SHORT CASES RESPIRATORY COMPLICATIONS OF SICKLE CELL DISEASE

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Hemoglobinopathy (AR)

- Amino acid substitution in the beta globin chain of hemoglobin = HbS
- Hb S is poorly soluble when deoxygenated
- Hypoxia -> HbS polymerizes -> distortion of red cells into crescent -> obstruction of vessels
- Complications 2nd to vaso-occlusive phenomena or hemolysis
SICKLE CELL DISEASE 101

- 8-10% of African Americans have sickle cell trait (HbAS)
- 1:2647 children
- 1:400 African American children
- At risk populations
  - Africans, Mediterranean, Middle East, Indians, Caribbean, Latinos
- Newborn screening
- Dx = hemoglobin electrophoresis

## TABLEAU 25.1 | Profils hématologiques des différents phénotypes d’anémie falciforme

<table>
<thead>
<tr>
<th>Phénotype</th>
<th>SS</th>
<th>Sβ⁰-thalassémie</th>
<th>SC</th>
<th>Sβ⁺-thalassémie</th>
<th>AS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (g/L) (50ᵉ percentile)</td>
<td>85</td>
<td>85</td>
<td>105</td>
<td>110</td>
<td>N</td>
</tr>
<tr>
<td>Volume globulaire moyen</td>
<td>N</td>
<td>↓↓</td>
<td>↓</td>
<td>↓</td>
<td>N</td>
</tr>
</tbody>
</table>

N : normal ; ↓ : diminué ; ↓↓ : très diminué
Clinical manifestations

- Functional asplenia
  - Increased risk of infection by encapsulated bacteria
  - Salmonella typhi osteomyelitis
- Vaso-occlusive crisis
- Splenic sequestration
- Stroke
- Aplastic crisis
- Renal complications
- Other complications
Sickle Cell Disease 101

- Multidisciplinary team
- Folic acid
- Prophylactic antibiotic
- Hydroxyurea
- Blood transfusions
- Hematopoietic cell transplantation
SICKLE CELL DISEASE 101

- Acute and chronic respiratory complications are frequent
- They contribute to morbidity and mortality
CASE #1

- 6-year-old girl
- Previous medical history
  - Born in Quebec
  - Sickle cell disease, Hb SS (Hb 85-90)
  - Multiple vaso-occlusive crisis
  - 1 previous acute chest syndrome in 2015
  - 3 previous transfusions (last 09/2016)
  - Last echocardiogram 06/2016 normal
- Family medical history
  - Parents sickle cell trait
- Rx: folic acid, hydroxyurea
CASE #1

- Admitted for vaso-occlusive crisis + fever
  - Morphine 0.1 mg/kg q3h
  - Hydration
  - Ceftriaxone

- Day 2
  - Morphine 0.15 mg/kg q3h -> morphine perfusion 0.08 mg/kg/h
  - Blood cultures negative
**CASE #1**

- **Day 3**
  - Desaturation 85%, which required 0.5L of oxygen
  - New cough
  - No respiratory distress
  - Bilateral crackles at bases and bronchial breath sounds on left base on exam
CASE #1 - ADMISSION
CASE #1

- Acute chest syndrome with left lower lobe opacity on chest X-ray
  - Cefotaxime + clarithromycin
  - Respiratory physiotherapy
  - Monitoring
  - Transfusion
CASE #1

- What is the definition of acute chest syndrome?
- What were the possible etiologies for this patient?
- What is the management of acute chest syndrome?
ACUTE CHEST SYNDROME

- Most common acute respiratory complication
- 2nd cause of hospitalization
- 1st cause of death
- 50% of HbSS patients will have at least 1 episode
- Peak incidence 2-4 years old
- 50% of patients were initially hospitalized for another reason, most frequently a vaso-occlusive crisis
**ACUTE CHEST SYNDROME**

- **Definition**
  - New pulmonary infiltrate on chest X-ray involving at least one lung segment and not consistent with atelectasis
  - At least one
    - Chest pain
    - Fever > 38.5
    - Tachypnea, wheezing, cough, increased work of breathing
    - Hypoxemia
Pathogenesis is complex

Multiple possible etiologies
- Atelectasis
- Pulmonary edema
- Bronchospasm
- Vaso-occlusive crisis
- Excessive administration of opioid
- Pneumonia/infection
- Fat embolus
- Thromboembolism

Acute Chest Syndrome

- National Acute Chest Syndrome Study Group

Causes and Outcomes of the Acute Chest Syndrome in Sickle Cell Disease

Elliott P. Vichinsky, M.D., Lynne D. Neumayr, M.D., Ann N. Earles, R.N., P.N.P., Roger Williams, M.D., Evelyne T. Lennette, Ph.D., Deborah Dean, M.D., M.P.H., Bruce Nickerson, M.D., Eugene Orringer, M.D., Virgil McKie, M.D., Rita Bellevue, M.D., Charles Daeschner, M.D., and Elizabeth A. Manci, M.D., for the National Acute Chest Syndrome Study Group*

- Multicenter prospective study
- Hb SS, SC ou SB thal
- Usual definition of acute chest syndrome
- 671 episodes 1993-1997

# ACUTE CHEST SYNDROME

## Table 4. Causes of the Acute Chest Syndrome.*

<table>
<thead>
<tr>
<th>Cause</th>
<th>All Episodes (N=670)</th>
<th>Age at Episode of Acute Chest Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N=670)</td>
<td>0–9 YR (N=329) 10–19 YR (N=188) ≥20 YR (N=153)</td>
</tr>
<tr>
<td>Fat embolism, with or without infection†</td>
<td>59 (8.8)</td>
<td>24</td>
</tr>
<tr>
<td>Chlamydia‡</td>
<td>48 (7.2)</td>
<td>19</td>
</tr>
<tr>
<td>Mycoplasma§</td>
<td>44 (6.6)</td>
<td>29</td>
</tr>
<tr>
<td>Virus</td>
<td>43 (6.4)</td>
<td>36</td>
</tr>
<tr>
<td>Bacteria</td>
<td>30 (4.5)</td>
<td>13</td>
</tr>
<tr>
<td>Mixed infections</td>
<td>25 (3.7)</td>
<td>16</td>
</tr>
<tr>
<td>Legionella</td>
<td>4 (0.6)</td>
<td>3</td>
</tr>
<tr>
<td>Miscellaneous infections¶</td>
<td>3 (0.4)</td>
<td>0</td>
</tr>
<tr>
<td>Infarction</td>
<td>108 (16.1)</td>
<td>50</td>
</tr>
<tr>
<td>Unknown**</td>
<td>306 (45.7)</td>
<td>139</td>
</tr>
</tbody>
</table>

ACUTE CHEST SYNDROME

- Management
  - Admission
  - Fluid
  - Analgesia
  - Oxygen for Sat $\geq 95$
  - Respiratory physiotherapy
  - Bronchodilators
  - Antibiotics
  - Fever control
Transfusions

- RBC transfusion in the setting of acute chest syndrome results in improved oxygenation. Some studies have observed equivalent outcomes whether patients are treated with exchange transfusion (HbS% goal of 30%) or simple transfusion (Hb goal of 100 g/L). Other studies have found, however, that patients receiving top-up transfusions may progress to requiring a full exchange.

- In the absence of evidence from randomized controlled trials, most patients with acute chest syndrome should be transfused, with exchange transfusions reserved for patients with more severe or rapidly progressing disease. Signs of severe disease include:
  - altered mental status
  - persistent heart rate >125 beats/minute, respiratory rate >30 breaths/minute, temperature >40°C, or worsening hypotension
  - arterial pH <7.35; peripheral capillary oxygen saturation (SpO2)% <88% despite aggressive ventilatory support
  - serial decline in SpO2% or alveolar-arterial gradient
  - fall in hemoglobin >20 g/L
  - platelet count <200/fl.
  - elevated troponin or brain natriuretic peptide (BNP)
  - evidence of multiorgan failure (e.g., renal or hepatic dysfunction)
  - pleural effusions or progressive pulmonary infiltrates

ACUTE CHEST SYNDROME

Complications

- Neurologic
- Respiratory failure
- Pulmonary infarction
- Pulmonary fibrosis
- Pulmonary hypertension
- Unexpected death
ACUTE CHEST SYNDROME

- Prevention
  - Prophylactic antibiotic and vaccination
  - Pulmonary function tests and resting saturation
  - Aggressive treatment of asthmatic patients
  - Hydroxyurea
  - Transfusion therapy
Case #2

- 15-year-old boy
- Admitted for hypoxemia

Past medical history
- Born at 35 weeks of gestation, in Boston
- Sickle cell disease, HbSS (Hb 70)
- No previous acute chest syndrome.
- Last echocardiogram 2011 normal
- Arnold Chiari type 1
- Eczema

Family medical history
- Mother known for sickle cell disease
CASE #2

- No animals. No smoking.
- Lives with his mother.
- Immunization up to date.
- Rx: Folic acid
- Does not take his hydroxyurea because of nausea.
Admitted for hypoxemia on a routine visit
At last visit 3 months ago: SpO2 93%
He now presents to the clinic for his PFT
SpO2 is 86-87%
He does not have acute symptoms
Chronic dyspnea on exertion
No improvement after Fluticasone 125 mcg
BID for 3 months
Snoring, fatigue, school difficulties
CASE #2

- RR 18 SpO2 91%
- No tonsillar hypertrophy
- Pulmonary exam normal
- Grade 2 systolic murmur. P2 N.
- Clubbing grade 1
What is your differential diagnosis for this 15-year-old patient with sickle cell disease and hypoxemia?
Saturation often decreased in sickle cell disease patients

- Mean daytime saturation 94%, median 95%
- 10% of asymptomatic patients have SpO2 < 90%
- Measurements recommended at every visit
Hypoxemia - Differential Diagnosis

- Acute chest syndrome
- Pneumonia
- Pulmonary embolism
- Sepsis
- Asthma
- Pulmonary hypertension
- Thromboembolism
- Obstructive sleep apnea
- Lung infarctions
- Pulmonary fibrosis
- Cardiac dysfunction
- Low Hb F
- Elevated Hb Meth
CASE #2

What investigation do you want to do for this patient?
CASE #2

- Hb 61
- WBC normal
- pCO2 38
CASE #2

- Overnight oximetry
  - Mean SpO2 86.5%
  - Min SpO2 75%
  - 96% of time < 90%!
<table>
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<tr>
<th></th>
<th>Ref</th>
<th>Meas</th>
<th>%</th>
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<tr>
<td>FVC</td>
<td>5.42</td>
<td>4.54</td>
<td>83.6</td>
</tr>
<tr>
<td>FEV1</td>
<td>4.54</td>
<td>4.04</td>
<td>89.1</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>85.24</td>
<td>89.14</td>
<td></td>
</tr>
<tr>
<td>FEF 25-75%</td>
<td>4.67</td>
<td>4.72</td>
<td>101.1</td>
</tr>
<tr>
<td>CV</td>
<td>4.89</td>
<td>4.53</td>
<td>92.6</td>
</tr>
<tr>
<td>RV-He</td>
<td>1.26</td>
<td>1.34</td>
<td>106.1</td>
</tr>
<tr>
<td>RV/TLC</td>
<td>20.24</td>
<td>22.80</td>
<td>112.7</td>
</tr>
<tr>
<td>TLC-He</td>
<td>6.22</td>
<td>5.87</td>
<td>94.3</td>
</tr>
<tr>
<td>DLCOc</td>
<td>32.65</td>
<td>31.40</td>
<td>96.3</td>
</tr>
</tbody>
</table>

**CASE #2**
CASE #2

- V/Q scan normal
- ECG normal
- Echocardiography normal
- 6MWT:
  - SpO2 88-93%
  - Walked distance 360 m

Li et al, Standard Reference for the Six Minute Walk Test in Healthy Children Aged 7 to 16 Years, American Journal of Respiratory and Critical Care Medicine, vol 176, 2007.
CASE #2

- Respiratory investigation normal
- Chronic low saturation because of poor adherence to hydroxyurea with low HbF
- Transfusion
- PSG
  - AHI 2 (0.65 obstructive, 1.35 central)
  - Mean SpO2 93%
  - 1.2% of time < 90%
CASE #2

- Conclusion: Chronic low saturation because of poor adherence to hydroxyurea with low HbF
- No oxygen therapy
- Close follow-up
CHRONIC RESPIRATORY COMPLICATIONS
**Chronic Dyspnea**

- Common
- Often not reported
- Decreased exercise capacity that begins in adolescence
- Etiology often multi-factorial
  - Anemia
  - Deconditioning
  - Asthma
  - Pulmonary hypertension
  - Thromboembolism
  - Pulmonary fibrosis
  - Myocardial dysfunction
Relationship between sickle cell disease and asthma not well understood, but increased risk

- Severe airway narrowing -> local hypoxia -> sickling and systemic inflammation?
- Recurrent acute chest syndrome -> pulmonary inflammation -> increased airway reactivity?
Clinical manifestations similar to other pulmonary complications
Demonstration of variable airflow obstruction
Usual management
Associated with increased incidence of acute chest syndrome and vaso-occlusive crisis
PULMONARY HYPERTENSION

- Severe complication
- 6-10% of adults
- 10-20% of children have increased TRV
- Independent risk factor of mortality in adults and morbidity in children
- Pathogenesis unknown but potential contributing factors implicated
Variable and non-specific clinical presentation

- Dyspnea on exertion
- Chest pain
- Palpitations
- Syncope/near-syncope
- Decreased exercise capacity
- Decreased activities without other reported symptom
- Fatigue

If symptoms: oximetry at rest and exertion
Investigation

- Echocardiography
- pro-BNP
- Pulmonary function tests with diffusion
- Six minute walk test
- Definitive diagnosis: cardiac catheterization with PAP >= 25 mmHg
PULMONARY HYPERTENSION

- Echocardiography
  - Estimates PAP via TRV
    - PPV 25% in adults
    - >= 2.5 m/sec abnormal
    - >= 3 m/sec suggests moderate to severe pulmonary hypertension
  - Evaluates cardiac function, ventricular hypertrophy and dilatation

- Six minute walk test
  - Evaluates desaturation on exertion and walked distance

- Pro-BNP
  - Correlates with severity

ATS recommendations

4. For children with SCD who have evidence of PH by echocardiogram, the following are recommended:
   a. Children with SCD should undergo further cardiopulmonary evaluation, including pulmonary function testing, polysomnography, assessment of oxygenation, and evaluation for thromboembolic disease (Class I; Level of Evidence C).
   b. Children with SCD should undergo cardiac catheterization before the initiation of PAH-specific drug therapy (Class I; Level of Evidence C).

5. BNP and NT-proBNP measurements can be useful in screening for PH in patients with SCD (Class IIa; Level of Evidence C).
PULMONARY HYPERTENSION

- **Management**
  - Multidisciplinary team!
  - O2 for Sat \( \geq 90\% \) rest/exertion
  - Treat OSA
  - Diuretics
  - Hydroxyurea and transfusions
  - Anticoagulation
PULMONARY HYPERTENSION

- ATS recommendations

6. With the diagnosis of PH in children with SCD, optimization of SCD-related therapies (e.g., blood transfusions, hydroxyurea, iron chelation, and supplemental oxygen) is recommended (Class I; Level of Evidence C).

7. PAH-targeted therapy should not be used empirically in SCD-associated PH because of potential adverse effects (Class III; Level of Evidence C).

8. PAH-targeted therapy may be considered in patients with SCD in whom there is confirmation of PH with marked elevation of PVR without an elevated pulmonary capillary wedge pressure by cardiac catheterization (Class IIb; Level of Evidence C).

Adman et al., «Pediatric Pulmonary Hypertension Guideline from the American Heart Association and American Thoracic Society», Circulation, nov 2015
Screening

- Studies do not demonstrate a better outcome with screening BUT
- Symptoms often late in the course of disease
- TRV > 2.5 m/sec
  - Associated with increased risk of death in adult
  - Associated with future reduced exercise capacity in children &ge; 8 years old

Canadian consensus recommendation

- Echocardiography every 5 years starting at 3 years old

Increased incidence and severity
Nighttime desaturations +/- OSA frequent
OSA
- Frequent comorbidity
- Estimated prevalence 10-20%
- Contributes to frequency of vaso-occlusive crisis and chronic cardiovascular disease
Prevalence in asymptomatic patients?
- 1 screening study in 38 patients: 20 (53%) nocturnal desaturations (SaO2 < 92% > 5% of time)

Etiology? Probably multifactorial
- Reduced upper airway diameter
- Increased adenoid and tonsillar size
- Alteration of the O2 dissociative curve
- Decreased O2 transport capacity due to anemia
- Ventilation-perfusion anomalies

Look for symptoms!

Usual indications PSG
- Snoring, non-restorative sleep, gasping, choking, apneas, hypersomnolence, pulmonary hypertension

Consider PSG
- Unexplained hypoxemia, recurrent acute chest syndrome or vaso-occlusive crisis
SLEEP DISORDERED BREATHING

- Usual management
  - Including evaluation of adenotonsillar hypertrophy
- Hydroxyurea may decrease nocturnal hypoxia
Hypercoagulable state

D-dimers are increased at baseline and change with vaso-occlusive episodes

Screening scores have bad predictive value

Diagnosis by Angio-scan if clinical suspicion

- Acute or progressive dyspnea
- Lower extremity edema
- Failure to respond to treatment of acute chest syndrome
- Presence of other risk factors
PULMONARY FIBROSIS

- Recurrent acute chest syndromes with pulmonary infarction
- Clinical presentation
  - Dyspnea
  - Honeycombing
  - Restrictive pattern
  - Decreased DLCO
- No specific treatment
- Prevention of acute chest syndrome
Evolution of PFT:
    normal -> obstructive -> restrictive

Spirometry 5-18 years old
- 71% normal
- 16% obstructive pattern
- 13% restrictive pattern

Most frequent abnormality during adolescence
- Restrictive pattern
  - 0.9% of 8-year-old children
  - 18.7% of 17-year-old adolescents

PFT are recommended annually from 6 years old

Plethysmography is recommended starting from 6 years old

- Every 5 years if no asthma or acute chest syndrome
- Every 2-3 years if asthma or acute chest syndrome
Sickle cell disease
- Frequent AR hemoglobinopathy with multiple respiratory complications

Acute chest syndrome
- New infiltrate on chest X ray + respiratory symptoms or fever
- Rapid management

Pulmonary hypertension
- Echocardiographic screening every 5 years
- Diagnosis by cardiac catheterization
CONCLUSION

- Obstructive sleep apnea is frequent
  - Look for it on history
  - Consider PSG if symptoms, unexplained hypoxemia, recurrent acute chest or vaso-occlusive episodes or enuresis

- Asthma is also frequent
  - Look for it since it ↑ acute chest and vaso-occlusive episodes

- PFT often abnormal
  - Recommended every year

- Saturation often decreased
  - Measure it at every visit
BIBLIOGRAPHY

- Verhovsek et all, «Consensus Statement on the Care of Patients with Sickle Cell Disease in Canada», 2015.
Google images

Uptodate
  - Hydroxyurea use in sickle cell disease
  - Overview of the clinical manifestations of sickle cell disease
  - Overview of the pulmonary complications of sickle cell disease
  - Pulmonary hypertension associated with sickle cell disease
  - Sickle cell trait
  - The acute chest syndrome in children and adolescents with sickle cell disease
THANK YOU!

KEEP CALM AND
SPREAD SICKLE CELL AWARENESS