Acute Chest Syndrome of Sickle Cell Disease

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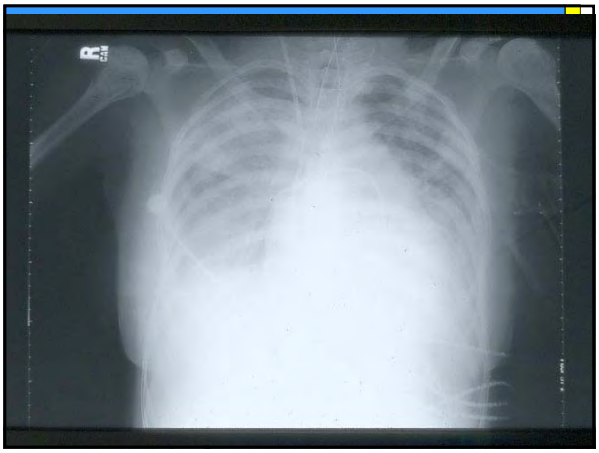
- No relevant conflicts
- Unapproved use of the following drugs will be discussed:
  - Nitric oxide
  - Dexamethasone

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 - CSSCD & NACSSG

ACS: 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 $S\beta^0$ thal patients (9.4/100 pt-yrs)
- ACS incidence in SC patients was 5.2/100 pt-yrs and in $S\beta^+$ 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)

Age Group (yrs)	Episodes of ACS (per 100 patient years)
< 2	20.8
2-5	25.3
5-10	15.6
10-20	9.3
> 20	8.8

from Castro et al., Blood, 1994

Acute Chest Syndrome - Incidence (SC)

Age Group (yrs)	Episodes of ACS (per 100 patient years)
< 2	10.3
2-5	10.1
5-10	4.3
10-20	4.0
> 20	3.3

Castro et al., Blood, 1994

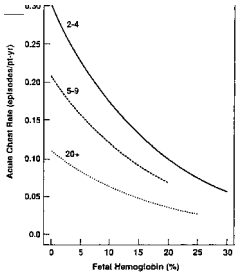
Acute Chest Syndrome - Risk factors

Significant in multivariable analysis

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

Castro et al., Blood, 1994

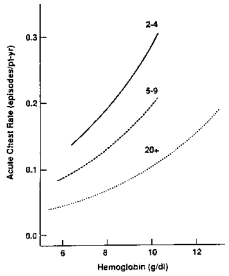
Acute Chest Syndrome - Effect of Hgb F Level on Risk



Relationship between Hb F and ACS for the age groups shown

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

Castro, et al., Blood, 1994

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

	Percent Requiring Mechanical Ventilation	Odds Ratio (95% CI)§	P Value
Respiratory failure‡			
History of cardiac disease			
No	12	1.0	
Yes	44	6.7 (2.1–22.3)	0.002
No. of lobes involved on radiographic examination			
0 to 1	3	1.0	
2 to 3	11	2.2 (1.0–4.6)	0.04
≥4	54	9.0 (2.5–32.7)	<0.001
Platelet count at diagnosis			
0 to 199,000/mm³	23	1.0	
200,000 to 399,000/mm³	11	0.9 (0.37–2.1)	0.75
≥400,000/mm³	8	0.3 (0.10–0.96)	0.04

Acute Chest Syndrome
Mortality (CSSCD)

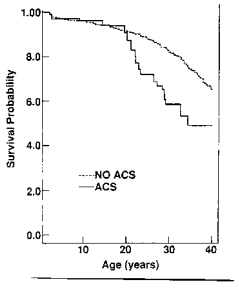
Overall death rate: 1.8% (32 deaths in 1741 events, 949 patients)

- **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**



Castro, et al., Blood, 1994

Etiology of Acute Chest Syndrome (*NACSSG*)

(Total # of episodes = 671 in 538 pts)

- ~ Half of patients were admitted with 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%)
- After excluding incomplete data, a specific cause was found in 70% of cases
- Pulmonary infarction presumed to be cause in 16% of episodes with complete data but no identified etiology

Acute Chest Syndrome – Etiology

TABLE 4. CAUSES OF THE ACUTE CHEST SYNDROME.*

CAUSE	ALL EPISODES (N=670)	AGE AT EPISODE OF ACUTE CHEST SYNDROME		
		0–9 YR (N=329)	10–19 YR (N=188)	≥20 YR (N=153)
		no. of episodes (%)		
Fat embolism, with or without infection†	59 (8.8)	24	16	19
Chlamydia‡	48 (7.2)	19	15	14
Mycoplasma§	44 (6.6)	29	7	8
Virus	43 (6.4)	36	5	2
Bacteria	30 (4.5)	13	5	12
Mixed infections	25 (3.7)	16	6	3
Legionella	4 (0.6)	3	0	1
Miscellaneous infections¶	3 (0.4)	0	3	0
Infarction‖	108 (16.1)	50	43	15
Unknown**	306 (45.7)	139	88	79

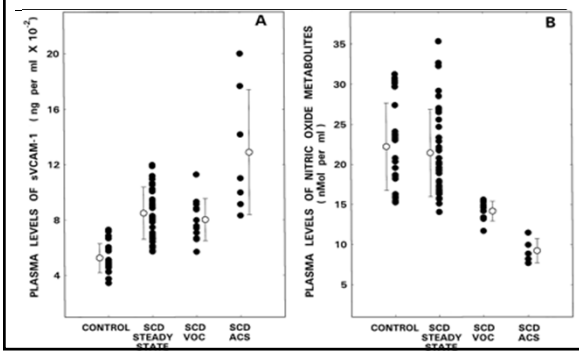
Vichinsky, et al., NEJM, 2000

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

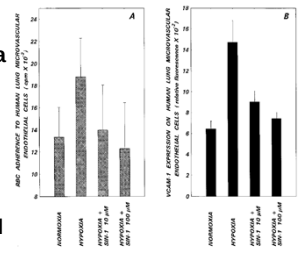
Pathogenesis

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



In-Vitro Studies in Presence of Hypoxia and Oleic Acid

- ↑ adherence of sRBC to endothelial cell monolayers with hypoxia
- NO substrates reduce adhesion of sRBC to endothelial cells after exposure to hypoxia
- ↑ expression of VCAM-1 in pulmonary endothelial cells with hypoxia



Acute Chest Syndrome
Pathogenesis

- In-vitro studies show that in the presence of both hypoxia and oleic acid:
  - There is ↑ expression of VCAM-1 in pulmonary endothelial cells
  - There is ↑ adherence of sRBC to endothelial cell monolayers
- 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

Prevention of Acute Chest Syndrome –
Styles et al, Br J Haematol, 2007

- 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)

Prevention of Acute Chest Syndrome –
Styles et al, Br J Haematol, 2007

- 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!