

RESPIRATORY DISORDERS IN DOWN'S SYNDROME: OVERVIEW WITH DIAGNOSTIC AND TREATMENT OPTIONS

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In this presentation I am going to talk about that portion of the respiratory tract which is distal to the epiglottis. Problems related to the upper airway – from the nose to the epiglottis – are covered in Dr Martin Samuels' presentation on sleep-related upper airway obstruction.

Background

Despite evidence that respiratory conditions can be a serious problem for people with Down's syndrome (DS) most textbooks do not make reference to this. There is also a dearth of published research on the subject. What we do know has often not come from the UK.

A community-based Australian study looked at the incidence of significant health problems in non-hospitalised children with DS. Congenital heart disease was present in 35%, glue ear in 50% and significant lower respiratory illness in 8%.¹ Respiratory problems are a common cause of hospitalisation in children with DS. It has been reported that up to 88% of children with DS will be hospitalised at some stage before their 16th birthday, and about 16% of these will have more than four hospitalisations.² A retrospective chart review of 232 admissions to hospital for children with DS over a 6.5-year period in a teaching hospital in Australia gave over half the causes for admission as respiratory problems (Figure 1).³ Approximately 75% of the children were less than 5 years old and congenital heart disease was present in about a third of them. Hence, respiratory problems are an important component for children with DS, and a primary cause of admission to hospital.

Respiratory problems also contribute significantly to the need for intensive care. In this same group of 232 admissions, 21 (approximately 10%) culminated in admission

to the Paediatric Intensive Care Unit (Table 1). Over half of these were for respiratory problems. So it seems that not only are respiratory problems more likely to bring children with DS into hospital, they are also much more likely to take them to intensive care.

Aetiology and pathology

What are the factors that could be contributing to children with DS having an excess of lower respiratory airway problems? *Hypotonia* has to be important – any child who is hypotonic has an increased risk of respiratory problems. Relative *obesity* will also play a part. *Cardiac disease* clearly has an important role, not only because of respiratory problems secondary to cardiac failure but also because of effects on large airways. *Immune dysfunction*, *small upper airways*, *small lower airways*, and a degree of *pulmonary hypoplasia* all have a role to play, and *gastro-oesophageal reflux* is a very important factor which has to be excluded. I think there is rarely a single causative factor; often several factors are operating together, and it's fine-tuning those different causes that is important.

Anomalies of the large airways

Congenital anomalies of the lower airways are common (in the general population, 7.5–20% of all congenital anomalies are of the respiratory tract) and are strongly associated with cardiovascular anomalies. They can be divided broadly into stenotic or malacic (airway collapse) anomalies, tracheo-oesophageal fistula and branching anomalies. From studies in Wales, it appears that congenital lower airway problems are significantly more common in children with DS, particularly if there are associated cardiac defects, but published data are lacking.

Vascular compression of the large airways

It is important to remain aware that the heart can cause vascular compression of the large airways 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 inominate arteries can cause respiratory problems. For example, the inominate artery often can be aberrant. This can be almost a 'chance finding' in an

otherwise well child, but in a sick child with a respiratory problem the role of a chance finding cannot be dismissed.

Figure 2 is an X-ray of a child with DS who presented with lower airway symptoms and has cardiac disease. The enlarged heart is obvious, but there is also left lower lobe collapse which is not as easy to see. This child did have some cardiac failure but the lung collapse was disproportionate to this and was in fact due to the enlarged left atrium pressing on and partially occluding the left main bronchus. In this case there was evidence of cardiac failure, but in a similar situation without evidence of cardiac failure it is simple for the heart to be dismissed as the cause of the lower airway symptoms.

After a barium swallow in another child, an aberrant vessel could be seen compressing the oesophagus. Although this may be unrelated to the respiratory symptoms it must be fully investigated. My preferred method is bronchoscopy, but there are alternatives.

Tracheobronchomalacia

In most groups of children prone to respiratory problems, tracheobronchomalacia and bronchomalacia are probably both underdiagnosed. Part of the problem of diagnosis is that the presentation can be fairly non-descript and unless tracheobronchomalacia is thought about it won't be diagnosed. Presenting features include the following.

- Recurrent chest infections.
- Wheeze – classically the wheeze with a large fixed airway obstruction tends to be monophonic (a single note), whereas when listening to a child with asthma or bronchiolitis the wheeze is polyphonic (lots of tinkling notes).
- Stridor (with or without cough).
- Failure to extubate.
- Sudden collapse (death attacks) is characteristic of tracheo-oesophageal fistula, but children with tracheomalacia may also get these sort of death attacks where they are unable to breathe because the airway has become very floppy. If the child begins to panic they increase their intrathoracic pressure, compressing the airway and making it even harder for to breathe. The child enters a vicious circle where

they can't breathe so they get more panicked and as they try harder to breathe they squeeze their trachea more and more, eventually leading to collapse.

- Disproportionate ventilatory requirement relative to lung disease.
- Corticosteroid/ β_2 -agonist-resistant lung disease.

Tracheobronchomalacia can be diagnosed both by bronchoscopy and bronchography. Unlike the old bronchograph system where a large amount of a hyperosmolar contrast medium was put into the lungs – a very small amount (about 0.5 ml) of iohexol (Omnipaque, Nycomed Amersham PLC, UK) is introduced. This delineates the airways and may show dramatic narrowing during expiration.

The treatment options with trachea malacia are:

- Observation
The case series available suggest that children grow out of it.
- Oxygen
Just giving oxygen may be enough; this is quite a common approach in children with DS.
- Continuous positive airway pressure (CPAP)
CPAP via a nasopharyngeal or tracheostomy tube may be needed. Quite high pressures (20 cm H₂O) may be necessary to open the airway and keep it open.
- Negative pressure ventilation
- Surgery is sometimes needed – either aortopexy or, very rarely, a tracheal reconstruction.

Immune dysfunction

Children with DS have an increased risk of infection, autoimmune diseases and malignancy because, developmentally, their immune system is different. There are small cortical thymocytes, altered intrathymic maturation and decreased numbers of leucocytes and lymphocytes, which affect both cellular and humoral immunity (Table 2).⁴

Humoral immunity

Generally, children with DS have normal levels of immunoglobulins until the age of about 5 years, but, thereafter, have increased levels of IgA, IgM, IgG₁ and IgG₃ but decreased levels of IgG₂ and IgG₄. Children with DS, irrespective of the home environment, have an increased frequency of hepatitis B virus carriage and have a decreased response to hepatitis B vaccine, suggesting that you can vaccinate children with DS but they are less likely to develop a normal response. There is also an increased frequency of auto-antibodies.

Cellular immunity

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 the immune cells present don't work as well even though there are more of them than normal. There is also decreased production of interleukin 2, interferon gamma and tumour necrosis factor alpha. Thus, there are a number of subtle immune problems, but the extent to which these contribute to the increased rate of infection is as yet unclear.

Upper airway problems

Even though upper airways issues are outside the remit of this presentation it must be stressed that the lower airway cannot be looked at in isolation. A lot of what appear to be lower airway symptoms relate to upper airway problems. A holistic approach when treating children, especially those with DS, is essential. Factors affecting the upper airways include:

- hypotonia
- obesity
- mid-face hypoplasia
- relative glossoptosis
- small upper airway volume (approximately 2/3 normal volume)
- increased secretions

- tonsils and adenoids.

Lower airway and lungs

Airway size

There is good evidence that not only the upper airway but also the lower airway and lungs are small. Most of the anaesthetic literature relates to problems of intubation and the risk of subluxation etc., but a number of papers mention that children with DS require a smaller endotracheal tube than expected – even correcting for age and height. In a study of 14 adult patients with DS, the inner diameter of the trachea – 2 cm above the aortic arch – was measured on chest X-ray.⁵ Plain and lateral views were taken with subjects standing normally. There was a significant decrease in both the coronal and saggital diameter compared with normal controls. Interestingly, there was no association with the presence of heart disease or with height or weight. It appears that certainly adults with DS have smaller large airways inside the chest in addition to outside the chest.

Pulmonary hypoplasia

In 1982, a group with a particular interest in lung morphology and anatomy found that some children with heart disease had abnormal lung formation.⁶ It was then realised that only the children with DS showed these findings – six out of seven children with DS had hypoplastic lungs. Of those six, five had congenital heart disease (CHD; note that this was a post-mortem study and in the 80s children with CHD were likely to die younger). In all these children there was 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 (Figure 3).

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 DS is accelerated compared with children without DS.⁷ Pulmonary hypoplasia could explain this. 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 DS.

Subpleural cysts

Subpleural cysts have been well described in children with DS. This could relate to the findings on pulmonary hypoplasia. In a post-mortem study of 19 fetuses and 80 infants with DS, subpleural cysts were found in 18 of the infants (none of the fetuses). Of these 18 infants, 17 had CHD.⁸ Based on this, the investigators looked for evidence of subpleural cysts in other children with and without CHD. In 8000 children without DS, only two cases of subpleural cysts were found, and no cases were found in over 150 children with CHD who didn't have DS. It appeared that these subpleural cysts were specific to DS. There have been a number of studies since which have shown the same finding. The subpleural cysts can be detected by computed tomography but not by standard radiography.⁹ It is thought that they cannot be seen in fetuses because a large part of alveolar maturation takes place postnatally, and it is a postnatal event which leads to subpleural cysts.

Gastro-oesophageal reflux

Gastro-oesophageal reflux disease (GORD) is a very important issue in DS. I do not know of any prevalence data, but in my own practice I see quite a large number of children with DS who are misdiagnosed with asthma when it is gastro-oesophageal reflux that actually needs treatment. The symptoms of GORD 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.

There is a simplistic view of GORD that the gastric contents come up the oesophagus and spill into the trachea and cause aspiration pneumonia. There is now quite a lot of 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 conductivity of intra-oesophageal acid and oesophageal distension. Both decreased conductance compared with baselines, making it harder for the rabbit to breathe.¹⁰ In

both situations, this was reversed by vagotomy. There's a very complex and rich plexus of nerves associated with the oesophagus and the lungs and there's good animal evidence and increasing evidence in humans that just having acid in the oesophagus may affect respiratory status whether or not it spills over into the lungs.

Investigation of the child with DS and lower airway symptoms

A basic system can be worked through when investigating a child with DS and lower airway symptoms (Table 3). The first step is to eliminate the possibility of the lower airway symptoms being cardiac related, so the child should be referred to a cardiologist. The child should be formally assessed for upper airway obstruction, as some lower airway symptoms are a reflection of upper airway problems in children with DS. Immune dysfunction can be examined by a full blood count and immunoglobulin check, but in my experience identifying more subtle abnormalities doesn't particularly affect the management of the problem. The next step is to do gastrointestinal contrast series. This is useful for looking for vascular slings and rings and compression of the trachea, as well as GORD. After that a 24-hour pH probe can be done to check for GORD. In a recent audit in Cardiff, the respiratory team was found to be doing more 24-hour pH probes than the gastroenterology team. We find it a very useful investigation. Figure 4 shows the trace from a child with significant GORD. In this child the pH was less than four for 25% of the time – the upper limit of normal would be between 4 and 8%. If necessary, a flexible bronchoscopy can then be done to look for upper and lower airway compression. If there is still no positive result after these investigations, it is worth reviewing the cardiac status and upper airway obstruction again as these are the two major contributors to lower airway problems in children with DS.

An important point to note is that asthma appears to be over-diagnosed in children with DS. Some cross-sectional work in a population of children with DS in South Wales has been started, and over half of the children have been labelled as having asthma. Often, when a child is referred to me with asthma, asthma is the one thing they don't have. I think that asthma should be a diagnosis of exclusion in DS.

Treatment and management

- Treat the cardiac disease aggressively – If the child doesn't have evidence of respiratory failure secondary to tissue fluid, investigate further to ensure that the heart size is normal and not compressing large airways.
- Treat gastro-oesophageal disease aggressively – In dealing with GORD positioning is of limited use, but antacids and milk thickeners can help in mild to moderate cases. Although there are only anecdotal reports, some children get better on a cow's-milk-free diet – if there are symptoms suggesting cow's milk protein intolerance modifying the diet may be beneficial. Prokinetics can be used and, although unavailable to us at present, cisapride is very useful and seems to work better than domperidone. In moderate GORD, H₂ antagonists can be used, but omeprazole works much better. Severe gastro-oesophageal reflux with significant symptoms is a very good indication for fundoplication, a relatively large number are performed in children with severe respiratory problems. From a respiratory point of view it can be a number of months before any benefit from the treatment can be seen, but then the child usually carries on improving. I just saw a child who we started treating for gross reflux 3 years ago and who continues to get better all the time.
- Treat upper airway disease aggressively
- Treat lower airway disease – The mainstays of management are continuous prophylactic antibiotics and regular inhaled glucocorticosteroids. *Prophylactic antibiotics* There are no control data on the use of prophylactic antibiotics in almost any condition, but it is very useful for children with DS and lower airway problems. A once-daily regimen is ideal, and 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, but if there are concerns over the blood count, which is a particular concern in DS, Septrin tends not to be a good choice.
 - patient preference is very important, a child is more likely to be persuaded to take something if they vaguely like it.

At present in Cardiff we are using Septrin, Augmentin (amoxicillin with clavulanic acid) or cefixime. Augmentin is usually given twice-daily, but once a day is usually adequate for the other two. We always give parents a second-line recommendation. If the child is well they stay on their treatment once daily – if they have a respiratory exacerbation they can change to one of the others or, depending on cultures, they may be given something stronger like ciprofloxacin.

Inhaled glucocorticosteroids Ideally a metered dose inhaler with a large volume spacer should be used to administer inhaled steroids, with a mask for younger children. In practice it can be extremely difficult to get children to use a mask and spacer. In a child who may have behavioural problems, and is not keen to have any medicines, it can be almost impossible. Compliance is an important issue and, although the guidelines do not recommend it, nebulised corticosteroids can be useful. The parents and the children seem to prefer it and it could be considered that it is better to give something that isn't ideal that the child will take, than give them the ideal treatment that they never take. A point to note is that where nebulised corticosteroids are used, children often need higher doses, and with higher doses it is important to be aware of the potential effects on adrenal suppression and growth.

- Physiotherapy – For most children, whether they have DS or not, physiotherapy is not enjoyed, and trying to encourage children with lower airway problems to do regular physiotherapy is often difficult. However, it can be useful to teach the parent how to do physiotherapy so that it can be used if the child has a respiratory exacerbation when the child may tolerate it better. Increasingly, physiotherapists are teaching the parents physiotherapy to use when the child is unwell.
- Non-invasive ventilation – A large number of children may just be given oxygen, even if they've got large airway problems – non-invasive ventilation is relatively uncommon.

Summary

It is probably under-recognised that children with DS have significant respiratory morbidity and that this accounts for a large number of hospitalisations. There are a number of contributory factors, including hypotonia, obesity, cardiac disease – not just failure but the effect of the vessels and chambers on the large airway – small airways

and lungs, immune dysfunction and GORD. The causes are often multifactorial – a child may have severe reflux, which can be treated, but unless it is recognised that there is also some large airway compression or immune dysfunction, they will not get better. All the various factors must be taken into account and 'fine-tuned'. It is important that treatment aims to optimise all the contributory factors.

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Question Session

Andrew Tandy (Taunton, Somerset) In the use of prophylactic antibiotics you say that the choice is influenced by the pathogen. I know that it's important that we take a cough swab, but are there organisms about which you would not worry? Are there organisms for which you would definitely give an antibiotic and those for which you think that the jury is still out?

Iolo Doull I think we should be initiating treatment based on the symptoms and choosing the antibiotic based on current preferences. I would be giving a therapeutic trial, but it really comes down to the situation. With some children I know isolates (*not clear*), now in that situation giving Augmentin often keeps them very well, but your choice of second line antibiotic could be ciprofloxacin. I feel that we should be looking for pathogens, but it doesn't particularly alter whether or not I give antibiotics. If you are deciding to put a child on prophylactic antibiotics and they grow haemophilus, cefixime is a very good choice for that, noraceprim(?) is not quite as good, but the decision to give the antibiotic is really based on the child's symptoms and the problems they are having, rather than whether there is an organism there or not.

Andrew Tandy Thank you, I ask because I have a child with cerebral palsy who's colonised with haemophilus and in whom we've decided no amount of prophylactic antibiotics makes any difference. If you look at it from a symptomatic point of view then we will treat him with an antibiotic that will be appropriate for haemophilus. My second question is – do you think certain children with DS should have certain immunisations almost as a routine or should we be targeting those with respiratory tract infections and, if so, which immunisations?

Iolo Doull In children with DS with respiratory symptoms, given the problems with immunity, I would be giving the influenza vaccination every time. I would also normally advise them to have the Pneumovax. They get everything else anyway.

Sheila Macken (Dublin) We have quite a large population of children with DS and one of the things you didn't mention, and maybe the epidemiology in Britain is somewhat different, is that smoking in the home is a major factor in the ones who have respiratory problems. The other major factor is RSV infection which, in many children who are doing very well (whether or not they have congenital heart disease), seems to be the thing that triggers chronic lung disease. I have about five children who have had persistent atelectasis following RSV infection and are very difficult to manage – one of them actually turned out to have cystic fibrosis – but another of the children was recently at a clinic in the USA and an eminent specialist in DS told her that children with DS should not go to crèches before the age of 2 years for fear of contracting RSV. An area at which the DSMIG could look is the possibility of immunising children with Down's syndrome against RSV, as is being done for premature children, looking at cost-effectiveness studies and seeing the impact of hospitalisation.

Iolo Doull I would agree with you. Regarding the second point about RSV, I think the monoclonal antibody that's available at present has been shown to be effective at preventing hospitalisations for children born prematurely. As I'm sure you are aware, there's been a lot of correspondence in various journals, including *Archives of Disease in Childhood*, as to the number needed to treat to prevent that and I certainly know from experience the difficulties in getting the monoclonal antibody prescribed even for children who are oxygen dependent. The guidelines we have for the health authority I'm in are that I'm actually allowed to give it to children who are oxygen-dependent. Therefore, a child with DS who is oxygen-dependent I would give it to, but there's no evidence for that. I think to persuade the purchasers of the benefits of having an immunisation programme in a population that has never been studied (and this is not a cheap option) is difficult. Coming back to the smoking I think in large areas of Cardiff there's no need for street lighting because so many parents report they smoke outside the house. In my experience I always have a long chat about smoking and I remain completely unconvinced that I make any difference.

? Take a child who is about 2.5 years old; he's oxygen dependent; he's been on the ward for a week and you are being asked to see him. He has gastro-oesophageal

reflux and he's on maximal anti-reflux therapy. He had his heart fixed when he was 1 year old and the cardiologist assures you they can't do any more; he also doesn't have an upper airway obstruction, but he's still ill. The mother is asking you what to do. Could you take us through that because it's a problem we all meet?

Iolo Doull I think in a child on oxygen who has significant gastro-oesophageal reflux I would initiate maximal medical therapy and, if that failed, I would choose fundoplication. I accept that fundoplication is not the be all and end all and you have to go through the issues with the parents very carefully – that 20% of them will fail and it's not a cure-all. I think that if you can get rid of the acid from the oesophagus or the lungs for a period, you can buy a window, in which time the child grows and develops, gets better and they then grow out of it. In a situation where you've optimised everything, but you've still got significant gastro-oesophageal reflux and you are oxygen dependent I would have no question at all about doing fundoplication. I think it is important as well though to recognise that, and I've painted a fairly black and white picture today, sometimes you're just left with 'I still don't know why this child is oxygen-dependent,' and you then ask 'Is it hypoplasia?'. You can't do anything about it – it's difficult to quantify but you are left with various options.

Figure 1: Down's syndrome: Aetiology of hospitalisation. (From Hilton et al. Respiratory morbidity of hospitalized children with Trisomy 21. *Journal of Paediatrics and Child Health* [1999] Vol 35:383–6, reproduced with permission.)

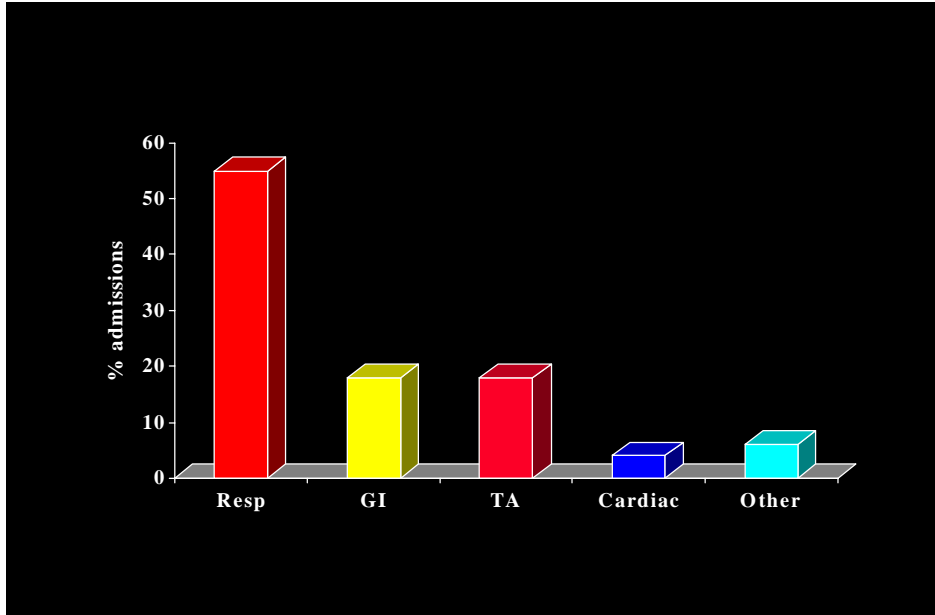


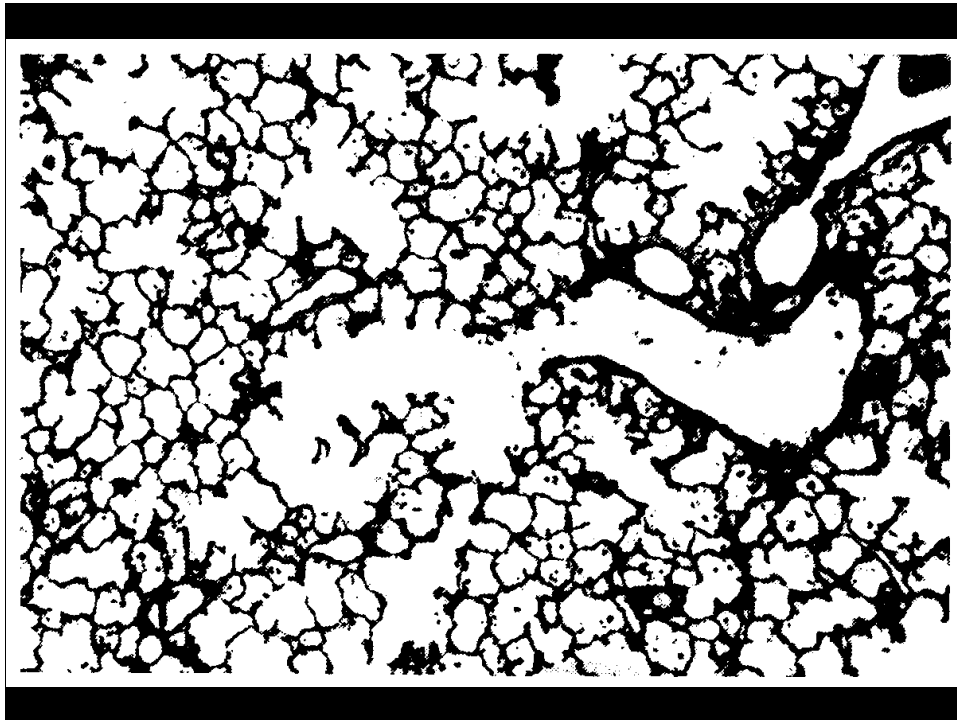
Figure 2: X-ray of a child with CHD



Figure 3: Alveolar ducts from (a) a child with normal looking alveoli and (b) a child with DS showing bigger, baggier alveoli in decreased number. (Cooney TP, Thurlbeck WM. Pulmonary hypoplasia in Down's syndrome. *N Eng Med J* 1982;**307**:1170-3.

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(a)



(b)

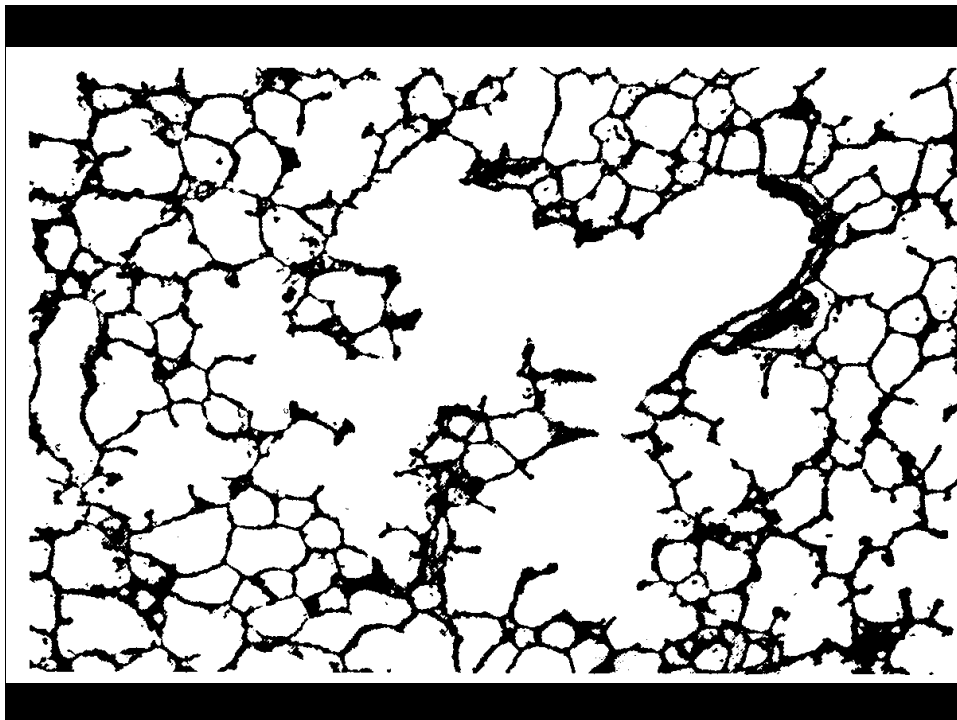


Figure 4: Results of a 24-hour pH probe in a child with severe GOR

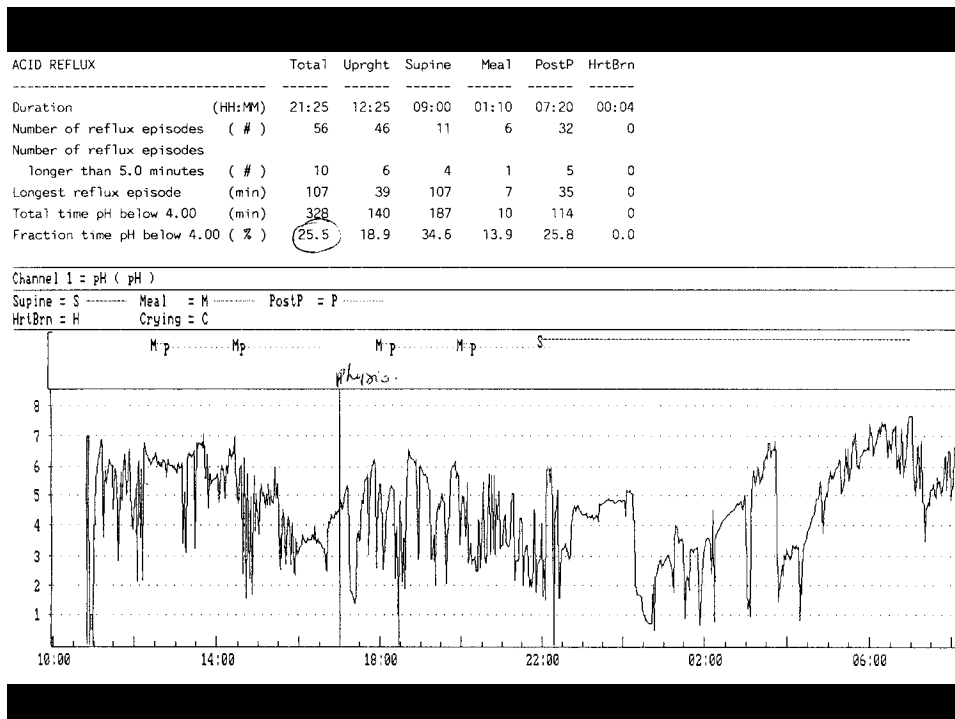


Table 1: Down's syndrome: Reasons for paediatric intensive care admissions. (From Hilton et al. Respiratory morbidity of hospitalized children with Trisomy 21. *Journal of Paediatrics and Child Health* [1999] Vol 35: 383–6, reproduced with permission.)

Reason for admission	Number of admissions
Pneumonia	7
Bronchiolitis	3
RSV pneumonia	3
Croup (+/- subglottic stenosis)	2
Post T+As (OSA)	2
Cardiac failure	2
IDDM and hyperosmolar coma	1
Head injury	1

Table 2: Down's syndrome: Immune dysfunction

- Increased infection, autoimmune disease and malignancy
- Small cortical thymocytes
- Altered intrathymic maturation
- Decreased leucocytes and lymphocytes
- Cellular immunity
 - Normal number of CD4 cells
 - Decreased number of CD4/CD45RA cells
 - Increased CD8 cells
 - Increased NK cells
 - Decreased PHA and Con A response from 10
 - Decreased IL2, INF α and INF γ production
- Humoral immunity
 - Normal immunoglobulins until age 5
 - Thereafter increased IgA, IgM, IgG $_1$ and IgG $_3$, decreased IgG $_2$ and IgG $_4$
 - Increased frequency of Hep B virus carriage
 - Decreased response to Hep B vaccine
 - Increased frequency of autoimmune antibodies

Table 3: Investigations for a child with DS and lower airway symptoms

1. Review cardiac status
2. Assess for upper airway obstruction
3. FBC and IgG A M E
4. Upper GI contrast series
5. 24 hour pH probe
6. Flexible bronchoscopy
7. Repeat steps 1 and 2