a concern for OSA who have a normal or non-diagnostic oximetry should go on to have cardiopulmonary polysomnography.

Children diagnosed with OSA should be seen and assessed by an ENT surgeon to determine whether there is a surgically reversible component. In comparison to the general population, adenotonsillectomy is infrequently curative in children with Down Syndrome, and medical staff should retain a high index of suspicion for OSA even in children who have had adenotonsillectomy.

For OSA that is non-surgically reversible, CPAP is usually the treatment of choice. This should be prescribed by a consultant in paediatric respiratory medicine after a comprehensive assessment of the history, co-morbidities, test results and overall clinical picture. CPAP therapy can lead to a complete reversal of symptoms and consequences of OSA but can be very hard to tolerate for some children. Families need a significant amount of support from multidisciplinary team members during the period of initiation and maintenance of CPAP treatment.

In some instances diagnostic tests may not be tolerated or may not provide useful information. In the context of the incomplete reliability of clinical history alone in the assessment of children with OSA, a trial of treatment with CPAP may be required to establish whether there is a clinical improvement in night-time and day-time symptoms on treatment.

Recommendations

- *Focused sleep history should be taken at **every clinic visit** to include daytime and night-time symptoms as detailed above.*
- *If OSA symptoms are present, children should be referred to a paediatric sleep service.*
- *Overnight oximetry is the first line diagnostic test for OSA but caution should be exercised in the interpretation of this test in children with Down Syndrome.*
- *Normal oximetry does not exclude OSA and if clinical concern persists despite normal or inconclusive oximetry, polysomnography will be required.*
- *Children diagnosed with OSA should be referred to an ENT surgeon to outrule a surgically reversible cause.*
- *Nocturnal CPAP is recommended for non-surgically correctable OSA.*

Recurrent Respiratory Infection

Respiratory tract infections (RTIs) occur more commonly in children with Down Syndrome. It is the most common cause of hospital admission and the most common reason for PICU admission (43%) and ventilation (50%) (11). Pneumonia is the most common diagnosis in this group. RTIs in Down Syndrome

may be both viral and bacterial. Children with Down Syndrome have also been shown to be more likely to require hospital admission with RSV infection and tend to have a more prolonged and severe course (12).

Bacterial infection may occur de novo, secondary to viral infection or secondary to chronic pulmonary aspiration. Children with Down Syndrome may suffer from either individual severe episodes of respiratory infection, low grade chronic infection or a combination of both. Chronic low grade infection can impair quality of life and negatively affect development. Children with Down Syndrome are at increased risk of developing persistent bacterial bronchitis, usually manifested as prolonged episodes of productive coughing for more that 4-6 weeks continuously. This is typically under-recognised but can lead to significant morbidity and affect quality of life. A persistent daily cough is never normal and should always be investigated.

The aetiology of recurrent respiratory tract infections in Down Syndrome is likely to be multifactorial. Structural abnormalities as detailed above and aspiration are likely contributory factors. Immunological defects have also been described in Down Syndrome. These include reduced lymphocyte subsets and immunoglobulins, impaired neutrophil chemoprophylaxis, and thymic abnormalities (14). These defects may affect responses to vaccinations. It is therefore recommended to check functional antibody responses and repeat immunisations as necessary.

In children with Down Syndrome who present with recurrent respiratory tract infections or severe respiratory tract infection, consideration should be given to investigation of swallow dysfunction, anatomical abnormalities and immunological defects.

Children with Down Syndrome should be dealt with differently from healthy children in the context of treatment of respiratory infection. A lower threshold for the use of antibiotics for persistent nasopharyngeal and respiratory symptoms is appropriate, as local immune function is frequently impaired in this group. Some children with Down Syndrome who have troublesome recurrent upper or lower airway symptoms will benefit from the use of preventative oral antibiotics (azithromycin 10mg/kg 3 days per week), particularly in the setting where parents feel recurrent infection impairs quality of life of developmental progress. If the indication is unclear, a trial of treatment for 3 months may give useful information in relation to effectiveness and secondary benefit. The majority of morbidity from recurrent respiratory infection occurs in the preschool years, and symptoms usually improve over time. Regular review of the necessity for treatment should occur.

Given the increase in infection related morbidity in children with Down Syndrome, prevention of respiratory infection is important in this group where possible. All children greater than six months should receive the annual influenza vaccine. Pneumococcal conjugate vaccine (PCV) should be given as part of the routine vaccination schedule, and in addition pneumococcal polysaccharide vaccine (PPV) should be administered once to children with Down Syndrome over the age of 2 years (at least 8 weeks after the last dose of PCV). In some children a second dose of PPV may be required if there is documented failure to respond adequately to the first dose, particularly if there are persistent symptoms.

Recommendations

- *A focused history should be elicited to at every clinic visit in relation to recurrent respiratory tract infection and chronic respiratory symptoms. A persistent daily cough is never normal.*

- *A diagnosis of persistent bacterial bronchitis should be considered in children with a daily productive cough for greater than 4-6 weeks. This should be treated with a prolonged course (4 weeks) of high dose oral antibiotics.*

- *Patients with symptomatic recurrent RTIs affecting quality of life and/or development may benefit from Azithromycin prophylaxis (10mg/kg three times weekly PO). This should be reviewed regularly with a view to discontinuing. Most children do not require ongoing use past school age.*

- *Patients with recurrent RTIs for a prolonged period, especially if severe, should have a basic immunological workup to include FBC, lymphocyte subsets, immunoglobulins and IgG subclasses, and vaccine responses to Tetanus, Pneumococcus and Haemophilus Influenza B.*

- *A high index of clinical suspicion regarding pulmonary aspiration and structural airway disorders should be maintained.*

- *Children with Down Syndrome who have persistent unexplained respiratory symptoms should be seen by a Respiratory consultant.*

- *Children with Down Syndrome should receive an annual influenza vaccine after the age of six months*

- *Children with Down Syndrome over the age of 2 years should receive a dose of the pneumococcal polysaccharide vaccine (PPV)*

Pulmonary Aspiration

Children with Down Syndrome have an increased prevalence of pulmonary aspiration, particularly silent aspiration (aspiration without coughing) (14). This is likely multifactorial in its aetiology and highly variable between children. Infants and younger children with Down Syndrome are more likely to be affected. Pulmonary aspiration can lead to chronic respiratory symptoms, pulmonary hypertension and structural lung damage. Pulmonary aspiration frequently presents with low grade daily symptoms as opposed to acute severe symptoms with feeding. Aspiration can occur with both oral intake and gastric refluxate. There can be significant overlap between the symptoms of aspiration and recurrent respiratory infection. A high index of suspicion for aspiration should be maintained in children with Down Syndrome with chronic persistent daily cough.

Table 3: Symptoms of pulmonary aspiration

Increased chestiness or coughing with or after feeds
Persistent low grade cough
Frequent respiratory tract infections
Chronic increased work of breathing
Unexplained oxygen requirement

There are no characteristic or pathognomonic radiological findings in children who aspirate, and the diagnosis is usually suggested on the basis of history. In a similar vein, examination findings are usually non-specific and relate to findings of airspace disease. Children with recurrent respiratory symptoms felt to be possibly related to aspiration should be referred for respiratory assessment and a clinical feeding evaluation with speech and language therap

The diagnosis of pulmonary aspiration in children is a challenging area. In children who feed orally, clinical feeding assessment by a speech and language therapist (SLT) and/or a videofluoroscopic swallow study (VFSS) can be helpful in detecting pulmonary aspiration. VFSS can look in detail at the swallow mechanism and determine whether risk factors exist for aspiration, and in some cases detect overt aspiration episodes. Failure to detect overt aspiration episodes on VFSS, particularly in children with risk factors, does not completely exclude the possibility of aspiration and clinical correlation is required in these cases. In some children, establishing the diagnosis of pulmonary aspiration requires a period of exclusive post-pyloric feeding (to ensure that the chances of aspiration from swallowed oral intake and gastric refluxate are effectively eliminated) for 1-2 weeks. This should be under the direction or supervision of the respiratory team.

The management of pulmonary aspiration in children with Down Syndrome is a challenging area with much controversy and little evidence. Management of aspiration should be directed by the respiratory team with input from SLT. The role of the SLT in the management of aspiration is to evaluate whether aspiration is happening or whether there are significant risk factors for aspiration. The SLT should also, if possible, suggest therapeutic measures aimed at eliminating or reducing the risk of aspiration. Evaluation of whether a child is safe to feed orally, and whether therapeutic interventions are successful should be led by the respiratory consultant with input from the multidisciplinary team.

Recommendations

- *A high index of suspicion for pulmonary aspiration should be maintained in children with Down Syndrome, particularly in the preschool age group.*
- *Children with persistent respiratory symptoms not easily explained by intercurrent infection should be referred to the respiratory team for evaluation of potential pulmonary aspiration. Children felt to be at risk for aspiration should be seen by a speech and language therapist and a low threshold maintained for VFSS*
- *Management of children with confirmed pulmonary aspiration should be directed by the respiratory team with input from the speech and language therapists.*

Pulmonary Hypertension

There is an increased incidence of congenital heart disease (40%) in children with Down Syndrome, most commonly AVSD (15). Congenital heart disease in children with Down Syndrome is often associated with increased pulmonary vascular resistance (16). It has long been recognised that children with Down Syndrome have abnormal lung development. Pathological and histological changes noted include reduced numbers of alveoli, enlarged alveolar ducts and smaller alveolar surface area (10). The tendency to develop pulmonary hypertension in children with Down Syndrome may be related to these underlying abnormalities of lung growth, particularly as they relates to the pulmonary vasculature. Children with Down Syndrome seem to have a lower threshold than the general population for the development of pulmonary hypertension in the context of cardiac or respiratory disease.

From a respiratory perspective, both OSA and pulmonary aspiration (particularly when it causes significant respiratory symptoms) can exacerbate pulmonary hypertension, particularly in the context of a child with congenital heart disease. Effective management of these conditions can have a

positive impact on pulmonary vascular pressures in children and facilitate management of the child's cardiovascular disease.

Recommendations

- *Children with Down Syndrome pulmonary hypertension (particularly in those with congenital heart disease also) should be seen by the respiratory team to exclude a contributing respiratory component to pulmonary hypertension.*
- *Management of pulmonary hypertension in Down Syndrome should be under the direction of the cardiac team.*

Summary

The prevalence of respiratory complications of Down Syndrome is high, although these are frequently under-recognised and under-treated. The common respiratory complications include:

- Proximal airway disorders
- Recurrent respiratory infection
- Obstructive sleep apnoea
- Pulmonary aspiration
- Pulmonary hypertension

Effective management of respiratory complications can have a strong positive impact on day to day symptoms, development, learning and quality of life. A high index of suspicion should be maintained for respiratory complications and early referral to the appropriate specialist considered.

Summary Recommendations

General Recommendations

- Parents should be counselled early in the child's life regarding the common respiratory manifestations of Down Syndrome
- Medical and health and social care team members looking after children with Down Syndrome should receive ongoing education in relation to respiratory complications. A focused respiratory history should be taken at every general consultation
- Children with significant morbidity as a result of respiratory manifestations should be referred to a consultant in paediatric respiratory medicine

Proximal Airway Disorders

- A history of stridor should be elicited at clinic visits. Children with stridor who have poor feeding or recurrent respiratory infection should be referred to respiratory and ENT services

Obstructive Sleep Apnoea

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- Normal oximetry does not exclude OSA and if clinical concern persists despite normal or inconclusive oximetry, polysomnography will be required
- Children diagnosed with OSA should be referred to an ENT surgeon to outrule a surgically reversible cause
- Nocturnal CPAP is recommended for non-surgically correctable OSA

Recurrent Respiratory Infection

- A focused history should be elicited to at every clinic visit in relation to recurrent respiratory tract infection and chronic respiratory symptoms. A persistent daily cough is never normal.
- A diagnosis of persistent bacterial bronchitis should be considered in children with a daily productive cough for greater than 4-6 weeks. This should be treated with a prolonged course (4 weeks) of high dose oral antibiotics

- Patients with symptomatic recurrent RTIs affecting quality of life and/or development may benefit from Azithromycin prophylaxis (10mg/kg three times weekly PO). This should be reviewed regularly with a view to discontinuing. Most children do not require ongoing use past school age
- Patients with recurrent RTIs for a prolonged period, especially if severe, should have a basic immunological workup to include FBC, lymphocyte subsets, immunoglobulins and IgG subclasses, and vaccine responses to Tetanus, Pneumococcus and Haemophilus Influenza B.
- A high index of clinical suspicion regarding pulmonary aspiration and structural airway disorders should be maintained
- Children with Down Syndrome who have persistent unexplained respiratory symptoms should be seen by a Respiratory consultant

Pulmonary aspiration

- A high index of suspicion for pulmonary aspiration should be maintained in children with Down Syndrome, particularly in the preschool age group
- Children with persistent respiratory symptoms not easily explained by intercurrent infection should be referred to the respiratory team for evaluation of potential pulmonary aspiration.
- Children felt to be at risk for aspiration should be seen by a speech and language therapist and a low threshold maintained for VFSS
- Management of children with confirmed pulmonary aspiration should be directed by the respiratory team in conjunction with the speech and language therapists

Pulmonary Hypertension

- Children with Down Syndrome pulmonary hypertension (particularly in those with congenital heart disease also) should be seen by the respiratory team to exclude a contributing respiratory component to pulmonary hypertension
- Management of pulmonary hypertension in Down Syndrome should be under the direction of the cardiac team

Link to References