Sickle Cell Disease and the Lungs
Acute Pulmonary Complications of Sickle Cell Disease in Children

Bankole Peter Kuti
Pulmonology unit
Obafemi Awolowo University
Ile-Ife, Nigeria

Presentation outline

• Introduction
• Burden of Sickle Cell Disease (SCD)
• Upper airway pathologies
  • Adenotonsillar inflammation/hypertrophy and sleep breathing disorders
• Lower airway pathologies
  • Acute chest syndrome/LRTI
  • Asthma
• Conclusion
Introduction

- Sickle Cell Diseases (SCD) Inheritance (AR) of two abnormal haemoglobin, at least one of which is HBS

- The most common and severe form is Sickle Cell Anaemia (SCA) homozygous HB SS

- First described by Herrick, 1910

- Others forms include HBSC, SCD-β+ thalassaemia and SCD-β-thal etc

- Occurs as a result of single point (Missense) mutation in the β-globin chain of HB

Point (Missense) mutation at position 6 of the B-globin chain

Ramadas N and Sparkenbaugh EM (2023) The APC-EPCR-PAR1 axis in SCD. Front. Med
Epidemiology of SCD

- Most common inherited haemoglobinopathy with worldwide distribution
- 25 million individuals live with SCD
- Approximately 300,000 infants are born annually with SCD, most in SSA
- 1 in 2,500 live births in the US where an estimated 100,000 individuals with SCD live, majority of whom are African Americans (1 in 350)
- In the UK, 12 500 people live with SCD (NHS data, 2009)
- High-income countries (HICs) account for only 10% of the world’s SCD population

https://www.afro.who.int/health-topics/sickle-cell-disease

SCD in Africa

- >50% (12-15 million) individuals with SCD live in Africa, where 75% of all babies born with SCD are born
- Childhood mortality among SCD patients is highest between 6 months and 3 years of age
- Sub-Saharan Africa bears the largest burden of childhood mortality due to SCD; 500 children die daily of SCD in Africa (Shmona S www.thelancet.com/haematology, 2019)
- May exceed >50% mortality due to SCD in some parts of SSA. Highest burden in Nigeria and DR Congo
- 0.7% reported from Uganda (Ndeez et al, Lancet Glob Health 2016)

Global prevalence of SCD


Data availability Global map

Upper airway pathologies and SCD

Adenotonsillar hypertrophy (ATH) and inflammation in children with SCD

- abnormal enlargement of the pharyngeal tonsils (adenoid vegetations) and palatine tonsils.

- Reported higher prevalence in SCD children vs. HBAA children.

- Palatine tonsils – 31.3% vs. 2.6% (p < 0.001); Hypertrophied Adenoids 54.2% vs. 15.8% (p < 0.001) covering 50% of choanae [Gois et al. Pediatr Pol 2019] 93.1% from a single centre study in Ghana [Opoku-Buabeng & Akoto, 2012]

Pathogenesis

- the compensatory adenotonsillar hypertrophy from autosplenectomy
- recurrent URTI due to decrease opsonization of pathogenic bacteria
- Site of extramedullary haematopoiesis due to haemolytic anaemia
Upper airway pathologies

Upper Airway Lymphoid Tissue Size in Children With Sickle Cell Disease

Terminia Strauss, BA; Sanghut Su, MS; Corale J. Marcus, MBBCh, FCCP; Thornton B. A. Mason, MD, PhD; Joseph M. McDonough, MS; Julian L. Allen, MD; Jason B. Coblett, MD; Cheryl Y. Boudre, PhD; Abbas F. Jezard, PhD; Kim Smith-Whitley, MD; Kwabia Okene-Frempong, MD, Allan L. Park, MD, PhD; and Raanan Arens, MD

Table 1—Demographics and Anthropometric Measures

<table>
<thead>
<tr>
<th>Measure</th>
<th>SCD (n = 36)</th>
<th>Control Subjects (n = 36)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>6.9 ± 4.3</td>
<td>6.6 ± 3.4</td>
<td>NS</td>
</tr>
<tr>
<td>Range, y</td>
<td>2.0-16.8</td>
<td>2.2-15.8</td>
<td></td>
</tr>
<tr>
<td>Ethnicity: black, No.</td>
<td>36</td>
<td>36</td>
<td>NS</td>
</tr>
<tr>
<td>Sex, male, %</td>
<td>55.6</td>
<td>55.6</td>
<td>NS</td>
</tr>
<tr>
<td>Height, cm</td>
<td>117.6 ± 24.8</td>
<td>117.4 ± 21.8</td>
<td>NS</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>23.5 ± 13.3</td>
<td>25.2 ± 11.7</td>
<td>NS</td>
</tr>
<tr>
<td>BMI z score</td>
<td>-0.4 ± 1.2</td>
<td>0.6 ± 1.0</td>
<td>&lt;.05</td>
</tr>
</tbody>
</table>

Data are displayed as mean ± SD unless otherwise noted. NS = not significant; SCD = sickle cell disease.
Upper airway lymphoid tissue size in Children with SCD - Strauss et al, Chest, 2012

Table 2 — Airway and Lymphoid Tissues Volumes

<table>
<thead>
<tr>
<th>Area Measured</th>
<th>SCD (n = 30)</th>
<th>Control Subjects (n = 30)</th>
<th>Difference</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Airway</td>
<td>2.8 ± 1.2</td>
<td>3.7 ± 1.6</td>
<td>-24.3</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>Lymphoid tissues</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenoid</td>
<td>6.4 ± 4.1</td>
<td>6.0 ± 2.2</td>
<td>40.0</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>Tonsils</td>
<td>7.0 ± 4.3</td>
<td>5.1 ± 1.9</td>
<td>37.3</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>Retropharyngeal</td>
<td>5.0 ± 9.1</td>
<td>2.2 ± 0.9</td>
<td>36.4</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>nodes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deep cervical</td>
<td>15.7 ± 5.7</td>
<td>12.7 ± 4.0</td>
<td>23.6</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>nodes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are displayed as mean ± SD. Units are cm³. % Difference = percent mean volume difference. See Table 1 legend for expansion of abbreviation.

Sleep study in SCD vs. controls - Strauss et al, Chest, 2012

Table 3 — Polysomnography

<table>
<thead>
<tr>
<th>Measure</th>
<th>SCD (n = 30)</th>
<th>Control Subjects (n = 30)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total sleep time, h</td>
<td>7.3 ± 1.2</td>
<td>7.7 ± 0.8</td>
<td>NS</td>
</tr>
<tr>
<td>Sleep efficiency, %</td>
<td>86.7 ± 1.4</td>
<td>90.4 ± 3.3</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>Arousal index, event/h</td>
<td>3.3 ± 1.7</td>
<td>10.8 ± 3.8</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>Baseline Spo₂, %</td>
<td>90.3 ± 2.9</td>
<td>97.1 ± 0.9</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>Spo₂, min %</td>
<td>54.3 ± 12.3</td>
<td>93.1 ± 4.2</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>Baseline PETCO₂, mm Hg</td>
<td>41.0 ± 3.1</td>
<td>37.5 ± 4.6</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Peak PETCO₂, mm Hg</td>
<td>53.4 ± 9.5</td>
<td>42.3 ± 5.3</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Obstructive apnea index, event/h</td>
<td>3.7 ± 2.0</td>
<td>0.2 ± 0.3</td>
<td>NS</td>
</tr>
<tr>
<td>AH1</td>
<td>1.9 ± 1.7</td>
<td>0.4 ± 0.3</td>
<td>NS</td>
</tr>
<tr>
<td>OSAS (AH1 &gt; 1.5)</td>
<td>7 of 30</td>
<td>0 of 20</td>
<td>&lt; .05</td>
</tr>
</tbody>
</table>

Data are displayed as mean ± SD. AH1 = apnea-hypopnea index; PETCO₂ = end-tidal CO₂; OSAS = obstructive sleep apnea syndrome; Spo₂ = arterial oxygen saturation. See Table 1 legend for expansion of other abbreviations.
AHI and lymphoid tissue volume in SCD
Strauss et al, Chest, 2012

Sleep breathing Disorders in SCD

Often underdiagnosed and poorly recognized, (Kuti and Kuti AJRM, 2017) but has been linked with:

- Increased frequency of VOC (Hargrave et al, 2003)

- Pulmonary hypertension (Tantawy et al, Annals of Hematology, 2023)


- Neurologic outcomes (CVD, TIA and seizures) 50% increase (Tsou PY et al. Kids' inpatient database study. Sleep. 2021; Hollocks et al, 2012)

- Increased severity of anaemia (Halpen et al, Plos one, 2014)
Nocturnal and nadir Oxygen saturation following interventions for SBD in children with SCD

Liguoro et al, Pediatric Pulmonology, 2021

Mean AHI and annual rate of VOC pain crises following interventions for SBD in children with SCD

Liguoro et al, Pediatric Pulmonology, 2021
Admission length and post surgery complications

Farrel et al, Int J Pediatr Otorh, 2018

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N (%)</th>
<th>Mean ± SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total admission length (days)</td>
<td>132 (100%)</td>
<td>3.5 ± 1.2</td>
<td>1–12</td>
</tr>
<tr>
<td>Other surgical procedure performed with T&amp;A (yes)</td>
<td>20 (15.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-operative complications</td>
<td>10 (11.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number of complications</td>
<td>10 (11.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-operative acute chest episode</td>
<td>3 (60%) of cases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper airway bleed</td>
<td>2 (1.5%) of cases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-operative pain crisis</td>
<td>1 (0.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoxemia without pressure requirement</td>
<td>1 (0.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension with pressure requirement</td>
<td>3 (1.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-operative stroke</td>
<td>0 (0%) of cases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number of complication among patients with elevated BMI percentile</td>
<td>4 (3%) of cases</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* A BMI percentile > 80%.

ATH, SBD in SCD- main facts

• SBD and OSA are highly prevalence in Children with SCD

• They are associated with increased morbidity and crises in SCD children

• Early detection and management of SBD and OSA in children is therefore of utmost importance

• T&A and other interventions can be a safe and effective option to treat OSA in pediatric patients with SCD

• T&A associated with improvement in SPO2, AHI events and fewer ER visits post-interventions; however more studies needed on effects on painful and other crises
Acute chest syndrome

First described in 1979 by Charache et al

Defined as:

• The presence of a new pulmonary infiltrate on chest X-ray

• Fever and/or new respiratory symptoms with hypoxaemia ± Leucocytosis

• ACS may manifest as mild pneumonic illness to acute respiratory distress syndrome and multi-organ failure. (Howard et al, 2021)

• ACS has a multifactorial aetiologies and infective cause is common

• A high index of suspicion of ACS is therefore required for early diagnosis

Pathogenesis of acute chest syndrome

Mak and Davies, Thorax, 2003

[Diagram showing the pathogenesis of acute chest syndrome with different causes and effects]
Acute chest syndrome

Causes and incidence of ACS

The Acute Chest Syndrome in Sickle Cell Disease: Incidence and Risk Factors

By Oswaldo Castro, Donald J. Brambilla, Bruce Thornton, Carl A. Reinof, Roland B. Scott, Peter Gillette, Juan C. Vera, Paul S. Levy, and The Cooperative Study of Sickle Cell Disease

The acute chest syndrome (ACS), a pneumonia-like illness in sickle cell patients, is one of the most frequent causes of their mortality and hospitalizations. Repeated ACS events may predict the development of chronic lung disease. ACS is reported as a frequent cause of death in these patients. We examine here the incidence and risk factors of ACS in 3,763 patients with sickle cell disease who were observed prospectively for at least 2 years (19,867 patient-years [pyrs]) as part of a multicenter national study group. The ACS, defined by a new pulmonary infiltrate on x-ray, occurred at least once in 1,085 patients (2,106 events). ACS incidence was higher in patients with homozygous sickle cell disease (SS; 12.8/100 pyrs) and in patients with sickle cell–δ-thalassemia (Hb SC; 1.9/100 pyrs). In patients with Hb SC disease and lower in patients with homozygous sickle cell disease (SS; 0.9/100 pyrs) and in patients with sickle cell–δ-thalassemia (Hb SC; 0.5/100 pyrs). β-Thalassemia did not affect the rate of ACS incidence in SS patients. Within each Hb type, the incidence was strongly but inversely related to age, being highest in children 2 to 4 years of age (28.7/100 pyrs in SS) and decreasing gradually to its lowest value in adults (2.8/100 pyrs in SS). In SS children (<10 years of age), we documented an age-related within-patient reduction in ACS attack rate. Adults with a higher ACS rate had a higher rate of mortality from all causes than those with low ACS rates. This increased rate of mortality might also have contributed to the decline in ACS rate with age. In multivariate analysis, other factors affecting incidence in SS patients were degree of anemia (lower ACS rates in patients with lower steady-state Hb levels) and fatal Hb (lower rates in patients with high fatal Hb). There was also a positive association between ACS rate and steady-state leukocyte count. The relationship of ACS rate to higher steady-state Hb levels in SS patients is unexplained but might be caused by increased blood viscosity.

© 1994 by The American Society of Hematology.
Cooperative Study of Sickle Cell disease (CSSCD)

- CSSCD- a national collaborative program started in 1979
- >3,000 American patients with SCD
- Objective: to understand the risk factors and natural course of ACS
- ACS incidence was higher in patients with:
  - HB SS (SS;12.8/100pt-yn) vs. HBS β<sup>0</sup>thalassemia (9.4/100pt-yrs) vs. HBSC (5.2/100pt-yrs) and HBα+thalassemia (3.9/100pt-yrs).
  - HBα-Thalassemia did not affect the rate of ACS incidence in SCD patients.

Causes and incidence of ACS

- Incidence of ACS is inversely proportional to age
- Highest at age 2-4 years (25.3/100pt-yrs in SS) and decreasing gradually to its lowest value in adults (8.8/100pt-yrs in SS)
- Lower incidence of ACS in those with lower steady state Hb level
- Lower incidence of ACS in those with higher Foetal HB
- Higher ACS incidence with higher steady-state Leucocyte count (blood viscosity)
Management and outcome of ACS
The Multicenter National Acute Chest Syndrome Study (NACSS)

- Evaluated 671 ACS episodes in 538 patients from 30 centres over a five year period
- and nearly half of the patients were children and adolescents (mean age 13.6 years)

Diagnostic criteria of ACS in NACSS:
- new pulmonary infiltrate involving at least one complete lung segment
- Chest pain,
- a temperature of more than 38.5°C,
- Respiratory symptoms - tachypnea, wheezing, or cough.


- The mean length of hospitalization was 10.5 days
- 13% required mechanical ventilation, and 3% (18 participants) mortality
- Neurologic events in 11% of study participants
- A specific cause of the acute chest syndrome was identified in 38% of all episodes
- the most common causes of death were pulmonary emboli and infectious bronchopneumonia
- Infection was a contributing factor in 56% of the deaths.
Causes of ACS


TABLE 4. CAUSES OF THE ACUTE CHEST SYNDROME.

<table>
<thead>
<tr>
<th>Cause</th>
<th>All Episodes (N=676)</th>
<th>Age at Episode of Acute Chest Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N=676)</td>
<td>0-9 yr (N=120)</td>
</tr>
<tr>
<td></td>
<td>no. of episodes (%)</td>
<td>24</td>
</tr>
<tr>
<td>Fat embolism, with or without infection†</td>
<td>59 (8.8)</td>
<td>19</td>
</tr>
<tr>
<td>Chlamydia</td>
<td>48 (7.2)</td>
<td>29</td>
</tr>
<tr>
<td>Mycoplasma$</td>
<td>44 (6.6)</td>
<td>56</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>0</td>
</tr>
<tr>
<td>Miscellaneous infection‡</td>
<td>2 (0.4)</td>
<td>0</td>
</tr>
<tr>
<td>Infection§</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>

Infectious causes of ACS


TABLE 5. INFECTIOUS PATHOGENS ISOLATED IN 676 EPISODES OF THE ACUTE CHEST SYNDROME.

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>No. of Episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlamydia pneumonia</td>
<td>12</td>
</tr>
<tr>
<td>Mycoplasma pneumonia</td>
<td>12</td>
</tr>
<tr>
<td>Respiratory syncytial virus</td>
<td>8</td>
</tr>
<tr>
<td>Conjugate pneumococcal vaccine</td>
<td>12</td>
</tr>
<tr>
<td>Hemophilus influenzae</td>
<td>11</td>
</tr>
<tr>
<td>Parainfluenza</td>
<td>11</td>
</tr>
<tr>
<td>Mycoplasma</td>
<td>6</td>
</tr>
<tr>
<td>Peripherotrichia</td>
<td>4</td>
</tr>
<tr>
<td>Pneumococcal influenza</td>
<td>4</td>
</tr>
<tr>
<td>Influenza A virus</td>
<td>1</td>
</tr>
<tr>
<td>C. pneumonia</td>
<td>1</td>
</tr>
<tr>
<td>Neisseria meningitides</td>
<td>1</td>
</tr>
<tr>
<td>Haemophilus</td>
<td>1</td>
</tr>
<tr>
<td>S. pneumonia</td>
<td>1</td>
</tr>
<tr>
<td>Parainfluenza</td>
<td>1</td>
</tr>
<tr>
<td>Others</td>
<td>1</td>
</tr>
</tbody>
</table>

*All infectious agents isolated during episodes of the acute chest syndrome are included.
Treatment plan

- **Multidisciplinary and multimodal management is recommended** – Critical care, pulmonologist, haematologists etc. (Reagan et al, Pediatr Blood Cancer, 2011)

- **Pain relief**: prompt and adequate pain relief according to National guidelines

- **Incentive spirometry** has proven benefit in preventing ACS in patients with chest or rib pain. 87% relative risk reduction in incidence (Bellet et al, N Engl J Med 1995)

- **Antibiotics**, with cover for atypical organisms, should be used even if blood cultures and sputum cultures are negative

- **Blood transfusion**: Early simple (‘top-up’) and exchange transfusion is necessary if severe or evidence of progression (aim: Hb conc. >10g/dl and HBs <30%)

---

Treatment of ACS

- **Bronchodilators** - clinical features suggestive of asthma or evidence of acute bronchospasm

- Hydroxycarbamide (hydroxyurea) should be recommended for prevention of recurrent ACS. (The Multicenter Study of Hydroxyurea (MSH) trial, 1990 HU vs. placebo (16.4% vs 34.7%, <.001). The Pediatric Hydroxyurea in Sickle Cell Anemia (BABY HUG) study

- Consider **chronic transfusion programme** for the prevention of recurrent ACS if hydroxycarbamide therapy is not effective.

- In children, consider **stem cell transplantation** for prevention of recurrent ACS if hydroxycarbamide therapy is not effective (Howard et al, 2015)
Predictors of severity of ACS

- Worsening hypoxia,
- increasing respiratory rate and WOB
- decreasing platelet count,
- decreasing haemoglobin concentration,
- multilobar involvement on chest X-ray and
- neurological complications

Howard et al, Br J Haematol 2020

SCD and acute asthma

- increased prevalence of asthma in patients with SCD has been documented
- increased morbidity and mortality amongst patients with SCD and asthma co-morbidities
- Childhood asthma exacerbation can mimic ACS and can precipitate ACS
- Elevated serum IgE has been reported in children with SCD which may drive asthma pathogenesis
- Asthma is reported in 15-28% of children with SCD in large multi-centre cohort studies
  (Strunk et al, J Pediatr 2014; Boyd et al, Blood 2006)

Boyd JH et al. Haematologica. 2007
Knight-Madden et al, Thorax, 2005
SCD and asthma in children

• Both conditions result in inflammation
• Both conditions increase susceptibility to respiratory infections,
• Both require specific interventions to mitigate complications
• Prevalence of childhood asthma and SCD are both increasing esp in SSA
• Asthma defined using questionnaire [An F et al,2012] or pulmonary function test [Boyd et al, 2009] significantly increased morbidities and mortality in children with SCD
• Asthmatic vs. non-asthmatic SCD children (2.5 vs 1.2 hospitalizations for pain or ACS per patient-year; p = 0.003; risk ratio: 2.6; 95% CI: 1.3–3.3) [Boyd et al, Paed pulm, 2009]

Asthma and ACS in children with SCD

• Early onset ACS may be a phenotype associated with an increased risk for future lung disease including asthma

• 80% of the children with SCD with a diagnosis of asthma after 5 years had at least one episode of ACS when younger than 4 years

• Children with SCD diagnosed with asthma at <4 years had a higher rate of severe VOC requiring hospitalisation (pain or ACS) 1 year after the event than did children older than 4 years at their first episode (62% vs. 39%; p=0.009).

Possible link between SCD and asthma

- Increased serum IgE is observed in both SCD and allergic asthma
- Increased levels of proinflammatory cytokines such as IL-3, GM-CSF, (Canalli et al, 2005)
- Dysregulated arginine metabolism and excess arginase activity (Morris et al, 2000; Meurs et al, 2003)
- Leukotriene pathway (secretory phospholipase A2 (sPLA2)) (Holgate et al, J Allergy Clin Immunol. 2003)
- Hypovitaminosis D and early use of acetaminophen (Freishtat et al, Journal of Pediatrics, 2010; Beasley et al, AJRCCM)
- Early antibiotic exposure in SCD and predisposition to asthma and allergies (Zeissig et al, 2014)

Inflammatory pathways in allergic asthma and SCD

Management of asthma in children with SCD

- Treat asthma based on **standard asthma guidelines** (NIH, GINA or local)
- inhaled bronchodilators as rescue medication and corticosteroids for moderate/severe exacerbations.
- Oral prednisone with slower taper at 1-2 mg/kg/day. A 5-day burst may be insufficient and a slower taper over 2 weeks may be indicated.
- Acute chest syndrome have been reported after corticosteroids are withdrawn; (Strouse et al, Pediatric Blood and Cancer, 2008)
- Use of controller medications (Inhaled corticosteroids) should be the **bedrock** for persistent asthma symptoms.
- Leukotriene inhibitors (Montelukast) often very useful

Gomez and Morris, BioMed Research Int, 2013

Management

- Multidisciplinary management is recommended -Consult pulmonary or hematology specialist when placing SCD patient on corticosteroids.
- Hospital admission for all asthma exacerbations requiring corticosteroids
- Low threshold to admit mild asthma exacerbations given associated complications.
- Close monitoring and follow up are essential.
- Pulmonary function testing as an outpatient should be followed annually.
- Screen SCD patients with asthma symptoms for pulmonary hypertension by Doppler echocardiography annually

Worthy of note

- Judicious use of oxygen therapy- possibility of compensatory increase in the production of sickled cells (Darbari et al, 2008)

- Prolonged QTc interval with SABA use in SCD children (Liem et al, Pediatric Blood and Cancer. 2009) Baseline ECG may be required

- Studies have shown that stimulation of β 2-adrenergic receptors on red and white blood cells promotes cellular adhesions and sickling (Zennadi et al, Blood, 2004; Zennadi et al, Blood, 2008)

- Systemic steroids concerns with AVN and rebound VOCs (Couillard et al, Haematologica, 2007)

Take home messages

- Pulmonary complications are common in children with SCD

- Are a leading cause of hospitalisation, increased morbidity and mortality

- Some (ATH, SBD) are often poorly recognized and often poorly managed (ACS) but they often predispose to increased risks of adverse neurologic, cardiovascular events

- High index of suspicion and deliberate screening for these pathologies is desirable to improve the QoL of these children
Thanks for your attention
Chronic lung disease & hypoxemia in children with sickle cell anemia (SCA)

Dr Michele Arigliani
Paediatric Respiratory Fellow
Royal Brompton Hospital, London

No conflict of interest to disclose

Respiratory complications in sickle cell anemia

- Acute chest syndrome
- Thromboembolisms
- Intrapulmonary shunt
- Obstructive sleep apnoea
- Bronchial hyperreactivity and asthma
- Chronic hypoxaemia
- Pulmonary hypertension
- Sickle Cell Chronic Lung Disease

HbSS & HbS-Beta0 genotypes most severely affected
Respiratory pathophysiology in SCA

- Hypoxia, intravascular hemolysis & vaso-occlusion
- Multiple inflammatory & non-inflammatory pathways (including NO depletion)
- Vascular remodelling
- Ischemia-riperfusion
- Increased endothelial cell adhesion & vasoocclusion
- More haemolysis & inflammation

Venous thromboembolism
Pain / hypoventilation
Respiratory infections
Fat embolism
Acute chest syndrome
Chronic airway inflammation
Chronic interstitial lung disease (interstitial fibrosis & vascular remodelling)
Pulmonary hypertension

Sickle cell chronic lung disease

<table>
<thead>
<tr>
<th>Physical Findings</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest pain</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Blood gas</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>X-ray</td>
<td>Normal</td>
<td>Diffuse, fine interstitial fibrosis involving all lobes of lung</td>
<td>Diffuse, fine interstitial fibrosis involving all lobes of lung</td>
</tr>
<tr>
<td>Pulmonary function tests*</td>
<td>Decreased FVC, TLC, FEV 1, and PWC; TLC/FRC ratio: 80% of predicted, or FRC/FRC ratio: 80% of predicted</td>
<td>Reduced FVC, TLC, FEV 1, and PWC; TLC/FRC ratio: 60% of predicted, or FRC/FRC ratio: 60% of predicted</td>
<td>Reduced FVC, TLC, FEV 1, and PWC; TLC/FRC ratio: 40% of predicted, or FRC/FRC ratio: 40% of predicted</td>
</tr>
<tr>
<td>ECOG and BCHI</td>
<td>Normal</td>
<td>Normal</td>
<td>Reduced respiratory capacity</td>
</tr>
<tr>
<td>Pulmonary artery pressure*</td>
<td>Normal</td>
<td>Normal</td>
<td>Elevated pulmonary hypertension</td>
</tr>
</tbody>
</table>

28 SCA young adults in Los Angeles
1964 to early 80s:
1) Exercise limitation and dyspnoea
2) Restrictive lung function
3) Interstitial lung fibrosis (autopsy confirmed)
4) PH and right heart dysfunction/failure

50% mortality over the study period
Lung function in adults with SCA

Klings et al AJRCCM 2006;173. 1264-1269

- Pre-Hydroxyurea era, USA
- 310 HbSS pts
- Mean age 30±10 yrs

- 74% of the cohort had a restrictive lung pattern (Total Lung Capacity (TLC) < 80% predicted)
- >50% decreased Diffusion Capacity of CO (DLco)

No differences between pts with or without h/o ACS

Field et al AJH 2008, Jul;83(7): 574-576

- 49 adults with SCA - mean follow-up 13 years
- Rate of FEV₁ decline (49 cc/year) twice that of non-smoking, healthy adults (20–26 cc/year)

Hodges et. al, Blood advances 2022

- Retrospective analysis of longitudinal FEV₁ data
- 192 adult with SCA and 309 with cystic fibrosis
- Rate annual FEV₁ decline similar in SCA vs CF pts
Low lung function & mortality in adults with SCA

Kassim et al, Bloods 2015; 126 (11):1344-9550
- 430 SCA adults, mean age 32± 9 yrs (21-67)
- Median follow-up of 5.5 years

Table 1. Final Cox regression model for death after lung function testing with reduced set of covariates (n = 404)

<table>
<thead>
<tr>
<th>Covariates</th>
<th>B</th>
<th>Hazard ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (PPT)</td>
<td>0.07</td>
<td>1.07 (1.04-1.19)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Male</td>
<td>0.14</td>
<td>1.09 (0.93-1.30)</td>
<td>.470</td>
</tr>
<tr>
<td>White blood cell count (WBC)</td>
<td>0.01</td>
<td>1.09 (0.98-1.21)</td>
<td>.696</td>
</tr>
<tr>
<td>ACR rate post-PPT (mL/L)</td>
<td>4.90</td>
<td>1.10 (1.00-1.21)</td>
<td>.033</td>
</tr>
<tr>
<td>PHV risk post-PPT (mL/L)</td>
<td>0.14</td>
<td>1.16 (1.09-1.23)</td>
<td>.015</td>
</tr>
<tr>
<td>Lactic dehydrogenase (mU/L)</td>
<td>0.003</td>
<td>1.02 (1.00-1.05)</td>
<td>.016</td>
</tr>
<tr>
<td>FEV1/VC predicted*</td>
<td>0.021</td>
<td>1.02 (1.00-1.04)</td>
<td>.037</td>
</tr>
</tbody>
</table>

*FEV1/VC predicted is derived from models that lower values are associated with hazard ratio >1.

FEV1 1% lower -> 2% increased mortality risk

Chaturvedi et al, AJH 2015; 2017 Feb;92(2):125-130
- 189 SCA adults, mean age 26 (IQR 23, 36)
- Median follow-up 7 years (IQR 2.41, 9.50)

Sickle cell chronic lung disease: chest CT findings

Sylvester et al, Eur Respir J 2006; 28: 832-838
- 33 SCA patients, unselected
- Median age 36 yrs (17-67 yrs)
- Lung function + HRCT

**TABLE 2**: High-resolution computed tomography (HRCT) data

<table>
<thead>
<tr>
<th>HRCT pattern</th>
<th>Prevalence % of tot</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lobar volume loss</td>
<td>67</td>
</tr>
<tr>
<td>Cavernous vessels</td>
<td>35</td>
</tr>
<tr>
<td>Pulmonary vessels</td>
<td>25</td>
</tr>
<tr>
<td>Irregular linear opacities</td>
<td>42</td>
</tr>
<tr>
<td>Interlobular septations</td>
<td>40</td>
</tr>
<tr>
<td>Ground glass opacification</td>
<td>67</td>
</tr>
<tr>
<td>Interlobular septa</td>
<td>13</td>
</tr>
<tr>
<td>Nodules</td>
<td>12</td>
</tr>
</tbody>
</table>

Restrictive lung function associated with lobar volume loss

Fine interstitial reticular pattern at lung bases

Ground glass changes

Volume loss
Sickle cell chronic lung disease: chest CT findings

- 22 SCA patients (mean±sd 37±13 yrs) 2006-2019
- 11/22 pts with shortness of breath
- On HRCT, several lungs cysts (up to >1000), ground glass, reticulations, emphysema

Sickle cell chronic lung disease: pathophysiology

Chronic lung injury, hypoxia & inflammation

Proliferation of interstitial fibroblast

Migration of fibrocytes in the lung

Increased extracellular matrix production

Interstitial fibrosis with disruption of the alveolar-capillary membrane and vascular remodeling
Circulating fibrocytes higher in SCA pts (n.114) than controls (n.19) (α) and they increase during pain crises (β).

**SCA chronic lung disease: SP-D as a potential biomarker?**

Egypt


- 50 SCA patients (13.9 ± 3.4 yrs), unselected, vs 30 healthy controls

Surfactant protein D (SP-D) blood levels associated with restrictive spirometry and ILD features on chest CT.
Lung function in children with SCA: high-income countries


- 104 SCA patients aged 6-19 yrs
- Hydroxyurea era; prospective FU~4.5 yrs

<table>
<thead>
<tr>
<th>Lung Function Parameter</th>
<th>All (N = 104)</th>
<th>Normal (n = 96)</th>
<th>Obstructive (n = 83)</th>
<th>Restriction (n = 76)</th>
<th>Non-specific (n = 81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (% predicted)</td>
<td>76.0 ± 13.4</td>
<td>69.1 ± 15.4</td>
<td>85.0 ± 15.3</td>
<td>67.0 ± 13.6</td>
<td>75.3 ± 8.5</td>
</tr>
<tr>
<td>FEV1/FVC ratio (Predicted)</td>
<td>0.78 ± 0.26</td>
<td>0.80 ± 0.30</td>
<td>0.76 ± 0.34</td>
<td>0.74 ± 0.29</td>
<td>0.70 ± 0.28</td>
</tr>
<tr>
<td>RV/TLC ratio</td>
<td>0.30 ± 0.07</td>
<td>0.31 ± 0.32</td>
<td>0.25 ± 0.12</td>
<td>0.36 ± 0.17</td>
<td>0.34 ± 0.10</td>
</tr>
</tbody>
</table>

- 8% of pts with restrictive or mixed lung function (LF) pattern
- 16% with obstructive physiology
- LF pattern not associated with h/o ACS or pain crises

UK - USA

Why an obstructive LF pattern in SCA?

Airway inflammation

- Asthma in 17-28% of children with SCA (Boyd, Blood 2006; Strunk, Journ of Ped 2014)
- Up to 50% of SCA pts with an obstructive LF pattern: no h/o asthma

Airway compression?

- 35 SCA pts; median age 43 yrs (17-73)
- Higher segmental pulmonary A/B ratio & more peripheral pulmonary vessels <5 mm diameter associated with air trapping (higher RV/TLC) & higher respiratory system resistance (Rrs)

De et al, Ped Pulmonol. 2018 Apr;53(4):400-411

Anaemia -> hyperdynamic status -> Prominent central vessels & peripheral vascular engorgement -> airways compression?
Lung function in children with SCA: low-middle income countries

**Sub-Saharan Africa**

- Unselected SCA children 6-18 yrs in UK, Nigeria and DRC; local healthy controls

<table>
<thead>
<tr>
<th>Region</th>
<th>Number</th>
<th>Spirometry pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK</td>
<td>101 pts</td>
<td></td>
</tr>
<tr>
<td>Nigeria</td>
<td>154 pts</td>
<td></td>
</tr>
<tr>
<td>DRC</td>
<td>112 pts</td>
<td></td>
</tr>
</tbody>
</table>

- Spirometry values 5-10% pred lower in SCA pts in Sub-Saharan Africa
- Around 25% of SCA patients in Africa had wasting (zBMI <-2)

**Egypt**

- 139 SCA pts (12.1±4 yrs), unselected vs healthy controls
- A h/o ACS associated with lower lung volumes and higher IL-6 sputum levels

**India**

- 99 HbSS pts (12.0±1 yrs), unselected vs 99 healthy controls

---

**Table 1**

<table>
<thead>
<tr>
<th>Index</th>
<th>SCA group (n=139)</th>
<th>Controls (n=139)</th>
<th>Mean difference (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1 (L)</td>
<td>1.19 (1.1)</td>
<td>1.64 (1.2)</td>
<td>-0.44 (-0.56 to -0.32)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEV1/FVC (%)</td>
<td>68.7 ± 12.2</td>
<td>73.0 ± 7.0</td>
<td>-4.3 (-10.3 to 1.7)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

---

**Table 2**

<table>
<thead>
<tr>
<th>SCA group (n=58)</th>
<th>Controls (n=58)</th>
<th>Mean difference (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>11.0 ± 2.7</td>
<td>10.4 ± 2.4</td>
<td>0.6 (-1.2 to 0.2)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>143.5 ± 4.9</td>
<td>143.0 ± 6.4</td>
<td>0.5 (-1.3 to 1.3)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>42.9 ± 14.0</td>
<td>42.9 ± 14.0</td>
<td>-0.1 (-12.3 to 12.1)</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>12.0 ± 2.1</td>
<td>12.0 ± 2.1</td>
<td>0.0 (-0.1 to 0.1)</td>
</tr>
<tr>
<td>Respiration rate (bpmm)</td>
<td>20.4 ± 6.3</td>
<td>20.4 ± 6.3</td>
<td>0.0 (&lt;0.2 to 0.2)</td>
</tr>
<tr>
<td>FEV1 (L)</td>
<td>0.9 ± 0.3</td>
<td>0.9 ± 0.3</td>
<td>0.0 (-0.1 to 0.1)</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>1.6 ± 0.6</td>
<td>1.6 ± 0.6</td>
<td>0.0 (&lt;0.2 to 0.2)</td>
</tr>
<tr>
<td>FEV1/FVC (%)</td>
<td>67.0 ± 12.2</td>
<td>73.0 ± 7.0</td>
<td>-6.0 (-10.3 to 1.7)</td>
</tr>
<tr>
<td>FEV1/FVC (%)</td>
<td>67.0 ± 12.2</td>
<td>73.0 ± 7.0</td>
<td>-6.0 (-10.3 to 1.7)</td>
</tr>
</tbody>
</table>
Lung function decline in children with SCA

**PRE-HYDROXYUREA**

- 312 SCA pts 6-18 years, retrospective data before 1989
- Annual decline in FEV1, 3% pred. & TLC 2.1-2.4% pred.

**HYDROXYUREA ERA**

- UK-USA: 194 SCA pts 4-19 years; 2005-2011:
  - 33% of pts on hydroxyurea
  - Average FU 4 yrs (1.1-6 yrs)
  - Annual FEV1 decline 0.3% pred. (95% CI -0.56 to -0.05)

---

### Table 1. Effect of Hydroxyurea Therapy on Annual Decline in Pulmonary Function Test Results

<table>
<thead>
<tr>
<th>SCD children</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1</td>
<td>90.7 (64.0-117.2)</td>
<td>81.2 (66.4-106.7)</td>
<td>0.0002</td>
</tr>
<tr>
<td>VC</td>
<td>97.6 (62.6-116.6)</td>
<td>85.4 (62.7-109.6)</td>
<td>0.0003</td>
</tr>
<tr>
<td>FEF_25-75</td>
<td>91.8 (45.9-149.9)</td>
<td>74.5 (38.9-122.7)</td>
<td>0.0001</td>
</tr>
<tr>
<td>FEV1/TLC</td>
<td>96.2 (69.7-119.4)</td>
<td>95.6 (64.9-108.1)</td>
<td>0.0048</td>
</tr>
<tr>
<td>TLC</td>
<td>95.5 (67.6-127.1)</td>
<td>81.6 (51.0-108.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RV</td>
<td>101.2 (79.7-121.20)</td>
<td>88.9 (54.8-149.2)</td>
<td>0.0090</td>
</tr>
<tr>
<td>RV/TLC</td>
<td>121.2 (73.4-194.3)</td>
<td>113.2 (67.5-221.5)</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

---

**Hydroxyurea & lung function decline in SCA**

**Canada**

- 56 SCA pts (11±4 yrs) annual spirometry before HU (~4 yrs) & after starting HU (~5 yrs)

**USA**

- Slower annual FEV1, and FVC decline after starting HU

**Table 2.**

<table>
<thead>
<tr>
<th>Hydroxyurea Group (N=62)</th>
<th>Control Group (N=36)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (%pred)</td>
<td>95.4±18.4</td>
<td>95.5±18.4</td>
</tr>
<tr>
<td>FEV1 (%pred)</td>
<td>93.3±23.5</td>
<td>93.1±23.5</td>
</tr>
<tr>
<td>FEV1/FVC ratio</td>
<td>72.5±17.1</td>
<td>73.4±18.2</td>
</tr>
<tr>
<td>FEV1% change between first and last test</td>
<td>88.6±19.0</td>
<td>92.4±18.3</td>
</tr>
<tr>
<td>FEV1% change between second and last test</td>
<td>92.4±17.5</td>
<td>89.5±17.5</td>
</tr>
<tr>
<td>FVC% change between first and last test</td>
<td>4.6±17.0</td>
<td>-3.0±19.2</td>
</tr>
<tr>
<td>FVC% change between second and last test</td>
<td>0.0±0.08</td>
<td>0.0±0.08</td>
</tr>
<tr>
<td>FEV1/FVC ratio</td>
<td>0.0±0.08</td>
<td>0.0±0.05</td>
</tr>
<tr>
<td>FEV1% change between first and last test</td>
<td>-0.05±1.00</td>
<td>-0.05±1.00</td>
</tr>
</tbody>
</table>

- Spirometry improved in the SCA group on HU (+7% pred.) & declined in the control SCA group (-3%)
How to detect early sickle chronic lung disease?

MBW measures ventilation inhomogeneity in the lung depending on:

1) Patchy conductive airway disease (e.g. early CF): S\text{cont} and Lung Clearance Index (LCI)
2) Patchy changes in lung compliance or in peripheral lung architecture: S\text{per} and LCI

Arigliani et al, Annals American Thoracic Society 2022
Sep;19(9):1507-1515

- 35 unselected SCA pts (16.4±3.5 yrs) & 31 healthy controls
- MBW, spirometry, body plethysmography

- LCI & S\text{cont} significantly higher in SCA patients than controls
- LCI abnormal in 29% (10/35) of SCA pts
- LCI -> tends to increase for decreasing FEV1 and FVC (figure A & B)
- 3 out 5 SCA pts with abnormal LCI & LF pattern had restrictive physiology

Ventilation inhomogeneity mostly related to patchy peripheral lung disease in SCA patients
Chronic hypoxaemia in children with SCA

Quinn, BJH 2005 Oct;131(1):129-3
- 390 unselected SCA pts 9.5±5.7 yrs
- Mean SpO2 day time 96.3±3%
- 33% of pts SpO2% <96% & 2.8% <90%

- 30 Unselected SCA pts (median age 10.8 – 5 to 17 yrs)
- 50% (15), mean night SpO2 ≤93%
- Night hypoxemia associated with lower Hb & lung function

- Mean Unselected SCA pts (median age 10.8 – 5 to 17 yrs)
- 50% (15), mean night SpO2 ≤93%
- Night hypoxemia associated with lower Hb & lung function

<table>
<thead>
<tr>
<th>Medical history</th>
<th>&gt;90% (n=15)</th>
<th>≤90% (n=15)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age yrs</td>
<td>10.3 (7-17)</td>
<td>11.6 (5-16)</td>
<td>0.6</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>19.6 (13-24)</td>
<td>20.3 (16-26)</td>
<td>0.29</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>5 (10.2%)</td>
<td>13 (26.5%)</td>
<td>0.04</td>
</tr>
<tr>
<td>% of %FVC in the past year</td>
<td>8 (0-10)</td>
<td>8 (0-10)</td>
<td>0.72</td>
</tr>
<tr>
<td>Pulmonary hypertension (mmHg)</td>
<td>1 (10)</td>
<td>1 (3-24)</td>
<td>0.52</td>
</tr>
<tr>
<td>History of at least one ACS episode</td>
<td>0 (0)</td>
<td>5 (10.2%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Abnormal lung function test</td>
<td>5 (10.2%)</td>
<td>28 (56.1%)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

- 380 unselected SCA pts 9.5±5.7 yrs
- Mean SpO2 daytime 96.3±3%
- 33% of pts SpO2% <96% & 2.8% <90%
- Night hypoxemia associated with lower Hb & lung function

SCA children with nocturnal or sustained hypoxaemia at higher risk of:
A) intracranial arteriopathy and CNS events (Dlamini, Neurology 2017; Kirkham, Lancet 2001)
B) LV diastolic dysfunction (Johnson, Blood 2010)
C) PH (TRV>2.5 m/s) (Haematologica 2009)

- >10,000 adults in-patients on O2 - ITU
- 11.7% of Black individuals with SpO2 92-96% had arterial SaO2 <88% vs 3.6% Whites

Chronic hypoxaemia in SCA: why?

- CHRONIC HYPOXAEIA IN SCA:

<table>
<thead>
<tr>
<th>Mechanism of hypoxia</th>
<th>Causes in SCD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoxia</td>
<td>SDB (OSA, upper airway obstruction); Thoracic splitting due to chronic pain; Restrictive pulmonaary disease; Reduced chest excursion due to hypotension; Central hypoxemia (eg. due to excessive use of narcotics)</td>
</tr>
<tr>
<td>Diffusion impairment</td>
<td>SCD-associated interstitial lung fibrosis; Pulmonary vascular disease</td>
</tr>
<tr>
<td>Shunt</td>
<td>Intracardiac shunt (eg. ventricular septal defect); Extracardiac shunt; Arterio-venous malformations; Intrapulmonary shunt (eg. due to consolidation or atelectasis resulting in decreased perfusion to affected area)</td>
</tr>
<tr>
<td>Ventilation-perfusion inequality</td>
<td>Chronic VTE; ACS; Plastic bronchitis; Obstructive lung disease without asthma; Chronic airway inflammation due to asthma</td>
</tr>
</tbody>
</table>

- CHRONIC VTE: 17-25% prevalence in adult studies
  - Machugo, Blood 2018;132(17):1770-1780

- PH: 6-11% SCA adults on cardiac cath, 20-46% children echo TRV >2.5 m/s (Machugo, Blood 2018;

- Intrapulmonary shunt: more frequent in SCA pts with stroke
  - Intracardiac shunt in 91 unselected SCA adults -> 74% (67/91) R-L shunt
  - 29/67 (43%) R-L shunt were pulmonary
  - 94% of pts with SpO2 <95% had R-L shunt
  - 15 subjects with pulmonary shunt had Angio-chest CT:
    1. classical pAVM (n=1)
    2. pulmonary telangiectasias (n=2)
    3. prominent peripheral pulmonary vessels (n=8)
    4. none (n=4)

- Intrapulmonary shunt: more frequent in SCA pts with stroke

- Chronic VTE: 17-25% prevalence in adult studies
  - Machugo, Blood 2018;132(17):1770-1780

- Chronic hypoxaemia in SCA: diagnostic work-up

<table>
<thead>
<tr>
<th>Intrapulmonary shunt</th>
</tr>
</thead>
</table>
  - Bubble echo in 91 unselected SCA adults -> 74% (67/91) R-L shunt
  - 29/67 (43%) R-L shunt were pulmonary
  - 94% of pts with SpO2 <95% had R-L shunt
  - 15 subjects with pulmonary shunt had Angio-chest CT:
    1. classical pAVM (n=1)
    2. pulmonary telangiectasias (n=2)
    3. prominent peripheral pulmonary vessels (n=8)
    4. none (n=4)

- CR poly (or night oximetry) if daytime SpO2 <95% of SDB symptoms

- Lung function:
  - If restrictive spirometry -> body pleth & TLco (be mindful of reference values); + 6-minute-walking test (6MWT)
  - If reduced TLC & RV -> consider chest CT or angio-chest CT to assess ILD

- Echo cardio for PH +/- bubble-echo to look for intrapulmonary shunt

- Angio chest-CT to r/o chronic VTE if no other causes identified
  - V/Q scan may help to characterize V/Q mismatch


- Machugo, Blood 2018;132(17):1770-1780

- Machugo, Blood 2018;132(17):1770-1780
Chronic hypoxaemia in SCA: management

**Hydroxyurea**

Guidelines for the use of hydroxyurea in children and adults with sickle cell disease

A British Society for Haematology Guideline

"In children and adults with chronic hypoxia, recommend treatment with hydroxyurea (1C)"


- 21 SCA patients – Median age 9 (range 1-18) daytime SpO2 & night oximetry pre & after starting HU (median 9 months later, IQR 3.5 – 15 m.)

**Home oxygen**

Home Oxygen Therapy for Children
An Official American Thoracic Society Clinical Practice Guideline
Hayes et al AARCCT 2013 Feb 1;139(3):e5-e23

Home-O2 therapy (HOT) recommended for SCA children if:
- >3 separate daytime SpO2 <90%
- >5% TST SpO2 <90%

Liguoro, Arigliani et al Arch Dis Child 2021; 106:258-262.

At 1 yr FU:
- Home O2 safe
- sleep study on O2 supplementation normalized
- Trend to lower rate of hospital admissions for pain crises
- Improvements in AST & LDH (haemolysis markers)

Qureshi et al BJH 2018, 181, 460–475

"In children and adults with chronic hypoxia, recommend treatment with hydroxyurea (1C)"

Hayes et al AJRCCM 2019 Feb 1;199(3):e5-e23

-19 SCA patients – Median age 12 (range 6-18) started on HOT 2014-2019

Future perspective:
new drugs and SCA chronic lung disease


Future perspective:
new drugs and SCA chronic lung disease

**Take home messages**

1. SCA chronic lung disease: significant comorbidity & earlier onset in low-income settings
2. Hydroxyurea likely to change the natural history of LF decline in SCA
3. Chronic hypoxaemia in SCA patients is not “normal” and should be fully investigated

**Areas to address in future studies:**
- Longitudinal prospective LF data in pts from low-income countries and in those starting HU/new SCA drugs
- The contribution of intrapulmonary shunting & chronic PTE to hypoxaemia in children
- Are the LCI or other LF measurements useful to detect early SCA chronic lung disease? (*correlation with chest imaging; response to SCA drugs; etc*)