

Respiratory Complications of Down Syndrome

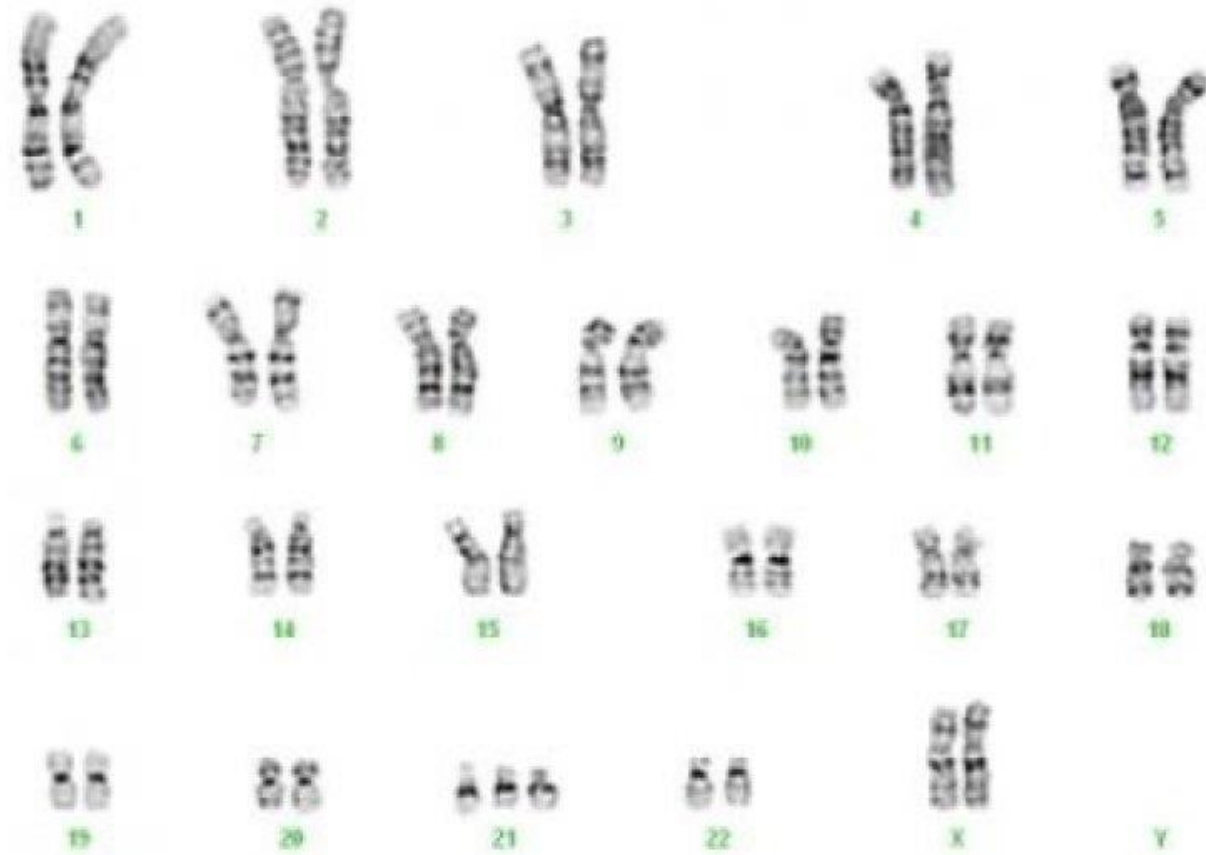
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The Hospital for Sick Children



One case, many things to learn...



Case #1

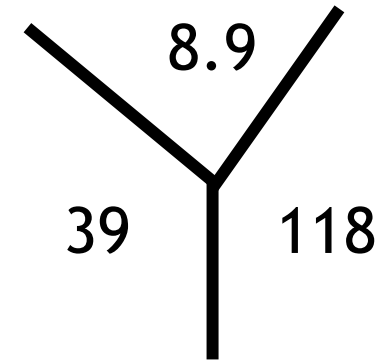
- 2.5 year old with Trisomy 21
- Past Medical History: AVSD repaired at 2 months of age, obesity, “reactive airways”
- Presented to Scarborough Hospital with 5 day history of fever and increased work of breathing
- CXR: LLL pneumonia → PO cefuroxime → home
- Back to the ED 3 days later with pallor, progressive WOB



Initial Presentation

- Transfusion pRBCs
- Criticall → transfer to Sickkids PICU

Anemia + thrombocytopenia in T21 → rule out leukemia



Initial Presentation

- H+N: protruding tongue, large tonsils
 - Resp: apneic episodes in ED, grunting, tracheal tug, bilateral wheeze
 - CVS: 2/6 SEM, no gallop, cool extremities, 2+ peripheral pulses
 - Abdo: soft, nondistended
-
- Repeat CBC: **Hb 42 Plt 52 WBC 10.4 Retic 250**
 - NP swab negative
 - Mycoplasma negative
 - Blood culture negative



Initial Presentation

- Initially on CPAP
- Respiratory failure leading to intubation
- What size tube would you use?
 - A. The same size tube as anyone else
 - B. A smaller tube than other kids at the same age
 - C. A larger tube than other kids at the same age



Course in PICU

- Initially on CPAP
- Respiratory failure leading to intubation
- What size tube would you use?
 - A. The same size tube as anyone else
 - **B. A smaller tube than other kids at the same age**
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Endotracheal tube size

- 1-2 sizes smaller

Age	Down Syndrome	Non-Down Syndrome
Premature	2.0–2.5	2.5–3.0
Full-term newborn to 9 months	2.5–3.0	3.5–4.0
9–18 months	3.0–3.5	4.0–4.5
1.5–3 years	3.5–4.0	4.5–5.0
4–5 years	4.0–4.5	5.0–5.5
6–7 years	5.0	5.5–6.0
8–10 years	5.5	6.0–6.5
10–11 years	5.5	6.5–7.0
12–13 years	6.0	7.0–7.5
14 years and older	6.5	7.5–8.0

From Shott SR. Down syndrome: analysis of airway size and a guide for appropriate intubation. *Laryngoscope*. 2000;110(4):585-592.

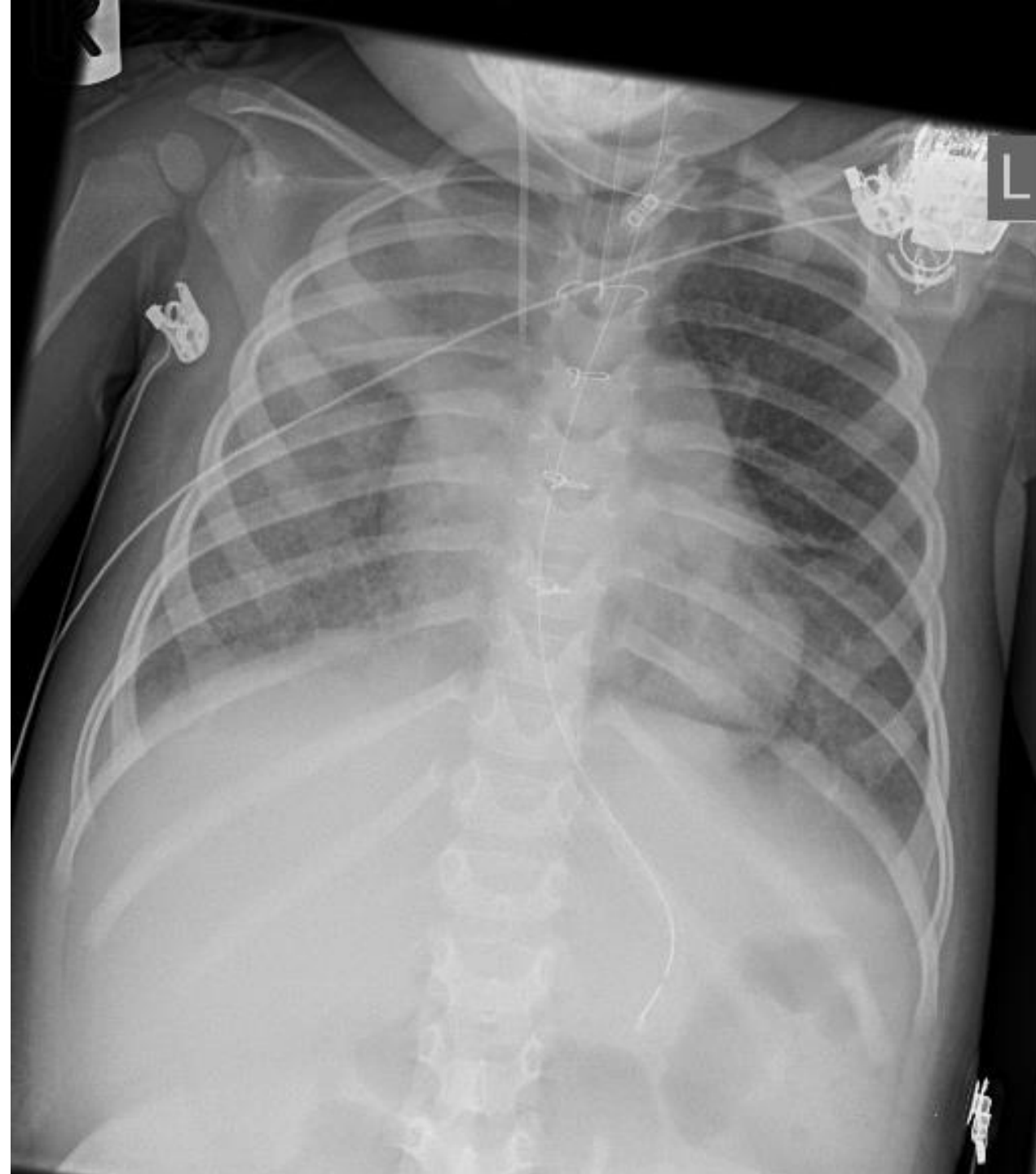


Upper airway disease - anatomy

- Narrowing above the vocal cords → midface hypoplasia, narrowed nasopharynx, choanal atresia, large tongue, tonsils and adenoids (relative), lingual tonsils, short palate
- Narrowing below the vocal cords → trachea narrow (2cm narrower than age-matched children)
 - Cause of post intubation stridor

Bottom line: narrowing can occur at any point in the airways





Course in PICU

- Post-intubation: **fresh blood seen in the ETT tube → **pulmonary hemorrhage**
- Low BP → dopamine infusion
- Multiple RBC and platelet transfusions
- Hemolysis screen: bili 38, haptoglobin<0.08
- DAT negative
- G6PD, PKD sent
- Smear for membranopathies
- Too unstable for a bone marrow biopsy
- Trial of multiple antibiotics (azithro, clarithro, vanco, meropenem)



PICU BAL

- BAL: positive for rhinovirus
- ++ hemosiderin laden macrophages



The consult train – all aboard

- Infectious Disease, Rheumatology, Hematology/Oncology, Respiriology, Cardiology



The consult train

- Hematology: infectious vs malignancy vs. cefuroxime induced hemolytic anemia vs consumptive thrombocytopenia
 - → bone marrow biopsy, G6PD, PKD
- ID: infection vs cefuroxime induced hemolytic anemia
 - → cefuroxime induced hemolysis test → vancomycin + meropenem
- Rheumatology:
 - ?HUS/TTP
 - MAS - CBC, ESR, CRP, urea, Cr, AST, ALT, LDH, albumin, ferritin, INR, PTT, D-dimer, TG, cholesterol, fibrinogen
 - Autoimmune workup - ANA, dsDNA, Ro, La, RNP, RF, ANCA, IgG, IgM, lupus anticoagulant
 - C3, C4, immunoglobulins, Anti TPO anti TTG
- Cardiology: ?CHF
 - repeat echo
- Respiriology: bronchoscopy for BAL



DDX of Pulmonary Hemorrhage

- Infection/Pneumonia
- Bronchiectasis (CF, PCD, immunodeficiency)
- Lung Abscess
- Trauma (foreign body, inhalational injury)
- Vascular (pulmonary embolism/thrombosis, AV malformation, hemangioma)
- Coagulopathy - ITP/TTP/HUS
- Congenital lung malformation
- Neoplasm/malignancy
- Diffuse alveolar hemorrhage syndromes



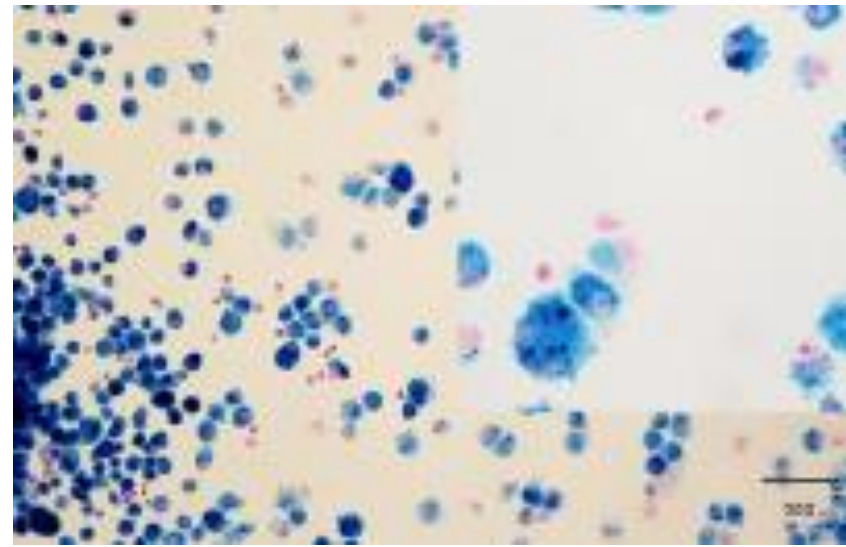
Differential Diagnosis

- 2.5 year old with T21, repaired AVSD
- Pneumonia, fever, severe anemia, thrombocytopenia
- Intubation for oxygenation failure
- Massive pulmonary hemorrhage

Should your differential diagnosis change because the patient has Trisomy 21?



Results



- Bone marrow biopsy - normal
- +Candida albicans from BAL and urine → started on fluconazole
 - Likely colonization
- ID - the rest negative or pending so far
- Autoantibody panel: negative ANA, dsDNA, RF, ENA, GBM
- ANCA weakly positive
- MPO and PR3 negative
- Echo - no residual ASD/VSD, good function, normal septal curvature → not the heart



Immune Mediated Causes of Diffuse Alveolar Hemorrhage

- Idiopathic pulmonary capillaritis
- Granulomatosis with polyangiitis (Wegeners) - most common ANCA vasculitis in kids
- Anti-GBM disease (Goodpasture's)
- Systemic Lupus Erythematosus
- Henoch Schonlein Purpura
- Behcet's disease
- Cryoglobulinemic vasculitis
- Juvenile idiopathic arthritis
- IgA nephropathy

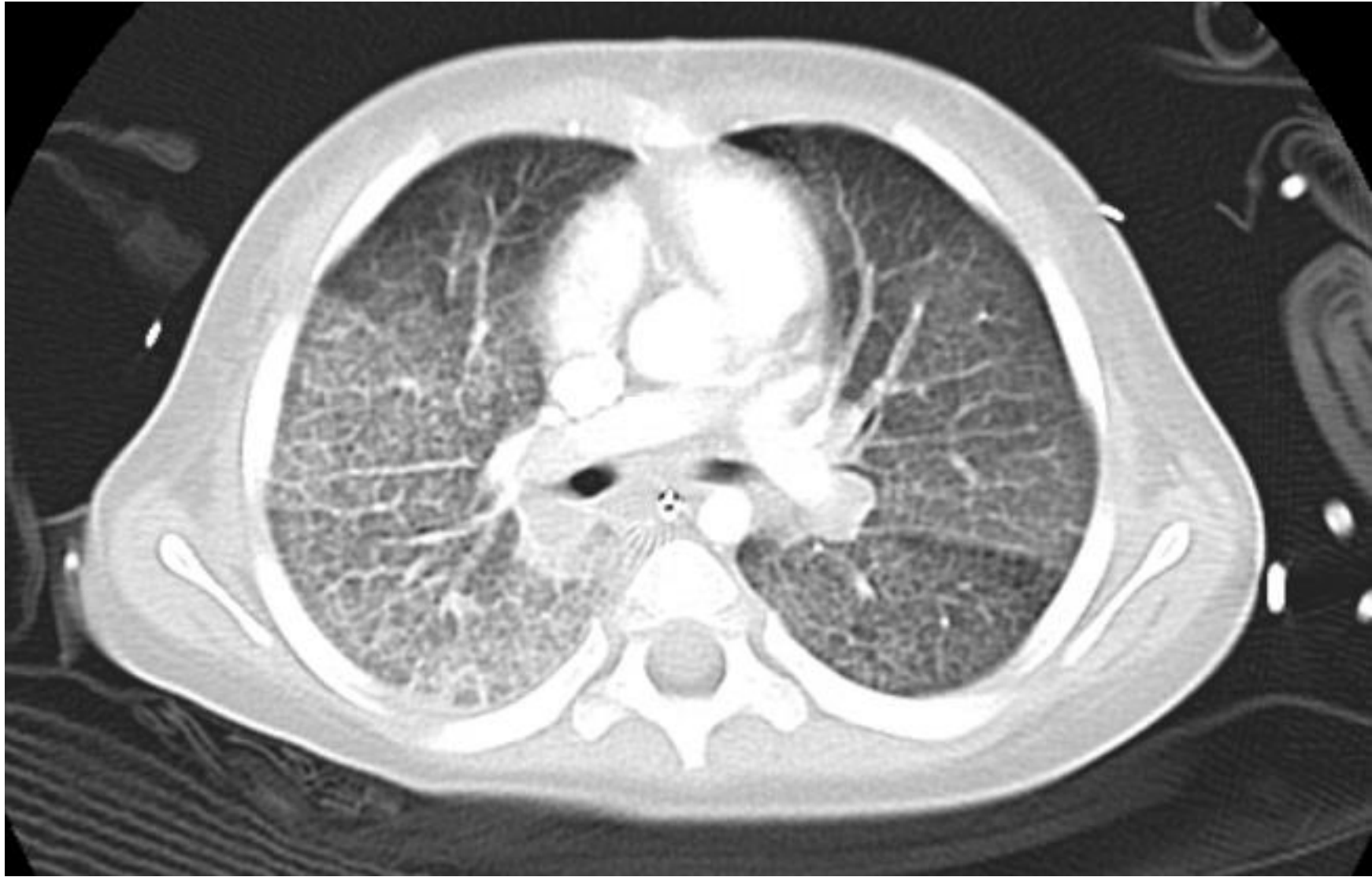


Non-Immune Mediated Causes of Diffuse Alveolar Hemorrhage

- Idiopathic pulmonary hemosiderosis - diagnosis of exclusion
- Asphyxiation
- Drug induced coagulopathy
- Malignancy
- Pulmonary vein atresia/stenosis
- Pulmonary veno-occlusive disease
- Mitral stenosis
- Pulmonary capillary hemangiomatosis
- Pulmonary telangiectasia









Findings on CT

- A. Extensive Tram Tracking
- B. Extensive Tree in Bud
- C. Sand storm sign
- D. Crazy Paving



Findings on CT

- A. Tram tracking
- B. Extensive Tree in Bud
- C. Sand storm sign
- **D. Crazy Paving**



CT Interpretation

- There is diffuse, bilateral **interlobular septal thickening** with **background ground glass opacity** throughout the lung parenchyma, slightly sparing the anterior portions of the lungs
- Focal opacity with air bronchograms in the RLL and LLL
- Prominent bilateral hilar, mediastinal, axial lymph nodes
- No AV malformation
- After reconstructive images of the vessels: filling defects seen in a few segmental branches in both lower lobes → suggestive of pulmonary embolus





Paving

- Abnormal thickening of lobular connective tissue or lobular bronchovascular interstitium due to inflammation or edema
- Causes: interstitial edema, hemorrhage, fibrosis, cellular infiltration or lymphangiectasia
- Previously thought to be specific, now thought to have a broad differential





Paving Differential Diagnosis

- **Pulmonary hemorrhage syndromes**
 - idiopathic pulmonary hemosiderosis, Wegener granulomatosis, goodpasture syndrome, collagen vascular disease (SLE, RA), drug induced coagulopathy, hemorrhage associated with malignancy
- **Immune mediated capillaritis/vasculitis**
- **Alveolar proteinosis**
- **Interstitial pneumonia**
- **Pulmonary veno-occlusive disease**
- **Drug induced pneumonitis**
- **Acute respiratory distress syndrome**
- **Infections: mycoplasma, PJP**
- **Alveolar sarcoidosis**
- **Cryptogenic organizing pneumonia**
- **Mucinous bronchoalveolar carcinoma**



What next?

- Pulse steroids and IVIG → Improved pulmonary hemorrhage



Lung Biopsy – Pulmonary Capillaritis

- Results: pulmonary capillaritis associated with diffuse alveolar hemorrhage recent and old

Pulmonary capillaritis:

- Histologic diagnosis
- Vasculitis in the lung vasculature; inflammation, interstitial infiltrate with neutrophils, fibrinoid necrosis in capillary walls, loss of integrity of BM, extravasation of RBC to alveolar space
- Can be isolated but usually there is an underlying systemic vasculitis or immune-mediate process
 - ANCA-associated vasculitis
 - Systemic disorder (SLE)



The consult train – end of the line



Management

Induction	Maintenance
Steroids Rituximab	Low dose steroids Azathioprine



Treatment

Induction:

- 1. Glucocorticoids + cyclophosphamide
- 2. Methotrexate and rituximab → effective/ non-inferior
- 3. Plasmapheresis → mixed evidence
- 4. IVIG - some evidence, can try especially if contraindications for other medications

Maintenance:

- 1. Low dose glucocorticoids
- 2. Low dose cyclophosphamide or methotrexate or azathioprine
- Not as good: infliximab, Mycophenolate mofetil



Trisomy 21 and Alveolar Hemorrhage

- Multiple other cases in the literature of patients with T21 presenting with diffuse alveolar hemorrhage caused by pulmonary hemosiderosis or ANCA-associated vasculitis
 - Often not recognized on first presentation, bleeding thought to be traumatic and then the patient returned with hemoptysis, SOB, severe anemia
- Delayed presentation → repeat admissions, worsening of symptoms
- Can mimic asthma and pneumonia
 - present nonspecifically with cough, thoracic pain, fever, generalized symptoms for weeks/months before acute presentation
- Kids swallow sputum → manifests as upper GI bleed



A French Cohort of Pulmonary Hemosiderosis

- 12 pediatric respiratory centres to collect data on rare respiratory diseases
- 25 cases of IPH: 20 female, 5 male
- 5 (20%) with T21
- Mean age diagnosis 4 years old
- Presentation: SOB, anemia, cough, febrile pneumonia, hemoptysis
- 50% had diffuse infiltrates on CXR
- Dx by BAL showing hemosiderin laden macrophages 19/25 or lung biopsy 6/25
- ANCA positive in 40%
- Patients with T21 had worse outcomes, one died and 4 relapsed



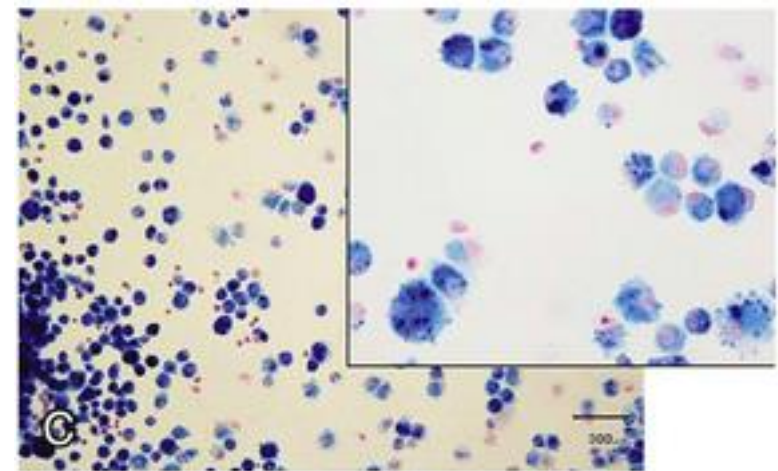
A French Cohort of Pulmonary Hemosiderosis

- 34 patients, 9 (26%) had T21
- T21: more severe presentation, early onset, severe anemia, more frequent mortality and complications such as pulmonary hypertension
- Diffuse interstitial pattern on CXR
- 22% had positive ANCA
- Prevalence estimate: 1.85 /1,000,000 vs. 138.5/1,000,000 in T21



Idiopathic Pulmonary Hemosiderosis

- Triad: recurrent hemoptysis, anemia and pulmonary infiltrates on CXR (rarely occur together)
- Clue: anemia requiring transfusions
- BAL: hemosiderin laden macrophages
- Diagnosis of exclusion: lung biopsy is necessary for diagnosis - RBC in alveoli and interstitium with no vasculitis and fibrosis
- Treatment: corticosteroids
- *children with unexplained anemia and respiratory failure → consider IPH



Background

- Respiratory disease is the second leading cause of death in T21
- 25% have an ICU admission before age 1 year (1/2 respiratory cause)



Health Supervision Guidelines

- Risk of pulmonary infections
- Screening for OSA
- If cardiac or pulmonary disease → give the 23 valent pneumococcal vaccine and the annual influenza vaccine

APPENDIX 1 Health Supervision for Children With Down Syndrome

	Prenatal	Birth-1 mo	1 mo-1 y	1-5 y	5-13 y	13-21 y
Counseling regarding prenatal screening test & imaging results						
Plan for delivery						
Referral to geneticist						
Parent to parent contact, support groups, current books and pamphlets						
Physical exam for evidence of trisomy 21						
Chromosomal analysis to confirm dx						
Discuss risk of recurrence of Down syndrome						
Echocardiogram						
Radiographic swallowing assessment if marked hypotonia, slow feeding, choking with feeds, recurrent or persistent respiratory vs. FTT						
Eye exam for cataracts						
Newborn hearing screen and follow-up						
HE and PE assessment for duodenal or anorectal atresia						
Reassure parents delayed and irregular dental eruption, hypodontia are common						
If constipation, evaluate for limited diet or fluids, hypotonia, hypothyroidism, GI malformation, Hirschsprung						
Cbc to > 80 transient moderate/severe disease polycythemia						
Hb annually; CRP & ferritin or Ctr if possible risk iron deficiency or Hb < 11 g					Annually	Annually
Hemoglobin						Annually
TSH (may be part of newborn screening)			6 and 12 mo		Annually	
Discuss risk of respiratory infection						
If cardiac surgery or hypotonic: evaluate apnea, bradycardia, or oxygen desaturation in car seat before discharge						
Discuss complementary & alternative therapies						
Discuss cervical spine positioning, especially for anesthesia or surgical or radiologic procedures						
Review signs and symptoms of myopathy						
If myopathic signs or symptoms: obtain neutral position spine films and, if normal, obtain flexion & extension films & refer to pediatric neurosurgeon or orthopedic surgeon with expertise in evaluating and treating atlanto axial instability						
Instruct to contact physician for change in gait, change in use of arms or hands, change in bowel or bladder function, neck pain, head tilt, torticollis, or new-onset weakness						
Advise risk of some contact sports, trampolines						
Audiology evaluation at 6 mo						
If normal hearing established, behavioral audiogram and tympanometry until bilateral ear specific testing possible. Refer child with abnormal hearing to ot				Every 6 mo		
If normal ear-specific hearing established, behavioral audiogram						
Assess for obstructive sleep apnea & sleep study by age 4 years						
Ophthalmology referral to assess for strabismus, cataracts, and myasthenia						
Refer to pediatric ophthalmologist or ophthalmologist with experience with Down syndrome				Annually	Every 2 y	Every 3 y
If congenital heart disease, monitor for signs & Sx of Congestive heart failure						
Assess the emotional status of parents and intrafamilial relationships						
Check for Sx of celiac disease; if Sx present, obtain tissue transglutaminase IgA & quantitative IgA						
Early intervention: physical, occupational, and speech therapy						
At 30 months, discuss transition to preschool and development of IEP						
Discuss behavioral and social progress						
Discuss self-help skills, ADHD, OCD, wandering off, transition to middle school						
If chronic cardiac or pulmonary disease, 23-valent pneumococcal vaccine at age > 2 y						
Reassure regarding delayed and irregular dental eruption						
Establish optimal dietary and physical exercise patterns						
Discuss dermatologic issues with parents						
Discuss physical and psychosocial changes through puberty, need for gynecologic care in the pubescent female						
Facilitate transition: guardianship, financial planning, behavioral problems, school placement, vocational training, independence with hygiene and self-care, group homes, work settings						Health maint. visits
Discuss sexual development and behavior, contraception, sexually transmitted diseases, recurrence risk for offspring						Health maint. visits



Pulmonary Complications of Down Syndrome during Childhood

Karen M. McDowell, MD and Daniel I. Craven, MD



Respiratory Disease Patterns

- Upper airway obstruction
 - Stridor
 - OSA
- Recurrent respiratory infections
 - Viral URTIs, LRTIs
 - Pneumonias
 - Aspiration
- Wheeze
 - Pulmonary edema/ pulmonary hypertension
 - Asthma



Respirology consult #3

- 3.5 years old
- Remains on steroids and azathioprine
- Obesity
- Snoring, neck hyperextension, sleeps on side and propped up by pillows
- PSG previously: obstructive AHI 0.2



Which of the following is false about OSA in T21?

- A. Parental report of sleep disordered breathing correlates well with PSG findings in T21
- B. Only 1/3 of patients with T21 will have resolved OSA after an adenotonsillectomy
- C. Kids with T21 are at a higher risk of obstructive sleep apnea, hypoventilation AND central sleep apnea
- D. All kids with T21 should have a sleep study by age 4 years



Which of the following is false about OSA in T21?

- A. Parental report of sleep disordered breathing correlates well with PSG findings - false
- B. Only 1/3 of patients with T21 will have resolved OSA after an adenotonsillectomy -true
- C. Kids with T21 are at a higher risk of obstructive sleep apnea, hypoventilation AND central sleep apnea - true
- D. All kids with OSA should have a sleep study by age 4 years - true



Sleep Disordered Breathing

- Increased risk of OSA 30% to 75%, compared with 2-4% in other kids
- Crowded upper airway, midface and maxillary hypoplasia, posterior displacement of the tongue, lymphoid hyperplasia, pharyngeal hypotonia, obesity
- 69% of the parents of patients with T21 reported no sleep problems, 54% of these had abnormal PSG
- Higher risk of hypoventilation with obstructive episodes and central sleep apnea
- All should have PSG by age 4 years



Sleep Disordered Breathing

Post op T+A

- Higher operative and postoperative complications: apnea, hypoxemia, and post-obstructive pulmonary edema
- 1/3 resolve completely after T+A, others have partial response
- Many improve initially and then have residual symptoms → **need a follow up PSG**
- Reasons for lack of response to T+A:
 - Lingual tonsils, increasing obesity, adenoidal regrowth, hypotonia
- Investigations and Management:
 - Lateral neck X-ray and refer back to ENT
 - Treat comorbidities: rhinitis, asthma, GERD, hypothyroidism
 - Tongue reduction
 - CPAP



Upper airway disease - anatomy

- Narrowing above the vocal cords → midface hypoplasia, narrowed nasopharynx, choanal atresia, large tongue, tonsils and adenoids (relative), lingual tonsils, short palate
- Narrowing below the vocal cords → trachea narrow (2cm narrower than age-matched children)
 - Cause of post intubation stridor

Bottom line: narrowing can occur at any point in the airways



Upper airway disease

- Subglottic stenosis: common cause of post-operative stridor
- Tracheal stenosis: can be associated with vascular rings and hypoplasia of aortic arch

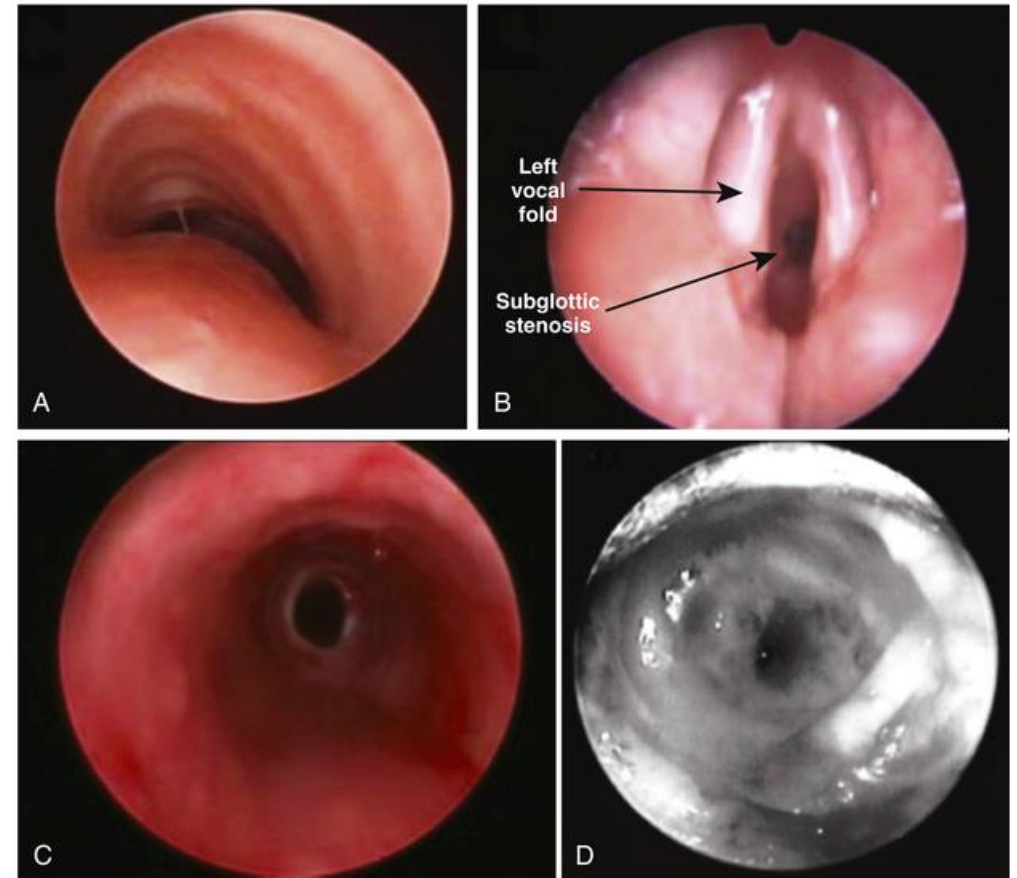
A. Tracheomalacia

B. Subglottic stenosis

C. Mid-tracheal stenosis

D. Pinpoint severe tracheal stenosis

Tracheomalacia is the most common upper airway abnormality seen on endoscopy



Recurrent Right Upper Lobe Pneumonia

- Consider a tracheal bronchus
- RUL bronchus originates directly from the trachea rather than the right mainstem bronchus
- Studies have shown high rates of T21 in patients with tracheal bronchus → suggests it is higher T21

Bertrand P, Navarro H, Caussade S, Holmgren N, Sanchez I. Airway anomalies in children with Down syndrome: endoscopic findings. *Pediatr Pulmonol*. 2003.

McLaughlin FJ et al. Tracheal bronchus: association with respiratory morbidity in childhood. *J Pediatrics*. 1985.



Lower Respiratory Tract Disease

Higher risk of pulmonary infection due to:

- Decreased pulmonary reserve
 - Poor immunologic function
 - GERD and aspiration
 - Interactions with congenital heart disease
 - Thoracic cage malformations
-
- More likely to have ICU admissions, require intubation



Which of the following does NOT contribute to decreased functional reserve in T21:

- A. They have a double capillary network
- B. They have decreased number of alveoli
- C. They have decreased alveoli size
- D. They have decreased alveolar surface area



Which of the following does NOT contribute to decreased functional reserve in T21:

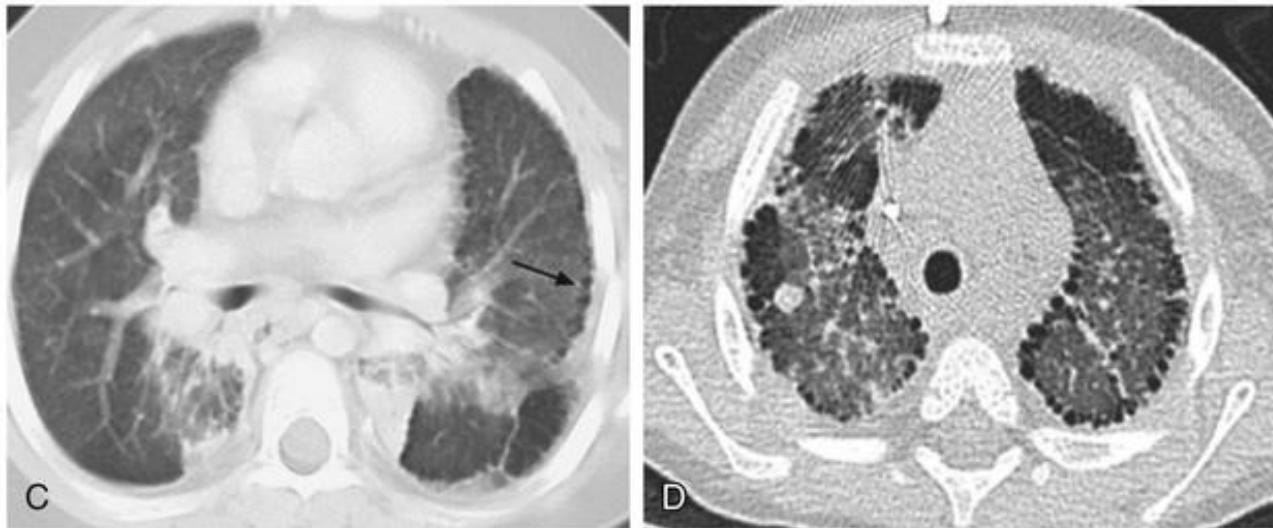
- A. They have a double capillary network
- B. They have decreased number of alveoli
- **C. They have decreased alveoli size**
- D. They have a decreased alveolar surface area

The alveoli are larger



Reduced Functional Reserve - histopathology

- Increased alveolar size
- Decreased alveolar count
- Failure of alveoli multiplication → acinar hypoplasia
- Can lead to subpleural cysts



Pulmonary Hypoplasia

- Since 1982
- Autopsies of 7 patients with T21 were compared to children without T21 who had CHD
- 6/7 T21 had pulmonary hypoplasia
- **Decreased number of alveoli**
 - Total number of alveoli: 36% in T21, 80% in CHD (age and height matched)
 - Radial alveolar count 72% predicted (index unaffected by short stature)
- **Enlarged alveoli** and alveolar ducts
 - Average alveolar volume calculated to be 2x larger in T21
- Smaller alveolar surface area
 - 44% predicted
- Some patients had **double capillary network** in alveolar septa- usually only seen intrauterine/postnatally, retention of fetal structure



Pulmonary Hypoplasia

- Potent antiangiogenic agents are expressed on chromosome 21, including endostatin, beta-amyloid peptide → early overexpression of antiangiogenic factors may disrupt vascular development → abnormal lung development
- Higher incidence of prominent bronchial vessels + intrapulmonary and bronchopulmonary anastomoses
- Leads to chronic hypoxemia

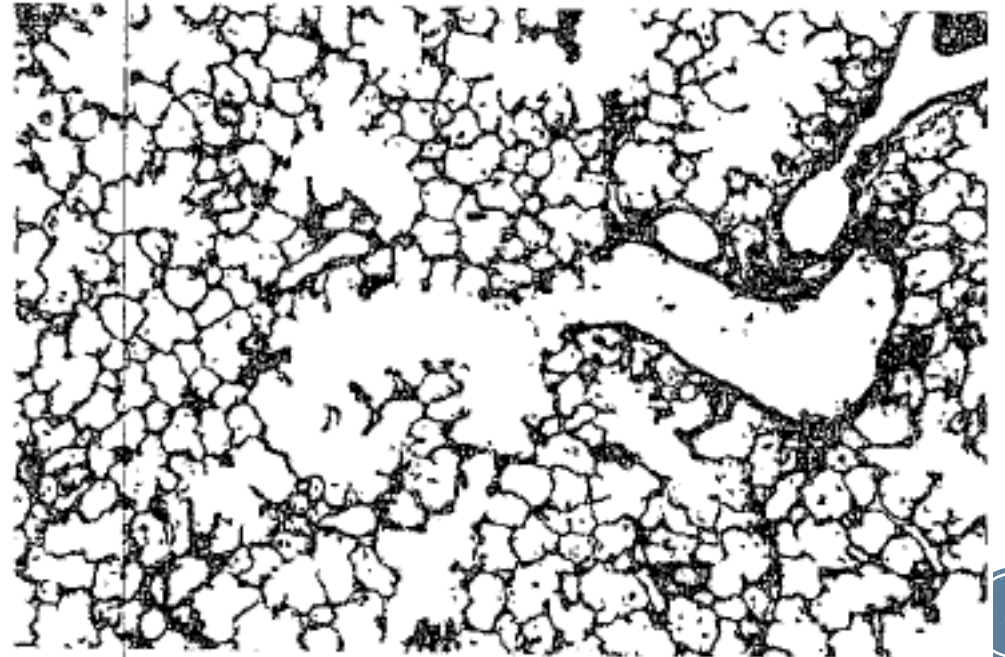
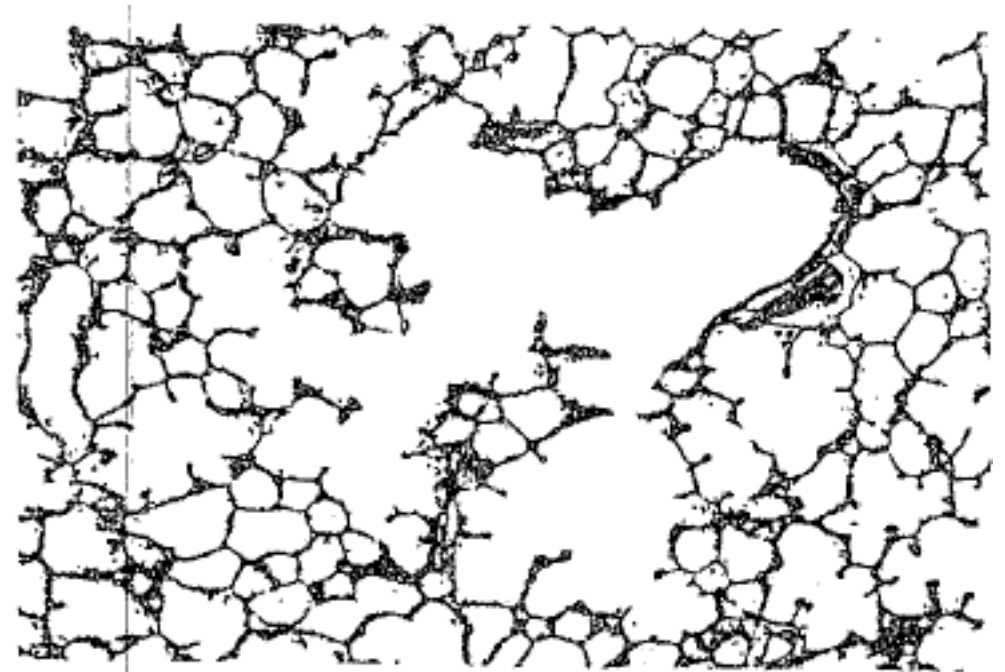
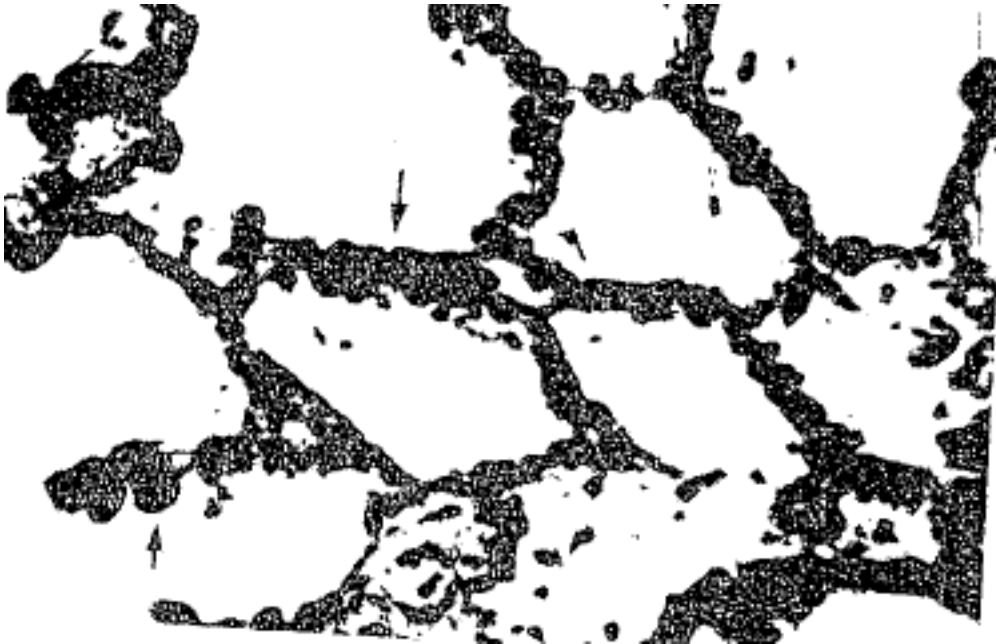


Pulmonary Hypoplasia

- Children with Interstitial Lung Disease (CHiLD) research corporation
- Classification of pediatric diffuse lung disease
- “growth abnormalities reflecting **deficient alveolarization**”
- Other diagnoses in this category:
 - Prematurity/chronic lung disease
 - Pulmonary hypoplasia



- Top: alveolar tissue from T21
 - Bottom: alveolar tissue from a healthy child
-
- Double capillary network



Subpleural Cysts in Down Syndrome

- First described in 1986
- 1991 study found 20% had subpleural cysts, all had CHD
- Rarely seen in CHD without T21
- Detected poorly on X-ray
- 20-36% of children with DS
- May increase the risk for pneumothorax



Clinical Sequelae

- Pulmonary hypertension
- Pulmonary edema
- Pulmonary hemorrhage



Poor Immunologic Function

- Reduction of multiple immune cell lines and antibody levels
- Reduced titres to immunization (pertussis, pneumococcus)
- Reduced neutrophil chemotaxis
- Reduced natural killer cells

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
Anatomic	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



GI-Resp Interactions

Functional

- Dysmotility
- Reflux
- Swallowing dysfunction

Structural

- GI malformations in 7% with DS
- Duodenal stenosis/atresia, anal stenosis/atresia, Hirschsprung disease, esophageal atresia +/- TEF, pyloric stenosis
- **Poor correlation with feeding symptoms and aspiration → low threshold for swallowing evaluation in recurrent respiratory infections**



Cardiopulmonary Interactions

Pulmonary Hypertension

- Altered maturation of capillary network → thick arterial walls and reduced total alveolar surface area
- Higher vascular resistance at baseline (abnormal vasculature + double capillary network)
- Recurrent hypoxic events: lung infections, recurrent aspiration, OSA, congenital heart disease, and pulmonary shunts



What is true about asthma in T21?

- A. Asthma is more common in patients with T21
- B. Asthma is less common in patients with T21
- C. Asthma has around the same prevalence in T21 than the rest of the population



What is true about asthma in T21?

- A. Asthma is more common in patients with T21
- **B. Asthma is less common in patients with T21??**
- C. Asthma has around the same prevalence in T21 than the rest of the population

But... wheeze is way more common



Asthma or Not Asthma

- High rates of wheeze
- Lower rates of atopy
- Multiple studies have documented lower prevalence of asthma in T21, particularly severe asthma
- **Need to consider alternate diagnoses** - anatomic abnormalities (malacias), chronic aspiration, reflux, vascular malformations



Take Home Points

1. So many reasons for OSA - airway is narrow.... everywhere
2. So many reasons for pulmonary hypertension - chronic hypoxia, double capillary network
3. So many reasons for recurrent infections - pulmonary reserve, immune system, aspiration
4. Respiratory distress and unexplained anemia → consider vasculitis/pulmonary hemosiderosis
5. Crazy paving has a broad differential diagnosis
6. Use a smaller ETT size in T21
7. Consider a tracheal bronchus for recurrent RUL pneumonias
8. Low threshold for PSG if snoring
9. Repeat the PSG after T+A (and think about lingual tonsils)
10. Low threshold for a feeding study if recurrent pneumonias
11. It's not always asthma... Consider other diagnoses
12. Remember to recommend the annual influenza vaccine



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Thank You!

Questions?

