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
- Critically → transfer to Sickkids PICU

Anemia + thrombocytopenia in T21 → rule out leukemia

8.9

39 118
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
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  - C. A larger tube than other kids at the same age
Endotracheal tube size

- 1-2 sizes smaller

<table>
<thead>
<tr>
<th>Age</th>
<th>Down Syndrome</th>
<th>Non-Down Syndrome</th>
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</thead>
<tbody>
<tr>
<td>Premature</td>
<td>2.0–2.5</td>
<td>2.5–3.0</td>
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<td>Full-term newborn to 9 months</td>
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<td>3.5–4.0</td>
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<tr>
<td>9–18 months</td>
<td>3.0–3.5</td>
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<td>1.5–3 years</td>
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<td>4–5 years</td>
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<td>8–10 years</td>
<td>5.5</td>
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<td>10–11 years</td>
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<td>6.5–7.0</td>
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<td>12–13 years</td>
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<td>7.0–7.5</td>
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<tr>
<td>14 years and older</td>
<td>6.5</td>
<td>7.5–8.0</td>
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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, Respirology, 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

- **Respirology:** 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
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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
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 $\rightarrow$ 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-mediated process
  - ANCA-associated vasculitis
  - Systemic disorder (SLE)
The consult train – end of the line
Management

<table>
<thead>
<tr>
<th>Induction</th>
<th>Maintenance</th>
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<tbody>
<tr>
<td>Steroids</td>
<td>Low dose steroids Azathioprine</td>
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<td>Rituximab</td>
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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
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

Trisomy 21 and Alveolar Hemorrhage
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
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
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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

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- Narrowing below the vocal cords → trachea narrow (2cm narrower than age-matched children)
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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

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
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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
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

<table>
<thead>
<tr>
<th>Cell numbers</th>
<th>Mild to moderate reduced T-cell counts</th>
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<tr>
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<td>Mild to moderate reduced B-cell counts</td>
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<td>Absence of normal lymphocyte expansion</td>
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<td>Mild to moderate reduced naïve T-cell percentages</td>
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<td>Anatomic</td>
<td>Reduced thymus size compared to age-matched controls</td>
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<td>Antibody production</td>
<td>Suboptimal antibody response to immunization</td>
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<td>Decreased total and specific immunoglobulin A in saliva</td>
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<td>Innate immunity</td>
<td>Decreased neutrophil chemotaxis</td>
</tr>
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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
References


References


Thank You!

Questions?