Acute Chest Syndrome of Sickle Cell Disease

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- No relevant conflicts
- Unapproved use of the following drugs will be discussed:
  - Nitric oxide
  - Dexamethasone

Acute Chest Syndrome

- Incidence
- Risk Factors
- Clinical Presentation
- Mortality
- Etiology
- Pathophysiology
- Treatment & Prevention

Acute Chest Syndrome - Introduction

- Charache suggested this name in 1979 for what he felt was a poorly understood process
- New pulmonary infiltrate in a clinically ill SCD patient with associated fever, cough, chest pain, tachypnea, wheezing, or rales on exam
- 2nd most common cause of hospitalization & leading cause of death in SCD patients

Acute Chest Syndrome - Sources of Data

- The Cooperative Study of Sickle Cell Disease (CSSCD)
- The National Acute Chest Syndrome Study Group (NACSSG)
Acute Chest Syndrome: Incidence and Risk Factors; Clinical Presentation and Course

(Castro et al., Blood, 1994 & Vichinsky et al., Blood, 1997)

- Data from 3751 patients with 19,867 pt-years of follow-up

Causes & Outcomes of ACS in SCD

(Vichinsky et al., NEJM, 2000)

- Data from 538 patients with 671 episodes of ACS

Acute Chest Syndrome - Incidence

- ACS incidence is higher in SS patients (12.8/100 pt-yrs) and Sβ0 thal patients (9.4/100 pt-yrs)
- ACS incidence in SC patients was 5.2/100 pt-yrs and in Sβ+ thal patients was 3.9/100 pt-yrs
- Within each Hb type, incidence of ACS was strongly, but inversely associated with age

Acute Chest Syndrome - Incidence (SS)

<table>
<thead>
<tr>
<th>Age Group (yrs)</th>
<th>Episodes of ACS (per 100 patient years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2</td>
<td>20.8</td>
</tr>
<tr>
<td>2-5</td>
<td>25.3</td>
</tr>
<tr>
<td>5-10</td>
<td>15.6</td>
</tr>
<tr>
<td>10-20</td>
<td>9.3</td>
</tr>
<tr>
<td>&gt; 20</td>
<td>8.8</td>
</tr>
</tbody>
</table>

from Castro et al., Blood, 1994

Acute Chest Syndrome - Incidence (SC)

<table>
<thead>
<tr>
<th>Age Group (yrs)</th>
<th>Episodes of ACS (per 100 patient years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2</td>
<td>10.3</td>
</tr>
<tr>
<td>2-5</td>
<td>10.1</td>
</tr>
<tr>
<td>5-10</td>
<td>4.3</td>
</tr>
<tr>
<td>10-20</td>
<td>4.0</td>
</tr>
<tr>
<td>&gt; 20</td>
<td>3.3</td>
</tr>
</tbody>
</table>

from Castro et al., Blood, 1994

Acute Chest Syndrome - Risk factors

Significant in multivariable analysis

- Young age
- Low fetal hemoglobin level
- High hemoglobin level in steady state
- High WBC in steady state

from Castro et al., Blood, 1994

Acute Chest Syndrome - Effect of Hgb F Level on Risk

Relationship between Hb F and ACS for the age groups shown

from Castro et al., Blood, 1994
Acute Chest Syndrome - Effect of Steady State Hgb Level

Relationship between total hemoglobin and rate of ACS in 3 age groups

Acute Chest Syndrome - Clinical Presentation

- Frequency of presenting symptoms in ACS is age-dependent
- Young children (2 – 4 years) present commonly with fever and cough
- The occurrence of chest pain, SOB, chills, productive cough and hemoptysis increase with age

Vichinsky et al., Blood, 1997

Acute Chest Syndrome - Clinical Presentation

- On x-ray, upper/middle lobe disease is predominant in children, while multilobe/lower lobe disease is more common in adults
- Children require less blood transfusions than adult patients
- Duration of hospitalization is ~ 5.4 days in children compared to 9 days in adults

Predictors of Respiratory Failure in Acute Chest Syndrome – Vichinsky et al, NEJM, 2000

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Respiratory Failure</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of cardiac disease</td>
<td>No</td>
<td>1.0</td>
<td>0.94</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>6.7 (2.1 – 22.3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Number of lobes involved in radiographic examination</td>
<td>0 to 1</td>
<td>1.0</td>
<td>0.94</td>
</tr>
<tr>
<td></td>
<td>2 to 4</td>
<td>2.2 (1.0 – 4.6)</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>&gt; 4</td>
<td>9.6 (2.5 – 32.7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Pneumococcal etiology diagnosis</td>
<td>No</td>
<td>1.0</td>
<td>0.75</td>
</tr>
<tr>
<td></td>
<td>199,000/mC/ml</td>
<td>0.9 (0.7 – 1.1)</td>
<td>0.36</td>
</tr>
<tr>
<td></td>
<td>&gt; 400,000/mC/ml</td>
<td>0.1 (0.10 – 0.96)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Vichinsky et al., Blood, 1997

Acute Chest Syndrome - Mortality

Overall death rate: 1.8% (32 deaths in 1741 events, 949 patients)
- In patients < 20 years, death rate = 1.1% (14 of 695 pts/1,322 events)
  - 9/14 were < 3 yrs
- In patients ≥ 20 years, death rate = 4.3% (18 of 271 pts/419 events)

Vichinsky et al., Blood, 1997

Acute Chest Syndrome - Mortality

- Patients with higher ACS rate have higher rate of mortality than those with low ACS rate
- Increased rate of mortality may contribute to decline in ACS rate with age
Etiology of Acute Chest Syndrome (NACSSG)
(Total # of episodes = 671 in 538 pts)

- Approximately half of patients were admitted with a diagnosis other than ACS – mainly pain
- Of patients not admitted with ACS, findings of ACS appeared ~ 2.5 days after admission
- Specific cause was identified in 256 (38%) episodes
- After excluding incomplete data, a specific cause was found in 70% of cases
- Pulmonary infarction presumed to be a cause in 16% of episodes with complete data but no identified etiology

### Acute Chest Syndrome – Etiology

<table>
<thead>
<tr>
<th>Causes of the Acute Chest Syndrome (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cause</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>Emphysema with or without infection</td>
</tr>
<tr>
<td>Chloroquine</td>
</tr>
<tr>
<td>Mycoplasma</td>
</tr>
<tr>
<td>Virus</td>
</tr>
<tr>
<td>Bacteria</td>
</tr>
<tr>
<td>Mixed infections</td>
</tr>
<tr>
<td>Leukocytes</td>
</tr>
<tr>
<td>Miscellaneous infections</td>
</tr>
<tr>
<td>Unknown*</td>
</tr>
</tbody>
</table>

*Synderg, et al., NEJM, 2000

### Acute Chest Syndrome – Pathogenesis

- Hypoxia enhances sickle RBC adherence to endothelial cells
- Hypoxia decreases production of NO which inhibits VCAM-1 upregulation
- ACS may be mediated by hypoxia- and cytokine-induced RBC-pulmonary microvessel adhesion
- Factors that inhibit this interaction may be potentially beneficial in treatment of ACS

Pathogenesis

Plasma levels of sVCAM-1 and NO from control and SCD patients – Stuart & Setty, Blood, 1999

- In-vitro studies show that in the presence of both hypoxia and oleic acid:
  - There is an increase in expression of VCAM-1 in pulmonary endothelial cells
  - Inhibition of adhesion of sRBC to endothelial cells after exposure to hypoxia
- Administration of NO substrates reduce adhesion of sRBC to endothelial cells after exposure to hypoxia

From Stuart & Setty, Blood, 1999
Acute Chest Syndrome
Pathogenesis

• A recent study in transgenic SCD mice suggests that acute elevation of plasma hemin causes findings consistent with ACS (Ofori-Acquah & Ghosh, ASH Abstract, 2010)

Acute Chest Syndrome
Treatment

• Early diagnosis is important, but crucial to recognize that VOC may be prodrome of ACS
• Broad spectrum antibiotics – cephalosporin + macrolide
• Bronchodilator, incentive spirometry ± chest physical therapy
• Early RBC transfusion (Simple vs Exchange)
  ➢ Phenotypically matched RBC
• Gentle hydration

Acute Chest Syndrome
Treatment

• Experimental treatments
  ➢ Steroids
  ➢ Inhaled nitric oxide
• Hydroxyurea
  ➢ Decreases the frequency of acute chest syndrome


• Patients admitted for pain crisis were followed with daily sPLA2 levels
• Patients with ↑ sPLA2 (> 100 ng/mL), fevers & -ve CXR were enrolled
• Patients randomized to transfusion to Hb of 10 g/dL or standard care
• 7 patients in Tx arm (sPLA2 = 303 ± 275 ng/ml) and 8 in non-Tx arms (sPLA2 = 434 ± 250 ng/ml, NS)


• 5/8 in non-Tx arm developed ACS in 48 Hrs
• 0/7 in Tx arm developed ACS (p =0.026, OR 23.6, CI: 1 to 557)
• Length of hospitalization was 1 day shorter in the transfused group
• This study suggests that RBC transfusion may prevent the development of ACS

Thank You!