An overview of respiratory problems in children with Down Syndrome

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Background

- Down Syndrome (DS; Trisomy 21) is the commonest chromosomal abnormality compatible with live birth.

- There is an incidence of approximately 1/800 live births, translating to approximately 700 live born children in England and Wales per year

- In the US, the prevalence is 14 / 10000 live births, with approximately 6000 births annually. However, the overall population prevalence is somewhat lower, at approximately 8.3 per 10000

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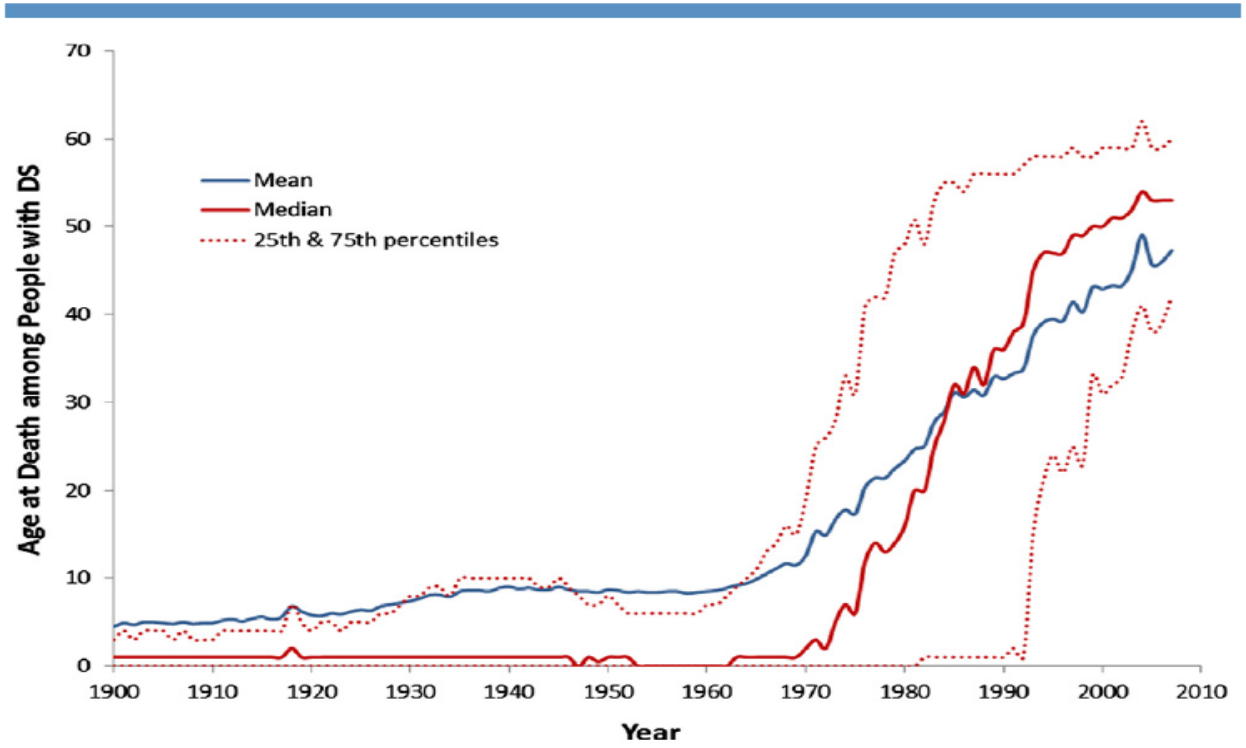
ORIGINAL ARTICLES

Current Estimate of Down Syndrome Population Prevalence in the United States

Angela P. Presson, PhD[1,2], Ginger Partyka, BS[1], Kristin M. Jensen, MD[3,4], Owen J. Devine, PhD[5], Sonja A. Rasmussen, MD, MS[5], Linda L. McCabe, PhD[3], and Edward R. B. McCabe, MD, PhD[3]



Improvement in survival in people with DS in the USA

Background

- Developmental delay and learning difficulties
- An increased incidence of multiple specific diseases
  - Congenital heart defects
  - Gastrointestinal malformations
  - Autoimmunity
  - Endocrine disease (in particular hypothyroidism)
- Respiratory illness is highly prevalent within the general pediatric population, but even more so in children with Down syndrome
- Respiratory infections commonest reason for admission to hospital and PICU

Multiple manifestations of respiratory diseases

- Overview
- Case Histories
- Anatomical
  - Upper
  - Lower
- Sleep disorders
- Lower respiratory tract infections
- Wheeze
- Other respiratory problems including rare ones
- Management

Respiratory disease patterns in Down Syndrome

Upper airway	**Stridor** **Obstructive sleep apnea / sleep disordered breathing.** **Post-extubation stridor**
Recurrent respiratory infections /LTRI	Viral Upper Respiratory Tract Infections Lower respiratory tract infections (viral / bacterial) Lobar pneumonia Aspiration pneumonia
Wheeze	Pulmonary edema / pulmonary hypertension Asthma

Anatomical features in DS and respiratory problems – Upper airways

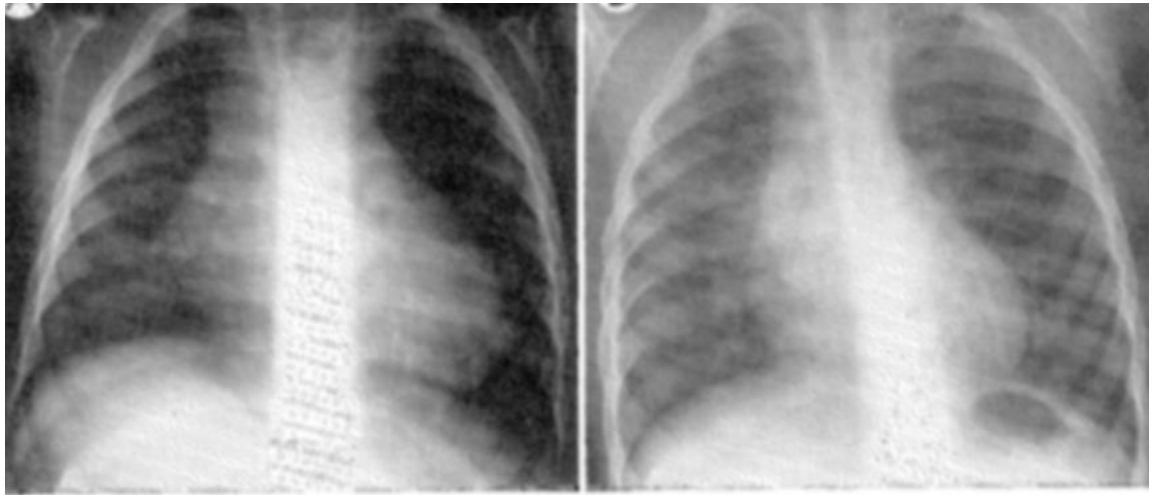
- Airway narrowed both above and below the cords
- Above trachea
  - Relative macroglossia
  - Narrow nasopharynx
  - Choanal stenosis
  - Enlarged tonsils and adenoids
  - Lingual tonsils and short palate
- Below vocal cords
  - Narrow trachea
  - Tracheo/Laryngomalacia
  - Subglottic and tracheal stenosis

Clinical presentation of URT disease in DS

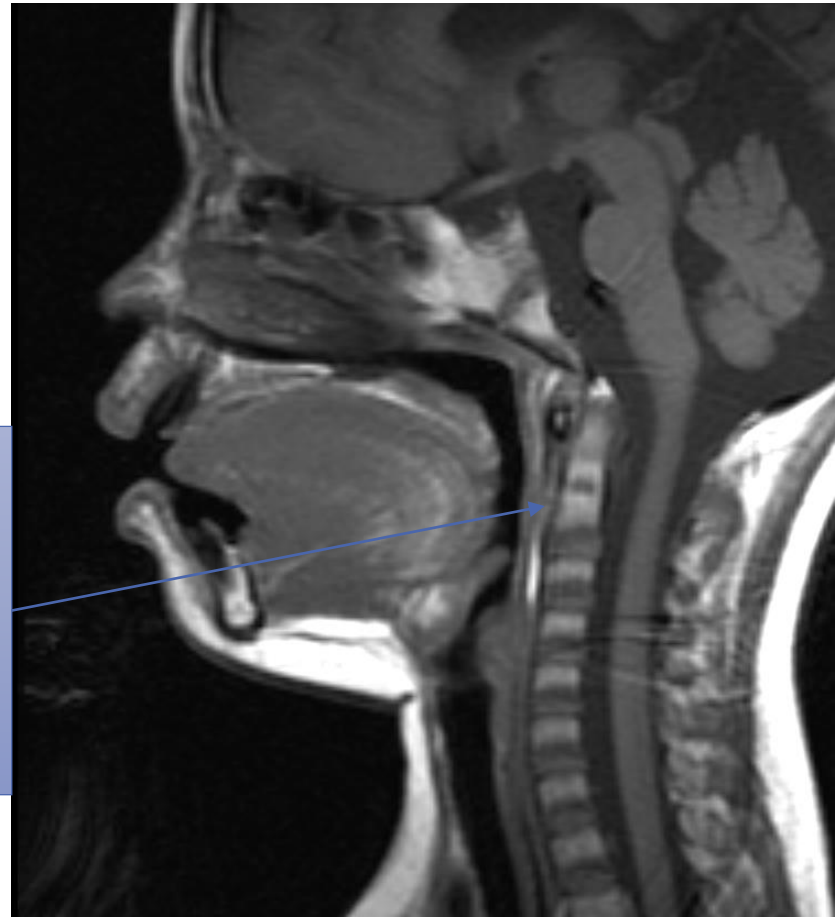
- Snoring
  - Should be specifically asked for not always spontaneously volunteered
- Parental report of noisy breathing
- Wide range of breathing associated sounds, with varying diagnostic utility
- Persistent cough, stridor, recurrent croup
- Increased work of breathing, and failure to thrive
- Symptoms worsen with self-limiting viral URTI
- LRTI may unmask previously asymptomatic upper airway disease
- Chronic aspiration, and difficulty in extubation

Case 1

- 4 year old male
- Previously well
- Noisy breathing
- Stertorous breathing
- Increase weight gain
- ENT referral
- Cyanosis
- Huge tonsils- near obstruction
- Ventilated
- Extubated 2 days later



Structural and functional factors for OSA



Note the apparent macroglossia caused by the small mid face.

- Mid-facial hypoplasia
- Relative macroglossia
- Small upper airway
- Superficial tonsils
- Increased secretions
- Obesity
- Hypotonia

Image courtesy of Prof. Lane F. Donnelly MD, Texas Children's Hospital, Baylor College of Medicine Texas Children's Hospital

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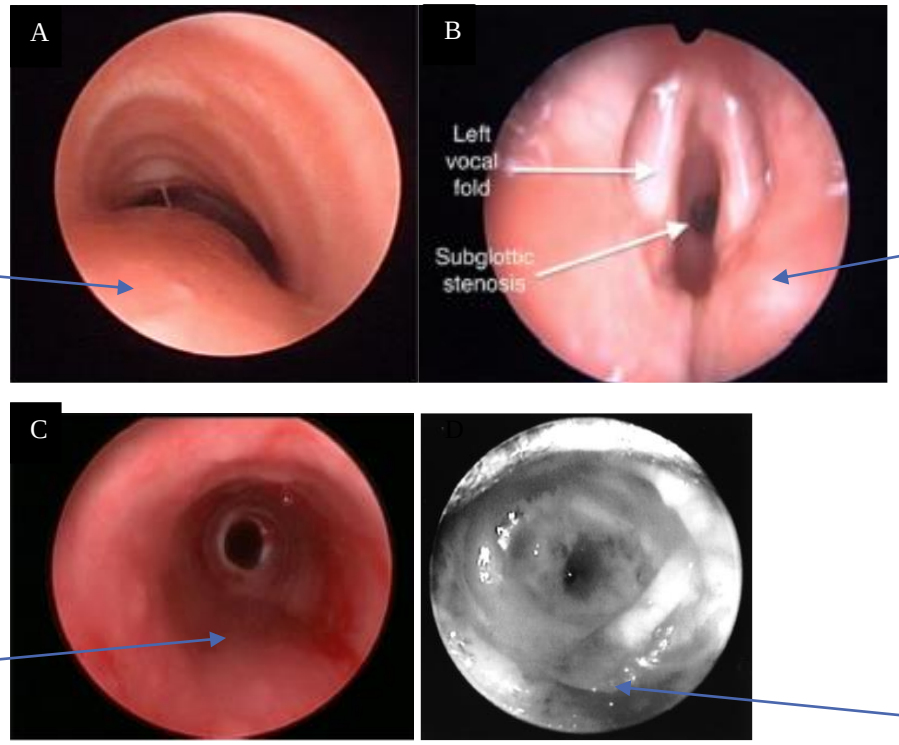
The prevalence of airway problems in children with Down's syndrome

Jane Hamilton [a], May Maxime Corazon Yaneza [b], William Andrew Clement [b], Haytham Kubba [b,*]

Lower trachea appearance under general anesthesia, showing severe airway malcia.



Appearance of subglottic stenosis immediately below the vocal fold

Mid tracheal stenosis due to previous intubation

"Pinpoint" severe tracheal stenosis

Figure 1 Airway endoscopy abnormalities in Down syndrome.

Obstructive sleep apnoea- Should all children with DS be tested

- Incidence of OSA is estimated to be between 30% and 60%
- Obstructive sleep apnoea syndrome
  - Complete and partial upper airway obstruction
  - Obstructive apnoea and obstructive hypopnoeas
  - Chronic obstructive hypoventilation with hypercarbia and oxygen desaturation
  - Sleep pattern abnormalities
  - Sleep fragmentation and sleep arousals
- OSAS
  - 0.7% to 2.0% general paediatric population
  - 4 weeks to 51years (mean age,7years) 100%. (Marcus et al)
  - Poor correlation between parental impressions of sleep problems and PSG results,
  - Baseline PSG is recommended in all children with Down syndrome at age 3 to 4 years.

Shott, SR, Amin, R, Chini, B, et al:Obstructive sleep apnea: Should all children with Down syndrome be tested? Arch Otolaryngol Head Neck Surg, 2006;132:432-436.

OSAS and PSG and parental observations

- 56/65 completed longitudinal study
- PSG abnormal in 57% of the children
- PSG plus arousal index abnormal in 80%
- 69% parents reported no sleep problems
- 54% of PSGs had abnormal results
- In those with reported sleep problems only 36% had abnormal sleep study results
- There is poor correlation between parental impressions of sleep problems and PSG results
- Baseline PSG is recommended in all children with Down syndrome at
- age 3 to 4 years.

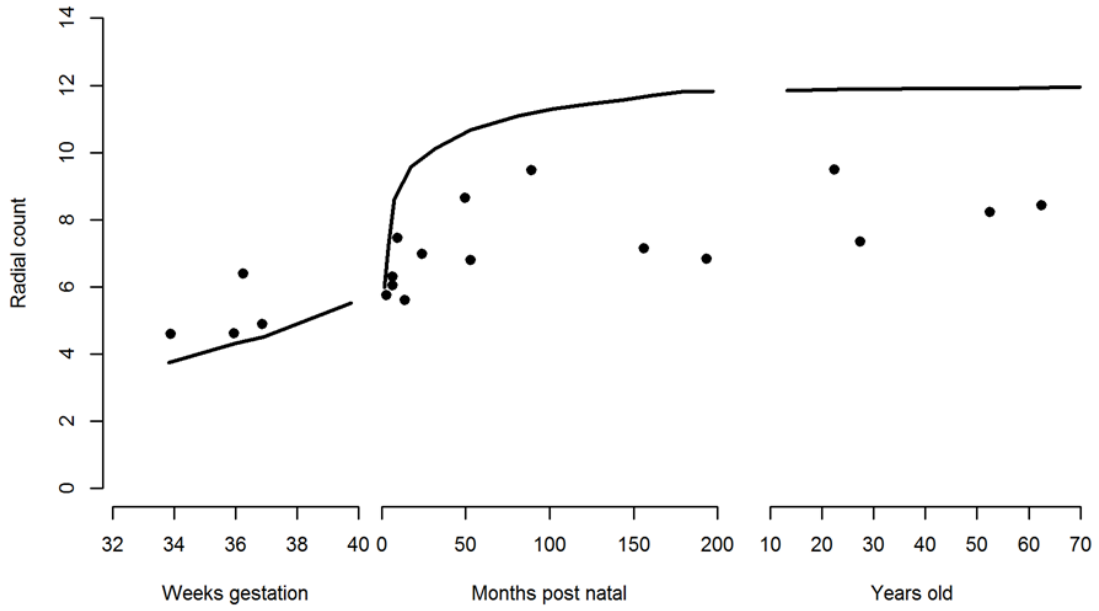
Arch Otolaryngol Head Neck Surg. 2006;132:432-436

An approach to diagnosis and management of upper respiratory tract disease in DS

- Treatment of upper airway disease
    - Liaison between the respiratory paediatrician, ENT, anaesthetist and intensive care team
    - Flexible and rigid bronchoscopy
- In ICU/anaesthetics
    - Appropriate sized endotracheal tube
    - Must have a leak around the tube
    - If previous airway problem present
    - Essential to rule out subglottic stenosis

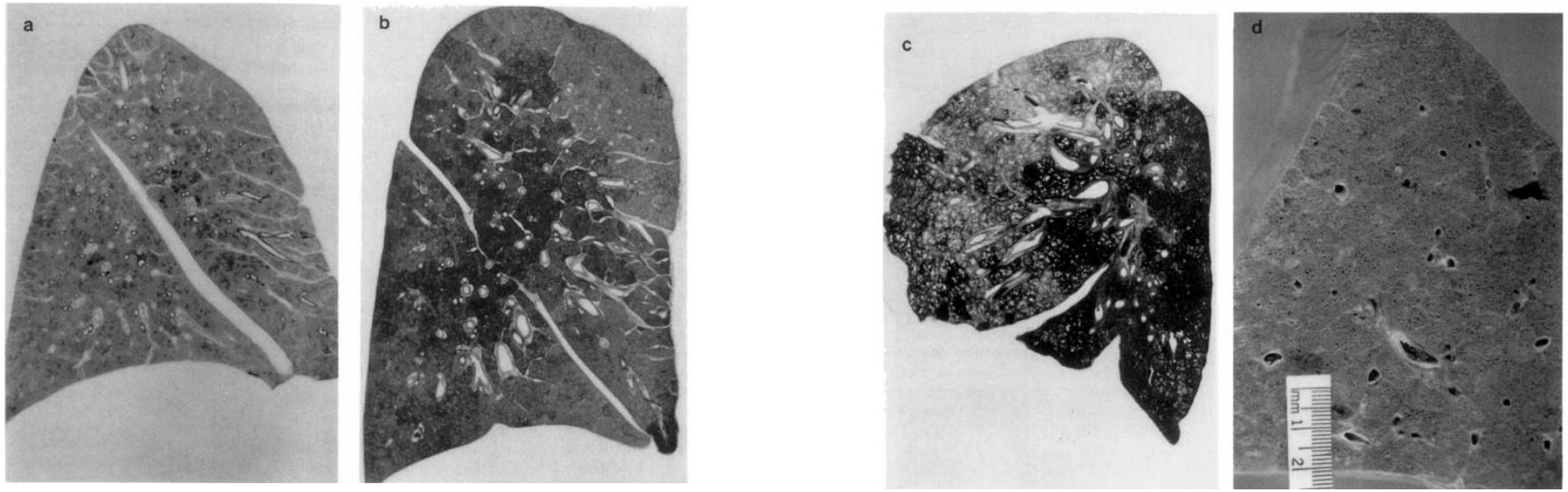
Lower respiratory tract – Morphological differences –Radial count

- In late gestation the radial count in DS is higher than controls
- Postnatally the radial count drops and remain throughout life
- Increased in alveoli size and alveolar ducts
- Reduced alveoli number, acinar hypoplasia and lung surface area.
- Reduced functional reserve
- Lung has a diffuse uniform porous pattern
- Independently of congenital heart disease in children with DS



Radial count in DS compared with normal individuals. Points represent individuals with DS or cardiac disease. Solid line indicates expected values for people without DS.

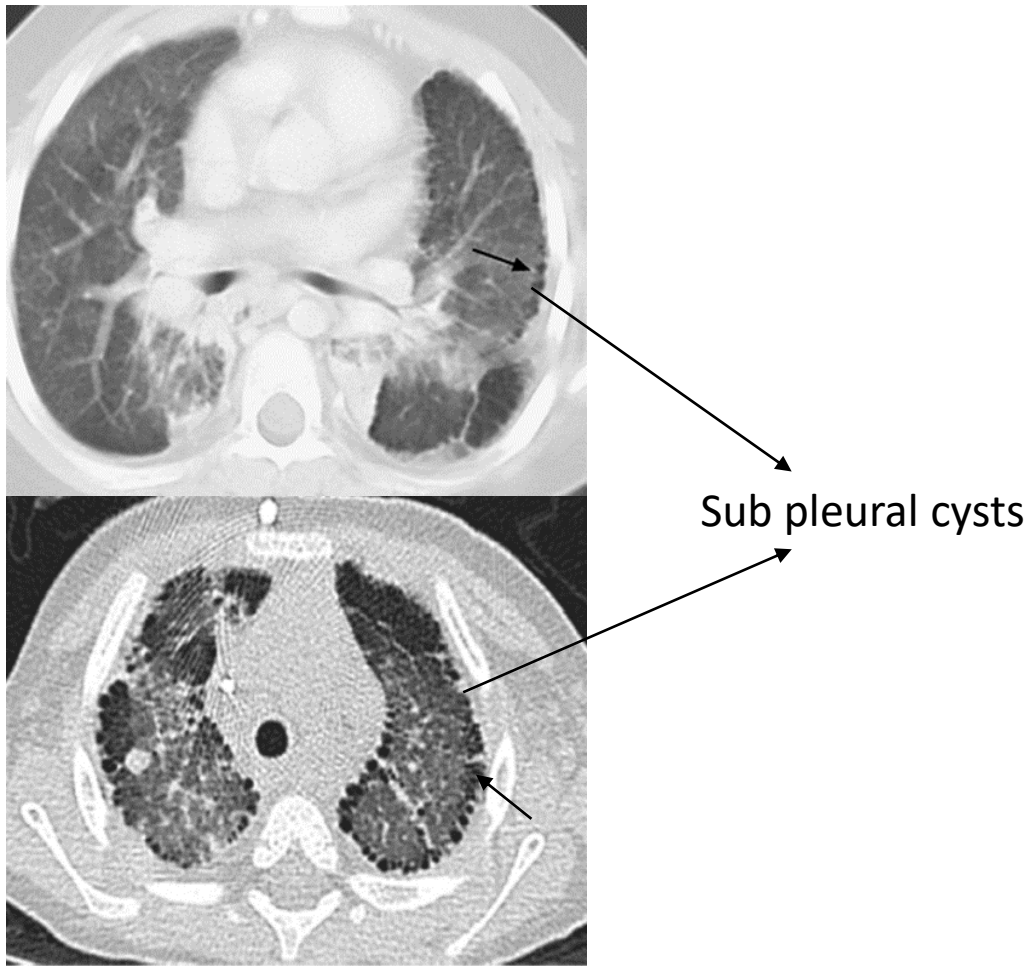
Gross appearance of the lung in Down's syndrome



a. Normal lung appearance in 9 month-old child
b. Appearance of lung in 10-month-old child with DS -Note the diffuse uniform porous pattern
c. 11 month-old with DS with superimposed pneumonia The appearance is "arborized," but the underlying porosity is evident
d. Lungs from a 27-year-old woman with DS. The porosity is striking

Lower respiratory tract: Sub pleural cysts

- Cysts are approximately 1 – 2mm in diameter
- Lined by cuboidal epithelium
- Up to 20% of patients with DS have them at post-mortem
- 36% of chest CT scans
- Not usually apparent on chest radiographs
- Secondary to reduced postnatal production of peripheral small airways and alveoli
- In early postnatal life.
- ?relevance of these to pulmonary disease

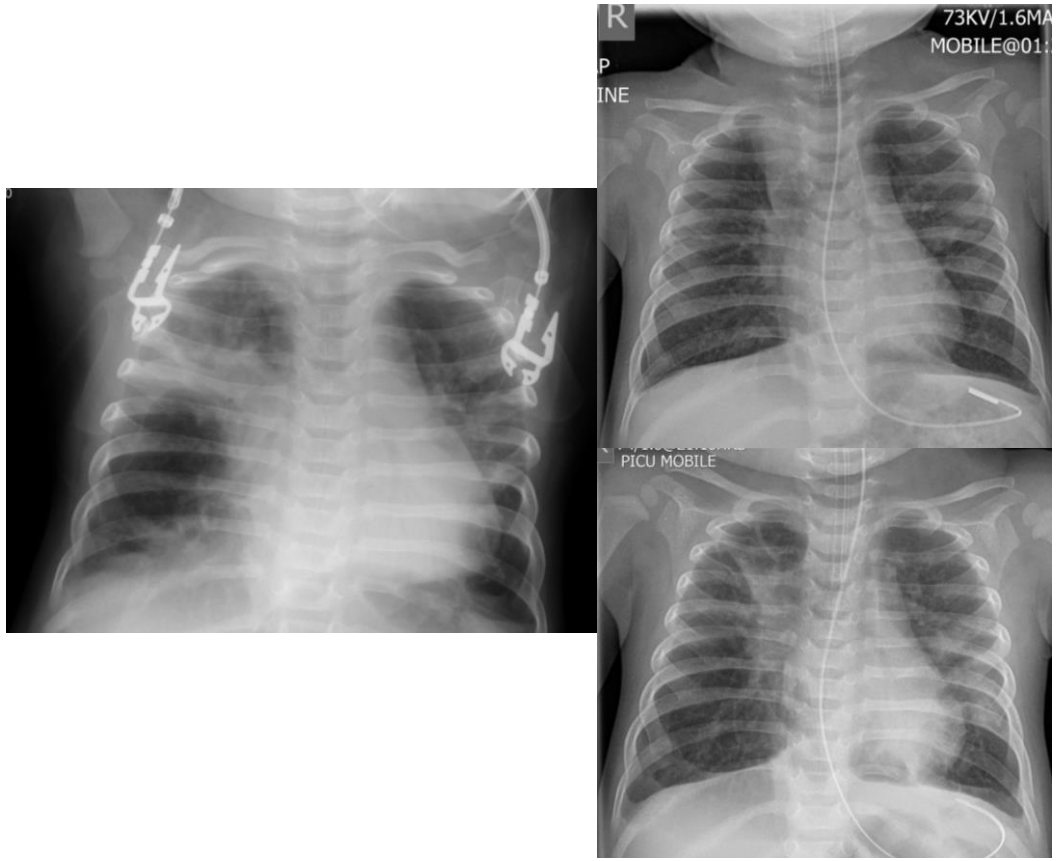


Epidemiology of lower respiratory tract infection in DS

- The most common reasons for admission (in order of frequency) are congenital heart disease, pneumonia, acute bronchitis and bronchiolitis, with respiratory disease occurring in approximately 50%.
- First 3 years of life median number of two admissions.
- The length of stay for children with DS tends to be 2-3 x times
- Respiratory support is more likely to be required.
- In a cohort of children with DS who survived to discharge from hospital after birth, half were admitted again at least

Case 2 – RSV

- 9 month female
- Previously well – no CHD
- Cough, wheeze, fatigue
- Admitted in respiratory failure
- Intubated, PICU
- ECMO
- Better by 10 days



RSV in DS

- 10 to 15% of children with DS without significant co-morbidity are hospitalized due to RSV
- The odds of admission 6 times higher, and of those hospitalized
- 10% require mechanical ventilation.
- RSV are more likely to produce fever, consolidation on chest radiograph and more wheeze compared to children without DS.
- Guidelines regarding the use of palivizumab in children with DS vary and this remains a controversial area
- Randomized trials are lacking, but non randomized studies from Canada and the Netherlands demonstrate some support for the notion that palivizumab may be beneficial for all children with DS

Bloemers, BL, van Furth, AM, Weijerman, ME, et al:Down syndrome: a novel risk factor for respiratory syncytial virus bronchiolitis--a prospective birth-cohort study. Pediatrics, 2007;120:e1076-1081.
Yi, H, Lanctot, KL, Bont, L, et al:Respiratory syncytial virus prophylaxis in Down syndrome: a prospective cohort study. Pediatrics, 2014;133:1031-1037

Significant impact of recurrent respiratory infections in children with DS

- The importance of even apparently mild respiratory tract infections in DS should not be underestimated
- Recurrent respiratory tract infections can have implications for neurodevelopment in DS
- Children with DS who report frequent LTRI
  - Lower developmental scores translating to a 5 month drop in abilities when measured at 8 years of age

Verstegen, RH, van Gameren-Oosterom, HB, Fekkes, M, et al:Significant impact of recurrent respiratory tract infections in children with Down syndrome. Child Care Health Dev, 2013;39:801-809

Acute lung injury and ARDS in DS

- Increased risk of Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS)
- ALI and ARDS occurs in DS with less severe underlying disease
- No increased mortality
- Low mortality and standardized mortality rates similar to children without DS
- ECMO is an option in severe respiratory failure
- In 623 patients with DS who received ECMO no increased risk of mortality
- Over time, the use of ECMO in DS has increased
- Progression to sepsis confers a much poorer prognosis.

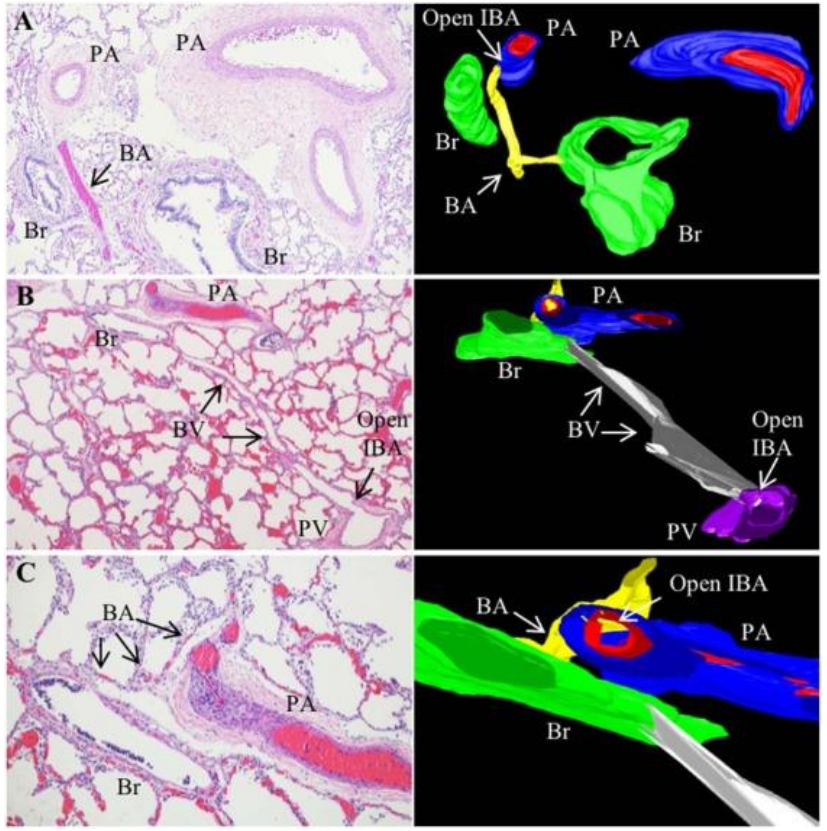
Bruijn, M, van der Aa, LB, van Rijn, RR, et al:High incidence of acute lung injury in children with Down syndrome. Intensive Care Med, 2007;33:2179-2182.

Cashen, K, Thiagarajan, RR, Collins, JW, Jr., et al:Extracorporeal Membrane Oxygenation in Pediatric Trisomy 21: 30 Years of Experience from the Extracorporeal Life Support Organization Registry. J Pediatr, 2015;167:403-408.

The pulmonary vasculature and respiratory disease in DS – Mechanisms of PHT

- Disturbance of the pulmonary vasculature occurs in tandem with the alveolar growth disruption
- Infants with DS who died in the 1st year
  - double capillary layer and and thickened pulmonary arteries
  - Reduced alveolar count
  - Abnormal foetal capillary network, and the reduced pulmonary vascular bed
- Intra-pulmonary bronchopulmonary anastomoses
  - Reduced lung surface area and recruitment of IBA
  - Worsen gas exchange DS

Prominent Intrapulmonary Bronchopulmonary Anastomoses and Abnormal Lung Development in Infants and Children with DS



BA =Bronchial artery
IBA = Intrapulmonary anastomoses
PA = Pulmonary artery

H&E slides with 3D reconstruction of open IBA pathway (IBA). Prominent bronchial artery (BA, yellow) connecting to pulmonary artery (PA; blue) via open anastomoses

The Journal of Pediatrics, 2016, Available online 22 September 2016 Douglas Bush, Steven H. Abman, Csaba Galambos

Wheeze in DS

- Wheeze is diagnosed in up to 30% of children with DS
- Appears independent from RSV infection
- Rates of atopy are low (positive skin testing)
- Lung function tests (especially spirometry) with reversibility can be difficult
- Other causes of wheeze
  - Intrathoracic airway malacia
  - Muscle hypotonia with upper airway collapse
  - Vascular malformations

The pulmonary vasculature and respiratory disease in DS

- Incidence PPHN 5.2% vs. 0.1% in the general population
- AVSD is recognized to be particularly associated with PHT
- Increased risk of transient pulmonary hypertension of the new-born (PPHN) (~10%) of NICU admissions
- Beyond neonatal period T's and A's can reduce the prevalence of PHT from 85% pre-operatively to 5% post-operatively
- High altitude pulmonary oedema (HAPE) at moderate altitudes appears more common in children with DS
- HAPE could be an initial sign of developing pulmonary hypertension

Roggla, G,Moser, B:High-altitude pulmonary edema at moderate altitude as first manifestation of pulmonary hypertension in a 14-year-old boy with Down Syndrome. Wilderness Environ Med, 2006;17:207.

Gastrointestinal – respiratory interactions in Down syndrome -Structural

- GI malformations occurred in 6.7%
- Duodenal stenosis or atresia (3.9%)
- Anal stenosis or atresia (1.0%)
- Hirschsprung disease (0.8%)
- Oesophageal atresia with or without trachea-oesophageal fistula (0.4%)
- Pyloric stenosis (0.3%).

Freeman, SB, Torfs, CP, Romitti, PA, et al:Congenital gastrointestinal defects in Down syndrome: a report from the Atlanta and National Down Syndrome Projects. Clin Genet, 2009;75:180-184.

Gastrointestinal – respiratory interactions in Down syndrome -Functional

- Dysmotilty
  - 25% have dysmotility of the oesophagus/retention of food
- Gastro-oesophageal dysmotility and reflux disease
  - 50% are asymptomatic
  - Dysphagia
  - Regurgitation
  - Chest pain.
- Swallow dysfunction
  - causes aspiration pneumonia
  - Pharyngeal dysfunction/associated with cardiac surgery
  - Failure to thrive, and often requires a gastrostomy.
- The choice of medical versus surgical therapy is difficult

Obesity in DS and its impact on the lung

- 5-50% of children have a Body Mass Index (BMI) over the 95th centile for age and sex (NDL/US)
- Higher BMI than the general population and increases over 12 years
- Both inactivity and overeating may contribute to obesity
- DS have hyperphagia scores between children with lifestyle related obesity and children with Prader-Willi syndrome
- High BMI
  - OSA
  - Reduced pulmonary function
  - Increased prevalence of asthma
  - Caudal movement of diaphragm - Reduced FRC - made worse in DS by hypotonia

Basil, JS, Santoro, SL, Martin, LJ, et al:Retrospective Study of Obesity in Children with Down Syndrome. J Pediatr, 2016.
van Gameren-Oosterom, HB, van Dommelen, P, Schonbeck, Y, et al:Prevalence of overweight in Dutch children with Down syndrome. Pediatrics, 2012;130:e1520-1526.

Immune function in DS

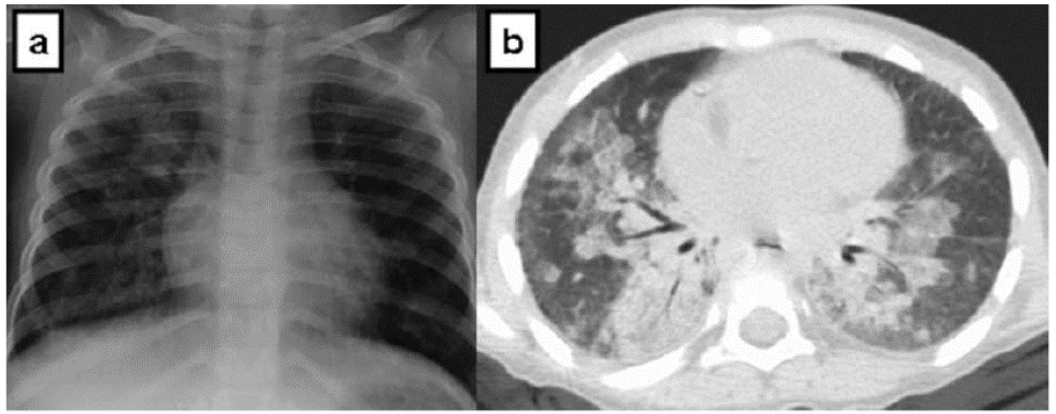
Cell numbers	**Mild to moderate reduced T cell counts**
	Mild to moderate reduced B cell counts
	Absence of normal lymphocyte expansion
	Mild to moderate reduced naïve T cell percentages
Anatomical	Reduced thymus size compared to age matched controls
Antibody production	Suboptimal antibody response to immunization
	Decreased total and specific immunoglobulin A in saliva
Innate immunity	Decreased neutrophil chemotaxis

Pulmonary complications of cardiac surgery

Pulmonary complication	Aetiology
Chylothorax	Direct injury to the thoracic duct or smaller vessels High central venous pressure Central vein thrombosis
Recurrent laryngeal nerve palsy	Surgery involving the ductus arteriosus, descending aortal or left pulmonary artery Manipulation of right common carotid artery or internal jugular vein for ECMO
Diaphragmatic paralysis	Direct trauma to the phrenic nerve / Stretching of the phrenic nerve / Disruption of blood supply to the phrenic nerve
Subglottic stenosis	Compression of the trachea by the ETT tube, in particular given the small size of the trachea in DS

Rare diseases of the lower respiratory tract in DS

- Unusual respiratory presentation
  - Disease progression does not proceed as normal
- idiopathic pulmonary hemosiderosis
  - Recurrent anaemia/presumed pneumonia
- Cystic fibrosis
- Primary ciliary dyskinesia
- Several interstitial lung diseases.
  - Alveolar Capillary Dysplasia (ACD)
  - Congenital Alveolar Dysplasia (CAD)
  - Pulmonary Interstitial Glycogenosis (PIG)
  - Congenital pulmonary lymphangiectasis (CPL)



Hemosiderosis in Down Syndrome.

What should we as carers do to minimise respiratory burden in our children with DS?

- Acute setting
  - Infection is the most likely cause
  - More severe course
  - Careful and aggressive management with oxygen monitoring
  - Appropriate care setting /severity of illness and any comorbidities
  - Stridor
  - Airway obstruction
  - Aspiration and pulmonary oedema
  - Intensive care should be aware

Management in outpatient setting

- A full history and examination
- Growth/BMI
- Recurrent respiratory symptoms
- Cough – is it wet?
- Wheeze or stridor?
- Snoring and upper airway noises
- Gastro-oesophageal reflux
- Sleep-disordered
- Immunisation status
- Pneumococcus and Flu
- IgG’s and FABS
- Sleep study(s)
- Prophylactic antibiotics
- Reduce tobacco exposure