Pulmonary Complications of Sickle Cell Disease

Enrico M Novelli, MD, MS
April 11, 2014
Prevalence of SCD in the United States

- More than 2.5 million people are carriers of the HbS gene
- 70-100,000 have sickle cell disease
- About 1,000 newborns are born with SCD each year
Sickle Cell Syndromes: Other Mutations

- **Homozygous S (HbSS, sickle cell anemia):** 70-75%

- **Compound heterozygous (SCD):**
  - Hb SC: 10-15%
  - S/β⁺⁻ thalassemia: 10%

Rarely others
## Definition of Sickle Cell Syndromes

<table>
<thead>
<tr>
<th>Table 1: Definition of sickle cell syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one β globin gene allele carrying the β 6 V mutation (HbS)</td>
</tr>
<tr>
<td>Vaso-occlusive events leading to ischaemia can be demonstrated in the tissues at sea level oxygenation</td>
</tr>
<tr>
<td>Abnormal haemolytic rate accompanies vaso-occlusion</td>
</tr>
</tbody>
</table>

*Galactéros: Sickle Cell Disease, a Short Guide to Management*
Pathogenesis of SCD: What Causes Sickling?

The polymer-based theory

Low $O_2$ state $\rightarrow$ polymerization of HbS $\rightarrow$
RBC sickling $\rightarrow$ vaso-occlusion

Hemoglobin A  Hemoglobin S  Polymer formation

From: k12education.uams.edu/
Magnified Structure of Polymer

Homogeneous nucleation

Growth

Heterogeneous nucleation

Growth & alignment

Intermolecular contact regions of the hydrophobic pocket within the deoxy HbS fiber

Axis

63 Å
Dynamics of Sickling

- Hb S polymerization is proportional to 3 factors:
  - **Degree of Hb desaturation** (pH, temp, DPG, oxygen tension)
    - Maintain alkalosis, maintain high mixed venous oxygen saturation
  - **Time**
    - Maintain cardiac output and blood flow, reduce inflammation (infection) which increases adhesion
  - **Hb S concentration**
    - Maintain red cell hydration by using hypotonic crystalloids (D5W or D5W with 1/2 saline)
The Lifespan of Sickle RBC is Reduced

- Normal: 15-30 days
- SS: 90-120 days
Pathogenesis of SCD

- The role of sickle RBC-endothelial adhesion
- The role of WBC: leukocytosis common in SCD → WBC-endothelium interactions?
- The role of hemostatic activation: increased VWF, TSP1, D-dimer, platelet activation
- Abnormal vasoregulation – NO dysregulation
- Ischemia-reperfusion → reactive oxygen species generation
Pulmonary Complications

- Associated with high morbidity and mortality
- Acute chest syndrome and pulmonary hypertension have the highest mortality of any SCD complication
Acute Chest Syndrome

1979

“Description for the combination of chest pain, fever, increased leukocytosis, and appearance of a shadow on chest x-ray films”

“Much disease diagnosed as pneumonia in adults with sickle cell anemia is probably pulmonary infarction”

‘Acute Chest Syndrome’ in Adults With Sickle Cell Anemia

Microbiology, Treatment, and Prevention

Samuel Charache, MD; Jean C. Scott, RN;
Patricia Charache, MD

- Fifty-two episodes of fever, chest pain, increased leukocytosis, and pulmonary infiltrate (“acute chest syndrome”) were studied in 28 adults with sickle cell anemia. Possible bacterial pathogens were identified in sputum cultures from less than half of the episodes; no pneumococci were found, and Staphylococcus aureus was the only bacterium associated with a longer illness than that seen when only normal flora were recovered.

   Much disease diagnosed as “pneumonia” in adults with sickle cell anemia is probably pulmonary infarction. Many of these patients will recover with no more than modest supportive care; if antibiotics are used they should be directed against S aureus (and possibly Hemophilus species). Pneumococcal polysaccharide vaccine has great potential for preventing life-threatening infection in children with sickle cell anemia, but may not change the incidence or severity of the acute chest syndrome in adults.

(Arch Intern Med 139:67-69, 1979)
Acute Chest Syndrome

- Acute lung injury syndrome
- Often accompanies vaso-occlusive crisis, mostly in patients with Hb SS
- 29% incidence in 3,751 subjects over a 2-year = 12.8 episodes per 100 patient-years (CSSCD)
- 25% mortality in pre-hydrea, pre-aggressive transfusion era
Acute Chest Syndrome

- New pulmonary infiltrate involving at least one complete lung segment, consistent with the presence of alveolar consolidation (excluding atelectasis), plus one of the following:
  - Chest pain
  - Temperature greater than 38.5°C
  - Tachypnea
  - Wheezing
  - Cough

Tachypnea, low $O_2$ saturation

Chest pain or dyspnea

Fever

Dropping Hb and platelet count
<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>ALL PATIENTS (N=537)</th>
<th>AGE AT FIRST EPISODE OF ACUTE CHEST SYNDROME</th>
<th>P VALUE†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0–9 yr (N=264)</td>
<td>10–19 yr (N=145)</td>
<td>&gt;20 yr (N=128)</td>
</tr>
<tr>
<td>Findings on physical examination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory rate &gt;30/min (%)</td>
<td>67</td>
<td>84</td>
<td>61</td>
</tr>
<tr>
<td>Mean peak respiratory rate/min</td>
<td>38</td>
<td>44</td>
<td>36</td>
</tr>
<tr>
<td>Mean peak temperature (ºC)</td>
<td>38.9</td>
<td>39.0</td>
<td>39.0</td>
</tr>
<tr>
<td>Rales (%)</td>
<td>76</td>
<td>75</td>
<td>74</td>
</tr>
<tr>
<td>Wheezing (%)</td>
<td>26</td>
<td>33</td>
<td>23</td>
</tr>
<tr>
<td>Nasal flaring (%)</td>
<td>26</td>
<td>37</td>
<td>19</td>
</tr>
<tr>
<td>Mean no. of lobes involved at diagnosis</td>
<td>1.7</td>
<td>1.7</td>
<td>1.7</td>
</tr>
<tr>
<td>Effusion at diagnosis (%)</td>
<td>36</td>
<td>34</td>
<td>47</td>
</tr>
<tr>
<td>Base-line laboratory values</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean hemoglobin (g/dl)</td>
<td>7.7</td>
<td>7.5</td>
<td>8.1</td>
</tr>
<tr>
<td>Mean decrease in hemoglobin from steady-state value (g/dl)</td>
<td>0.78</td>
<td>0.73</td>
<td>0.68</td>
</tr>
<tr>
<td>Mean white-cell count (per mm³)</td>
<td>23,000</td>
<td>25,000</td>
<td>22,000</td>
</tr>
<tr>
<td>Mean partial pressure of arterial oxygen at diagnosis (mm Hg)‡</td>
<td>70</td>
<td>71</td>
<td>68</td>
</tr>
<tr>
<td>Mean oxygen saturation (%)§</td>
<td>92</td>
<td>92</td>
<td>92</td>
</tr>
<tr>
<td>Mean maximal no. of lobes involved during hospitalization</td>
<td>2.2</td>
<td>2.2</td>
<td>2.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper lobes (%)</td>
<td>34</td>
<td>36</td>
<td>29</td>
</tr>
<tr>
<td>Lower lobes (%)</td>
<td>92</td>
<td>89</td>
<td>93</td>
</tr>
<tr>
<td>Middle lobes (%)</td>
<td>49</td>
<td>43</td>
<td>34</td>
</tr>
<tr>
<td>Effusion during hospitalization (%)</td>
<td>55</td>
<td>52</td>
<td>71</td>
</tr>
<tr>
<td>Treatment (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythromycin</td>
<td>87</td>
<td>89</td>
<td>89</td>
</tr>
<tr>
<td>Cephalosporin</td>
<td>92</td>
<td>93</td>
<td>94</td>
</tr>
<tr>
<td>Other type of antibiotic</td>
<td>37</td>
<td>28</td>
<td>33</td>
</tr>
<tr>
<td>Oxygen</td>
<td>85</td>
<td>80</td>
<td>90</td>
</tr>
<tr>
<td>Transfusion</td>
<td>72</td>
<td>73</td>
<td>81</td>
</tr>
<tr>
<td>Bronchodilator</td>
<td>61</td>
<td>69</td>
<td>62</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>13</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Complications (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaso-occlusive event¶</td>
<td>64</td>
<td>47</td>
<td>78</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>45</td>
<td>46</td>
<td>46</td>
</tr>
<tr>
<td>Pulmonary event†</td>
<td>14</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Neurologic event</td>
<td>11</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Cardiac event**</td>
<td>5</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Gastrointestinal event††</td>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Renal event</td>
<td>2</td>
<td>&lt;1</td>
<td>1</td>
</tr>
<tr>
<td>Death</td>
<td>3</td>
<td>&lt;1</td>
<td>2</td>
</tr>
<tr>
<td>Mean duration of hospitalization (days)‡‡</td>
<td>10.5</td>
<td>9.7</td>
<td>10.0</td>
</tr>
</tbody>
</table>

*Data not available as not all lobes are involved. **Higher values seen in hospitalization. ‡‡Higher values seen in hospitalization.
## Causes of ACS

<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></td>
<td>0–9 YR (N=329)</td>
</tr>
<tr>
<td></td>
<td>no. of episodes (%)</td>
<td>(%)</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></td>
<td></td>
</tr>
<tr>
<td>Unknown**</td>
<td>306 (45.7)</td>
<td>139</td>
</tr>
</tbody>
</table>
The Vicious Cycle of ACS

Vicious cycle of vaso-occlusive crisis and acute chest syndrome

- Decreased oxygen delivery
- Desaturated haemoglobin
- Regional hypoxia
- Microvasculature occlusion and bone-marrow infarction
- Increased endothelial VCAM-1 expression and adhesion
- Erythrocyte adhesion in lung pulmonary infarction
- Hypoventilation and atelectasis secondary to rib and vertebral infarction
- Acute chest syndrome
- Pulmonary infection

- Regional hypoxia
- Increased polymerisation and erythrocyte rigidity
- VCAM-1

- 29% Chlamydia pneumonia
- 20% Mycoplasma pneumonia
- 2% Legionella pneumonia
- 10% respiratory syncytial virus
- 4% parvovirus, 3% rhinovirus, 2% parainfluenza virus, 2% influenza A virus, 2% cytomegalovirus, 1% ebstein barr virus, 1% herpes simplex virus
- Staphylococcus aureus was isolated in 5% of cases and Streptococcus pneumonia in only 4% of cases

Gladwin et al, NEJM, 2008
Typical Radiographic Pattern

- Consolidations are most frequent opacities mostly in the bases
- Patients with a new complete lung segment consolidation on CT scan had a more severe presentation and outcome
- Bedside CXR had a good sensitivity but a weak specificity

Mekontso

Example of bilateral consolidations predominating at lung bases on CXR and CT
Complications

- Prolonged hospitalization
- Systemic fat embolization syndrome
- Respiratory failure
  - 22% of adults and 10% of children require mechanical ventilation
  - Mortality 9% in adults and 1% in children
- Neurologic events
  - 11% of patients
  - Altered mental status, seizures, neuromuscular weakness
  - Stroke

Hemolysis and ACS

Acute events (e.g. VOC)

Hemolysis

Free hemin in sickle RBCs

MetHb, hemin

Acute chest syndrome

TLR4

DAMP

Sterile inflammation

Endothelium

Edema

Hypoxemia

Infiltration

Congestion

Death

Ofori-Acquah (invited review)

Acute chest syndrome
Hemin-induced ACS

Ghosh et al., J Clin Invest, 2013; 123:4809-4820

![Graph showing survival over time after i.v. hemin](image)

**A**

Survival (%)

Time after i.v. hemin (min)

- AA: 9/9
- AS: 9/9
- SS: 3/9

**i.v. hemin**

SS mice

AA control
The Role of Hemopexin

Ghosh et al., J Clin Invest, 2013;

Hemopexin (mg/ml)

Humans

AA  SS

0.7 ± 0.1

0.17 ± 0.06

0.152 ± 0.018

0.149 ± 0.016

Time after heme injection (min)

Survival rate (%)
ACS Model Conclusions

- Acute hemolysis: established prodrome of ACS
- Hemoglobin S oxidation and *de novo* generation of hemin in SCD mice: extracellular hemin crisis
- Low baseline plasma hemopexin level is a risk factor for hemin induced ACS in sickle mice
- Impaired capacity to scavenge hemin in SCD patients and mice
- Infusion of hemopexin prevents hemin-induced ACS and sudden death in SCD mice
Pulmonary Thrombosis and ACS
Pulmonary Thrombosis and ACS

- PT identified in up to 50% of autopsy cases
- High incidence (50-100X non SCD)
- Usually *in situ*
- Complicates 17% of ACS cases
- D-dimer and LE Doppler unhelpful
- Cause or consequence of ACS?
- We should have high level of suspicion in ACS

Novelli, JTH 2012. Mekontso, AJRCCM 2011
INCENTIVE SPIROMETRY TO PREVENT ACUTE PULMONARY COMPLICATIONS IN SICKLE CELL DISEASES

Paul S. Bellet, M.D., Karen A. Kalinyak, M.D., Rakesh Shukla, Ph.D., Michael J. Gelfand, M.D., and Donald L. Rucknagel, M.D., Ph.D.

NEJM 1995
Rib Infarcts

BAL: There are scattered macrophages identified in a background of obscuring inflammation, including neutrophils and eosinophils suggestive of pneumonia or an acute inflammatory process. The macrophages have foamy cytoplasm, and an oil red O (ORO) stain performed on a cytospin slide shows moderate positivity within the cytoplasm of the scattered histiocytes present.
Lipid-Laden Macrophages

Oil Red O Stain
Consequences of Fat Embolism

Hagar, BJH 2008
Phospholypase in ACS

- ACS may be predicted by an increase in the plasma secretory phospholipase A2 type IIA (sPLA2-IIA) level 24 hours prior to its onset

Styles, Blood 1996
Model of PLA2-mediated ALI
Transfusion prevents acute chest syndrome predicted by elevated secretory phospholipase A2

Lori A Styles,1 Miguel Abboud,2 Sandra Larkin,1 Margaret Lo1 and Frans A. Kuypers1
1Department of Hematology/Oncology, Children’s Hospital and Research Center at Oakland, Oakland, CA, USA, and 2Department of Pediatrics, American University of Beirut, Beirut, Lebanon

Received 26 July 2006; accepted for publication 25 September 2006; first published online 30 November 2006

Summary

Acute pulmonary injury is known as acute chest syndrome (ACS) in patients with sickle cell disease (SCD). Secretory phospholipase A2 (sPLA2) was found to predict those at risk for ACS and a trial was designed to determine if red blood cell transfusion can be used to prevent ACS. Patients with an elevated sPLA2 were randomised to either receive a single transfusion or standard care. Five of the eight patients (63%) randomised to standard care developed ACS versus none of the seven patients randomised to the transfusion arm (P = 0.026, Odds ratio = 23.6, 95% confidence interval 1, 557). This study suggests that transfusion may prevent ACS.

Keywords: sickle cell disease, acute chest syndrome, secretory phospholipase A2, transfusion.
Effect of Early Transfusion for ACS

- VOC patients with high sPLA$_2$
- 22 episodes in 20 patients
- Standard care: 5/8 developed ACS
- Transfusion: 0/7 developed ACS
- OR 23.6, p = 0.026
- Refused enrollment: 4/5 developed ACS
Restrictive Lung Disease

- Usually presents with limited lung scarring

In CSSCD, 90% had abnormal PFTs

- mild restrictive defect (TLC of 70 +/- 15% predicted) and isolated reduction in the DLCO (57 +/- 20% predicted).

Klings et al. AJRCCM, 2006

<table>
<thead>
<tr>
<th>TABLE 4. Sickle chronic lung disease: Logistic regression analysis of clinical risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk Factor</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Recurrent Events</strong></td>
</tr>
<tr>
<td>Acute chest syndrome‡</td>
</tr>
<tr>
<td>Hospitalizations</td>
</tr>
<tr>
<td>All sickle crises</td>
</tr>
<tr>
<td>Sickle crisis with chest pain</td>
</tr>
<tr>
<td>Precipitated sickle crisis§</td>
</tr>
<tr>
<td>Cryptogenic sickle crisis‖</td>
</tr>
<tr>
<td><strong>Termination Events</strong></td>
</tr>
<tr>
<td>Aseptic necrosis (&gt;20 yrs old)</td>
</tr>
<tr>
<td>Aseptic necrosis (&lt;20 yrs old)</td>
</tr>
</tbody>
</table>
Asthma/Reactive Airway Disease

- Similar prevalence of AA children
- Association with increased mortality

Boyd, Haematologica, 2007

- Poor correlation with AHR
  Field, Chest 2011

- Steroids and asthma
Obstructive Sleep Apnea

- Increased prevalence in SCD children
  - Adenotonsillar hypertrophy post splenectomy
  - Skeletal changes from extramedullary erythropoiesis/marrow hyperplasia
- Nocturnal hypoxemia is associated with increased stroke risk in children
- Sleep disordered breathing is common in children with SCD
- 44% of adults had OSA

Kaleiya, J Ped Heme/Onc, 2008; Kadali, Chest (abstract), 2011
First Sickle Cell PH Autopsy Series

Figure 1. Autopsy specimen from the lung of Patient 2 showing a small, recanalized pulmonary artery with a triple lumen (L) (hematoxylin and eosin stain; original magnification × 400, reduced by 40 percent).

“Finally, although pulmonary hypertension was clinically diagnosed as the cause of death in only a few cases, the frequent finding of evidence of cor pulmonale and thrombi/emboli as underlying chronic organ injury suggests that pulmonary hypertension plays an important role in pulmonary failure in sickle cell disease.”

Manci et al., Br J Haem, 2003
Autopsy Data in SCD

Pulmonary hypertension findings in 33% of cases of sudden death in SCD

Graham et al., Am J Forensic Med & Path, 2007
Autopsy Data in SCD

Pulmonary Hypertension in Sickle Cell Hemoglobinopathy: A Clinicopathologic Study of 20 Cases

ABIDA K. HAQUE, MD, SUMITA GOKHALE, MD, BILL A. RAMPY, DO, PhD, PATRICK ADEGBOYEGA, MD, ALEX DUARTE, MD, AND MARIO J. SALDANA, MD

All 20 cases showed pulmonary hypertension histologic findings

Haque et al., Human Path, 2002
Pulmonary Hypertension as a Risk Factor for Death in Patients with Sickle Cell Disease

Mark T. Gladwin, M.D., Vandana Sachdev, M.D., Maria L. Jison, M.D.,

Survival by TRV Group

243 Adults with SCD

Fraction Surviving

p < 0.001

TRV < 2.5 m/s

TRV 2.5 - 2.9 m/s

TRV ≥ 3 m/s

0 10 20 30 40 50 60

Months

Machado et al., Advances in Pulmonary Hypertension 2007
Survival by NT-pro BNP

Machado et al. JAMA 2006
## PH by RHC

### Table

<table>
<thead>
<tr>
<th>Criteria for RHC</th>
<th>Castro et al., 2003 (71)</th>
<th>Anthi et al., 2007 (57)</th>
<th>Parent et al., 2011 (77)</th>
<th>Fonseca et al., 2012 (81)</th>
<th>Mehari et al., 2012 (80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. subjects screened</td>
<td>34</td>
<td>43</td>
<td>445</td>
<td>80</td>
<td>531</td>
</tr>
<tr>
<td>Exclusion criteria</td>
<td>None</td>
<td>None</td>
<td>Renal insufficiency</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Restrictive lung disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Liver disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Criteria for RHC</td>
<td>Clinical suspicion*</td>
<td>TRV ≥ 2.5 m/s</td>
<td>TRV ≥ 2.5 m/s</td>
<td>TRV ≥ 2.5 m/s</td>
<td>TRV ≥ 2.5 m/s and/or</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>clinical suspicion</td>
</tr>
<tr>
<td>Number RHCs</td>
<td>39†</td>
<td>35</td>
<td>96</td>
<td>26</td>
<td>84</td>
</tr>
<tr>
<td>Number of subjects with PH</td>
<td>20</td>
<td>26</td>
<td>24</td>
<td>8</td>
<td>55</td>
</tr>
<tr>
<td>% RHC with PH</td>
<td>Not reported</td>
<td>74</td>
<td>25</td>
<td>31</td>
<td>65.5</td>
</tr>
<tr>
<td>% of population screened</td>
<td>Not reported</td>
<td>Not reported</td>
<td>6</td>
<td>10</td>
<td>10.5</td>
</tr>
<tr>
<td>Mean age of subjects with PH</td>
<td>37</td>
<td>43</td>
<td>45</td>
<td>46</td>
<td>41</td>
</tr>
<tr>
<td>mPAP, mm Hg</td>
<td>36 ± 8</td>
<td>37 ± 1.5</td>
<td>30 ± 6</td>
<td>33 ± 9</td>
<td>Not reported</td>
</tr>
<tr>
<td>PVR, dyn·s/cm²</td>
<td>271 ± 90</td>
<td>206 ± 23</td>
<td>138 ± 58</td>
<td>179 ± 120</td>
<td>Not reported</td>
</tr>
<tr>
<td>CO, L/min</td>
<td>7 ± 2§</td>
<td>9 ± 0.5</td>
<td>9 ± 2</td>
<td>5 ± 2§</td>
<td>Not reported</td>
</tr>
<tr>
<td>6MWD, m</td>
<td>Not reported</td>
<td>320 ± 20</td>
<td>404 ± 94</td>
<td>460 ± 152</td>
<td>358 ± 113</td>
</tr>
<tr>
<td>Duration of follow-up, yr</td>
<td>1.9**</td>
<td>Not reported</td>
<td>2.2</td>
<td>2.8††</td>
<td>4.4**</td>
</tr>
<tr>
<td>Mortality in PH group</td>
<td>55%</td>
<td>Not reported</td>
<td>23%</td>
<td>38%</td>
<td>37%</td>
</tr>
</tbody>
</table>

*Miller et al. AJCCCM 2012*
PAH by RHC and Mortality

Mehari et al. JAMA 2012
Possible Causes of Pulmonary Hypertension

- Hemolysis
  - NO scavenging by free hemoglobin
  - Increased platelet activation
  - Endothelial dysfunction

- Hypoxia-inducible factors

- Portopulmonary hypertension from liver dysfunction

- Pulmonary embolism (CTEPH)
Hemolysis and PH

Table 3. Independent Predictors of Increased Tricuspid Regurgitation Velocity by Multiple Linear Regression Analysis (n=320)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>β, Estimated Increase in TRV (95% CI), m/s</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemolytic component (1-SD increase)</td>
<td>0.09 (0.06–0.12)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV lateral E/e’ ratio (natural log increase)</td>
<td>0.19 (0.09–0.29)</td>
<td>0.0001</td>
</tr>
<tr>
<td>BUN (natural log increase)</td>
<td>0.10 (0.05–0.16)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Serum erythropoietin (natural log increase)</td>
<td>0.07 (0.03–0.11)</td>
<td>0.002</td>
</tr>
</tbody>
</table>
Changes in PASP before and after Arg

Results: ↓15.4 % in PASP

Morris et al. AJRCCM 2003
Effects of Sildenafil on Pulmonary Pressure and Functional Capacity

Pulmonary Artery Systolic Pressure (mm Hg)

- Pre-Sildenafil
- Sildenafil

- 25
- 30
- 35
- 40
- 45
- 50
- 55
- 60
- 65
- 70
- 75

P = 0.043

6-minute walk (meters)

- Pre-Sildenafil
- Sildenafil

- 200
- 250
- 300
- 350
- 400
- 450
- 500
- 550
- 600
- 650

P = 0.0012

BNP (pg/ml)

- Pre-Sildenafil
- Sildenafil

- 0
- 100
- 200
- 300
- 400
- 500
- 600
- 700
- 800
- 900

P = 0.002

Machado et al. British Journal of Hematology 2005
Animal Models of SCD and PH

- Confirm role of hemolysis
- NO depletion
- Age-dependent decrease in CO
- No vascular remodeling

Hsu et al. Blood 2007
Novelli et al. Blood 2012 (abstract)
Standard Therapies

- Oxygen
- Anticoagulation
- Hydroxyurea (15 mg/kg/d)
- Exchange and simple transfusion
Embryonic
Hemoglobin Timeline

% of total globin synthesis

Post-conceptual age (weeks)

Postnatal age (weeks)
Hydroxyurea Therapy

No Therapy

100% Hb S

Flow

No Flow

SS Cells

Hydroxyurea

75% Hb S and 25% Hb F

Hb S to Hb F hybrid Polymer in cells

Hybrid Formation

+O₂ ↔ -O₂

Hb S Polymerization

Flow

SS Cells
Treatment

- Intensify SCD therapy – reduce hemolysis
  - Hydroxyurea
  - Transfusions
- PH-specific therapy
  - Sildenafil increased pain in SCD
- Anticoagulation
  - Particularly for CTEPH
- Arginine?
First successful lung transplantation for sickle-cell disease with severe pulmonary arterial hypertension and pulmonary veno-occlusive disease

M. Patricia George, Enrico M. Novelli, Norihisa Shigemura, Marc A. Simon, Brian Feingold, Lakshmanan Krishnamurthi, Matthew R. Morrell, Cynthia G. Gries, Syed Haider, Bruce A. Johnson, Maria M. Crespo, Jay K. Bhama, Christian Bermudez, Samuel A. Yousem, Yoshiya Toyoda, Hunter C. Champion, Joseph M. Pilewski, Mark T. Gladwin

PVOD
Questions?