Sickle Cell Disease and the Lungs

Acute Pulmonary Complications of Sickle Cell Disease in Children

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Presentation outline

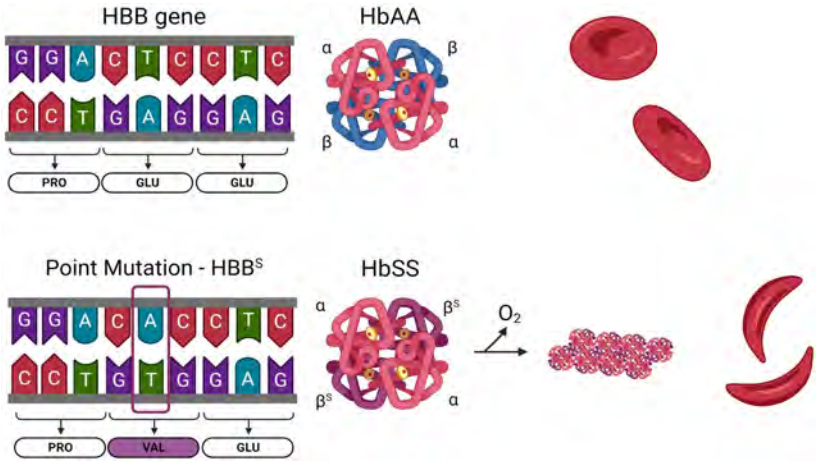
- Introduction
- Burden of Sickle Cell Disease (SCD)
- Upper airway pathologies
  - Adenotonsillar inflammation/hypertrophy and sleep breathing disorders
- Lower airway pathologies
  - Acute chest syndrome/LRTI
  - Asthma
- Conclusion

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-Sβ+ thalassaemia and SCD-Sβ-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

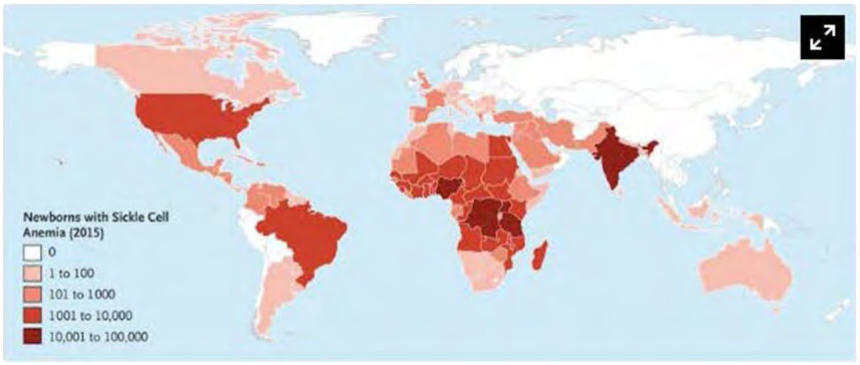
- Most common inherited haemoglobinopathy with worldwide distribution
- 25 million individuals live with SCD
- Approximately 300,000 infants are born annually with SCD, most in SSA
- 1 in 2,500 live births in the US where an estimated 100,000 individuals with SCD live, majority of whom are African Americans (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 **(Ndeezi et al, Lancet Glob Health 2016)**
  - **Makani et al, Annals of tropical medicine and parasitology, 2007**

Global prevalence of SCD Piel FB et al N Engl J Med (2017).



Data availability Global map Piel FB et al N Engl J Med (2017).

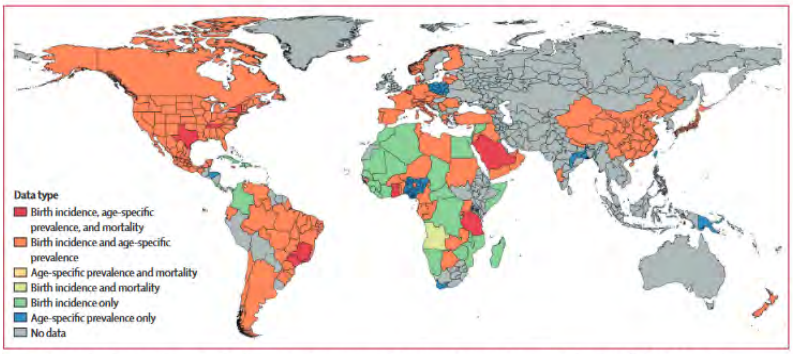
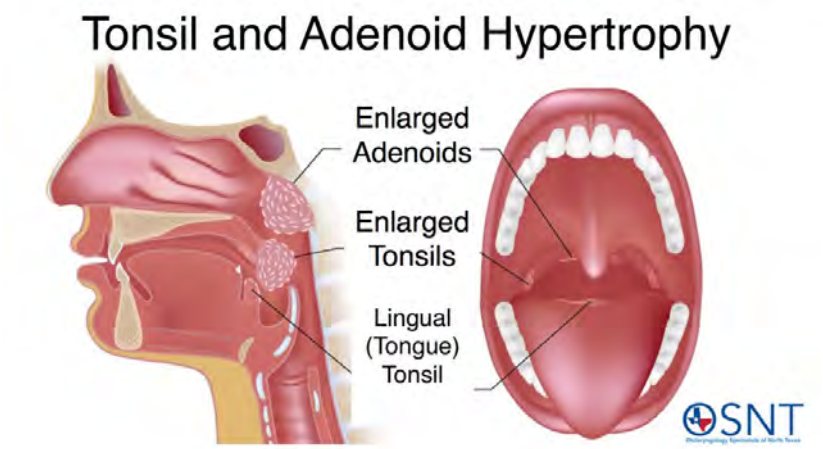


Figure 2: **Data availability map showing types of input data source measures present in each country for sickle cell disease DisMod-MR 2.1 models**
Each colour represents a different combination of birth incidence, age-specific prevalence, and survival or mortality data that were used as inputs for DisMod-MR 2.1 models for each of the three estimated genotypes of sickle cell disease. The outputs of these models include estimated birth incidence, age-specific prevalence, and total sickle cell disease mortality for each GBD location, age group, sex, and year (see appendix for genotype specific counts [pp 95–178] and for genotype specific rates [pp 207–90]). The specific sources are in the appendix (pp 15–22) and online at the Global Health Data Exchange; contributing counts of prevalence and mortality measures from each genotype are also in the appendix (p 50).

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

CHEST Original Research

SLEEP DISORDERS

Upper Airway Lymphoid Tissue Size in Children With Sickle Cell Disease

Temima Strauss, BA; Sanghun Sin, MS; Carole L. Marcus, MBBCh, FCCP; Thornton B. A. Mason, MD, PhD; Joseph M. McDonough, MS; Julian L. Allen, MD; Jason B. Caboot, MD; Cheryl Y. Bowdre, PhD; Abbas F. Jawad, PhD; Kim Smith-Whitley, MD; Kwaku Ohene-Frempong, MD; Allan I. Pack, MD, PhD; and Raanan Arens, MD

Upper airway lymphoid tissue size in Children with SCD- Strauss et al, Chest, 2012

Table 1—*Demographics and Anthropometric Measures*

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

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*

Area Measured	SCD (n = 36)	Control Subjects (n = 36)	% Difference	*P* Value
Airway	2.8 ± 1.2	3.7 ± 1.6	−24.3	< .01
Lymphoid tissues				
Adenoid	8.4 ± 4.1	6.0 ± 2.2	40.0	< .01
Tonsils	7.0 ± 4.3	5.1 ± 1.9	37.3	< .01
Retropharyngeal nodes	3.0 ± 1.9	2.2 ± 0.9	36.4	< .05
Deep cervical nodes	15.7 ± 5.7	12.7 ± 4.0	23.6	< .05

Data are displayed a mean ± SD. Units are cm^3. % Difference = percent mean volume difference. See Table 1 legend for expansion of abbreviation.

Sleep study in SCD vs. controls

Strauss et al, Chest, 2012

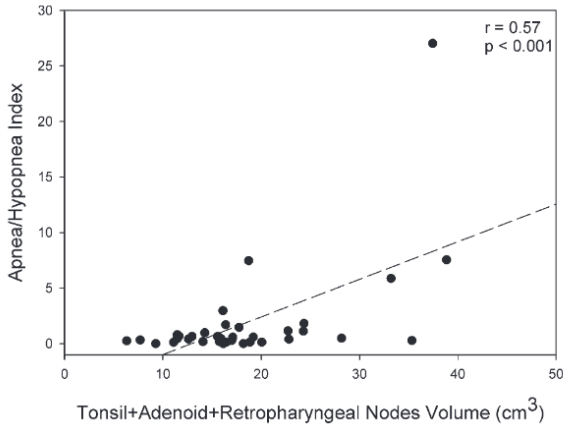
Table 3—*Polysomnography*

Measure	SCD (n = 36)	Control Subjects (n = 20)	*P* Value
Total sleep time, h	7.3 ± 1.2	7.7 ± 0.8	NS
Sleep efficiency, %	83.7 ± 12.4	90.4 ± 5.3	< .05
Arousal index, events/h	13.7 ± 4.7	10.8 ± 3.8	< .05
Baseline Spo_2, %	95.3 ± 2.9	97.1 ± 0.9	< .05
Spo_2 nadir, %	84.3 ± 12.3	91.1 ± 4.2	< .05
Baseline $ETCO_2$, mm Hg	43.0 ± 3.1	37.5 ± 4.6	< .001
Peak $ETCO_2$, mm Hg	53.4 ± 8.5	42.3 ± 5.3	< .001
Obstructive apnea index, events/h	0.7 ± 2.0	0.2 ± 0.3	NS
AHI	1.9 ± 4.7	0.4 ± 0.3	NS
OSAS (AHI ≥ 1.5)	7 of 36	0 of 20	< .05

Data are displayed as mean ± SD. AHI = apnea-hypopnea index; $ETCO_2$ = end-tidal CO_2; OSAS = obstructive sleep apnea syndrome; Spo_2 = 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)**
- Cardiovascular abnormalities **(Johnson et al, Blood. 2010; Elalfy et al, J Pediatr Hematol Oncol. 2018)**
- 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

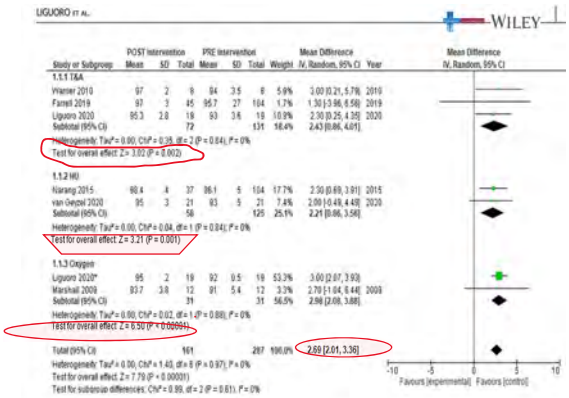


FIGURE 2 Mean nocturnal oxygen saturation (SpO_2) pre- and postintervention in children with sickle cell disease and sleep-disordered breathing: cumulative effect and subgroup analysis (adenotonsillectomy–T&A; oxygen; HU).[45] HU, hydroxyurea; T&A, tonsillectomy & adenoidectomy [Color figure can be viewed at wileyonlinelibrary.com]

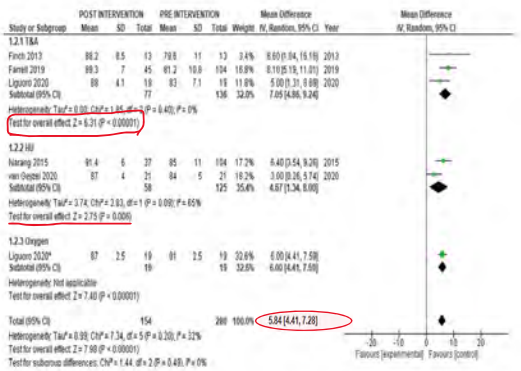


FIGURE 3 Mean nadir oxygen saturation (SpO_2) pre- and postintervention in children with sickle cell disease and sleep-disordered breathing: cumulative effect and subgroup analysis (adenotonsillectomy–T&A; oxygen; HU).[45] HU, hydroxyurea; T&A, tonsillectomy & adenoidectomy [Color figure can be viewed at wileyonlinelibrary.com]

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

Liguoro et al, Pediatric Pulmonology, 2021

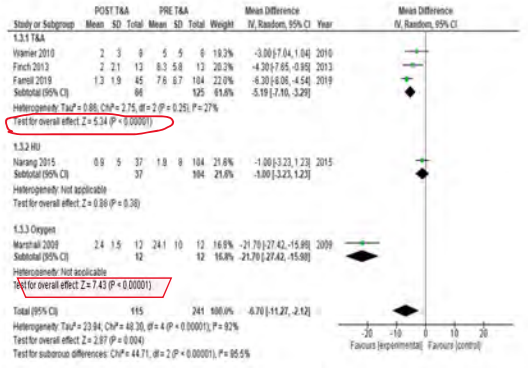


FIGURE 4 Mean AHI pre- and postintervention in children with sickle cell disease and sleep-disordered breathing: cumulative effect and subgroup analysis (adenotonsillectomy–T&A; oxygen; HU). AHI, apnea/hypopnea index; HU, hydroxyurea; T&A, tonsillectomy & adenoidectomy [Color figure can be viewed at wileyonlinelibrary.com]

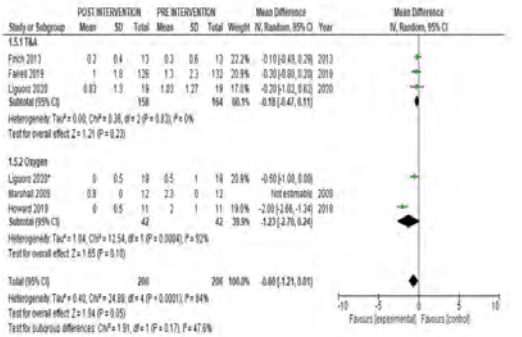


FIGURE 5 Mean annual rate per patient of vaso-occlusive pain crises pre- and postintervention (adenotonsillectomy–T&A; oxygen) in children with sickle cell disease and sleep-disordered breathing: cumulative effect and subgroup analysis.[47] T&A, tonsillectomy & adenoidectomy [Color figure can be viewed at wileyonlinelibrary.com]

Admission length and post surgery complications

Farrel et al, Int J Pediatr Otorh, 2018

Admission length and post-T&A complications in children with sickle cell disease.

Parameter	N (%)	Mean ± SD	Range
Total admission length (days)	132 (100%)	3.5 ± 1.2	1–13
Other surgical procedure performed with T&A (yes)	25 (18.9%)		
Post-operative complications			
Total number of complications	15 (11.4% of cases)		
Post-operative acute chest episode	8 (6% of cases)		
Upper airway bleed	2 (1.5% of cases)		
Post-operative pain crisis	1 (0.8%)		
Intubation	1 (0.8%)		
Hypotension without pressor requirement	1 (0.8%)		
Hypotension with pressor requirement	2 (1.5%)		
Post-operative stroke	0 (0% of cases)		
Total number of complications among patients with elevated BMI percentile[a]	4 (3% of cases)		

[a] A BMI percentile > 85%.

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 SPO_2 , 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*

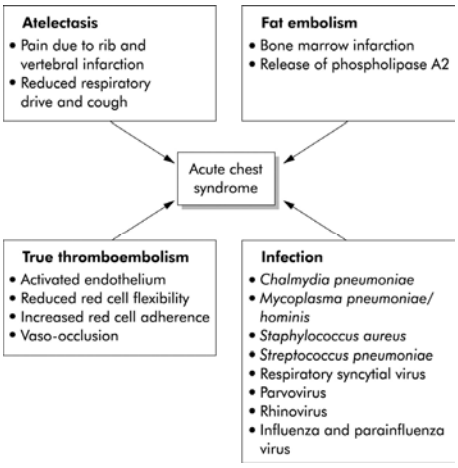
Defined as:

- 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

Charache et al, Arch Intern Med 1979.
Castro et al The CSSD, 1994
Vinchinsky et al N Engl J Med 2000;

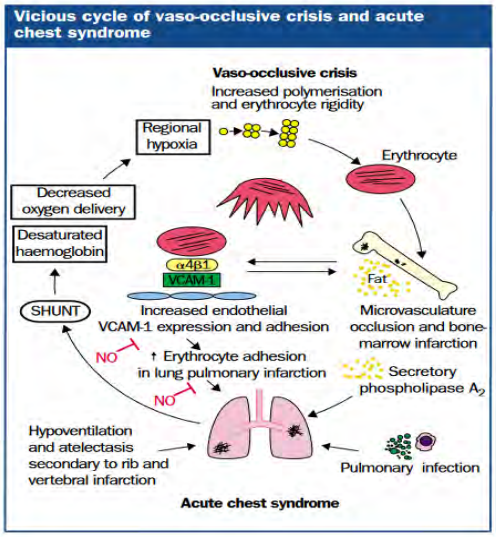
Pathogenesis of acute chest syndrome

Mak and Davies, Thorax, 2003



Acute chest syndrome

Gladwin, M. T., & Rodgers, G. P. The Lancet (2000).



Causes and incidence of ACS

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

By Oswaldo Castro, Donald J. Brambilla, Bruce Thorington,† Carl A. Reindorf, 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 morbidity 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 3,751 patients with sickle cell disease who were observed prospectively for at least 2 years (19,867 patient-years [pt-yrs]) 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 (2,100 events). ACS incidence was higher in patients with homozygous sickle cell disease (SS; 12.8/100 pt-yrs) and in patients with sickle cell-β^0 thalassemia (9.4/100 pt-yrs), and lower in patients with hemoglobin (Hb) SC disease (5.2/100 pt-yrs) and patients with sickle cell-β^+ thalassemia (3.9/100 pt-yrs). α-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 (25.3/100 pt-yrs in SS) and decreasing gradually to its lowest value in adults (8.8/100 pt-yrs in SS). In SS children (<10 years of age), we documented an age-related within-person reduction in ACS attack rates. 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 fetal Hb (lower rates in patients with high fetal 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.

Cooperative Study of Sickle Cell disease (CSSCD)

Castro et al The Cooperative Study of Sickle Cell Disease

- 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^0thalassemia (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)**

Castro et al The Cooperative Study of Sickle Cell Disease, 1994

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.

Vinchinsky et al N Engl J Med 2000; 342:1855-1865

The Multicenter National Acute Chest Syndrome Study (NACSS) Vinchinsky et al N Engl J Med 2000; 342:1855-1865

- 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

Vinchinsky et al N Engl J Med 2000

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

Infectious causes of ACS

Vinchinsky *et al* N Engl J Med 2000

TABLE 5. INFECTIOUS PATHOGENS ISOLATED IN 671 EPISODES OF THE ACUTE CHEST SYNDROME.*

PATHOGEN	NO. OF EPISODES
Chlamydia pneumoniae	71
Mycoplasma pneumoniae	51
Respiratory syncytial virus	26
Coagulase-positive *Staphylococcus aureus*	12
Streptococcus pneumoniae	11
Mycoplasma hominis	10
Parvovirus	10
Rhinovirus	8
Parainfluenzavirus	6
Haemophilus influenzae	5
Cytomegalovirus	4
Influenza A virus	4
Legionella pneumophila	4
Escherichia coli	3
Epstein–Barr virus	3
Herpes simplex virus	3
Pseudomonas species	3
Adenovirus	2
Branhamella species	2
Echovirus	2
Beta-hemolytic streptococcus	2
Mycobacterium tuberculosis	2
Enterobacter species	1
Klebsiella pneumoniae	1
Mycobacterium avium complex	1
Salmonella species	1
Serratia marcescens	1
Total	249

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

Treatment plan

Howard et al, 2015

- **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, *British Journal of Haematology,* 2015

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 **(An P et al, 2012)**
- 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
Vinchinsky et al N Engl J Med 2000

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 P 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: 2.0; 95% CI: 1.3–3.3) **(*Boyd et al, Paed pulm, 2009)***

Boyd JH et al. Haematologica. 2007

Vinchinsky et al N Engl J Med 2000;

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 5years 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).

(*Boyd et al, Paed pulm, 2009)* Boyd JH et al. Haematologica. 2007

Vinchinsky et al N Engl J Med 2000;

Possible link between SCD and asthma

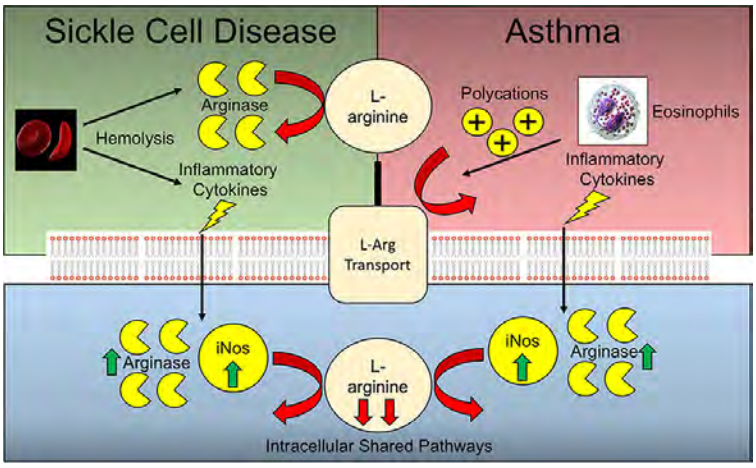
- Increased serum IgE is observed in both SCD and allergic asthma
- Increased levels of proinflammatory cytokines such as IL-3, GM-CSF, **(Canalli et al, 2005)**
- Dysregulated arginine metabolism and excess arginase activity **(Morris et al, 2000; Meurs et al, 2003)**
- Leukotriene pathway {secretory 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)**

(Nandedkar et al, 2008)

Sampson AP. Clin Exp Allergy, 1996

Holgate et al, J Allergy Clin Immunol. 2003

Inflammatory pathways in allergic asthma and SCD Samarasinghe AE and Rosch JW Front. Immunol. (2020)



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

Gomez and Morris, Bio Med Res Int, 2013

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

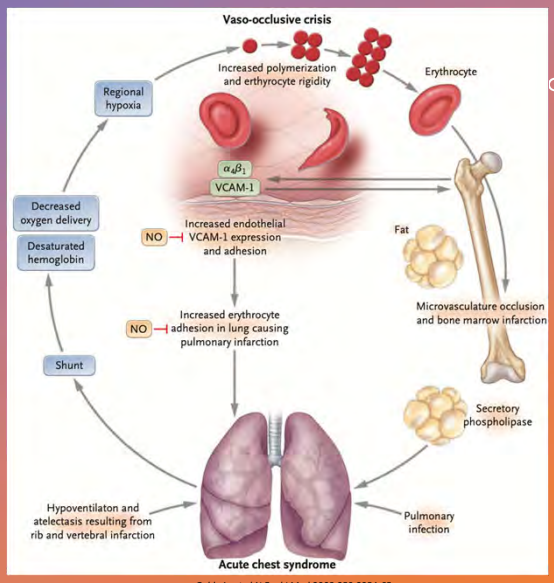
ERS EUROPEAN RESPIRATORY SOCIETY
every breath counts

PAN AFRICAN THORACIC SOCIETY

Chronic lung disease & hypoxemia in children with sickle cell anemia (SCA)

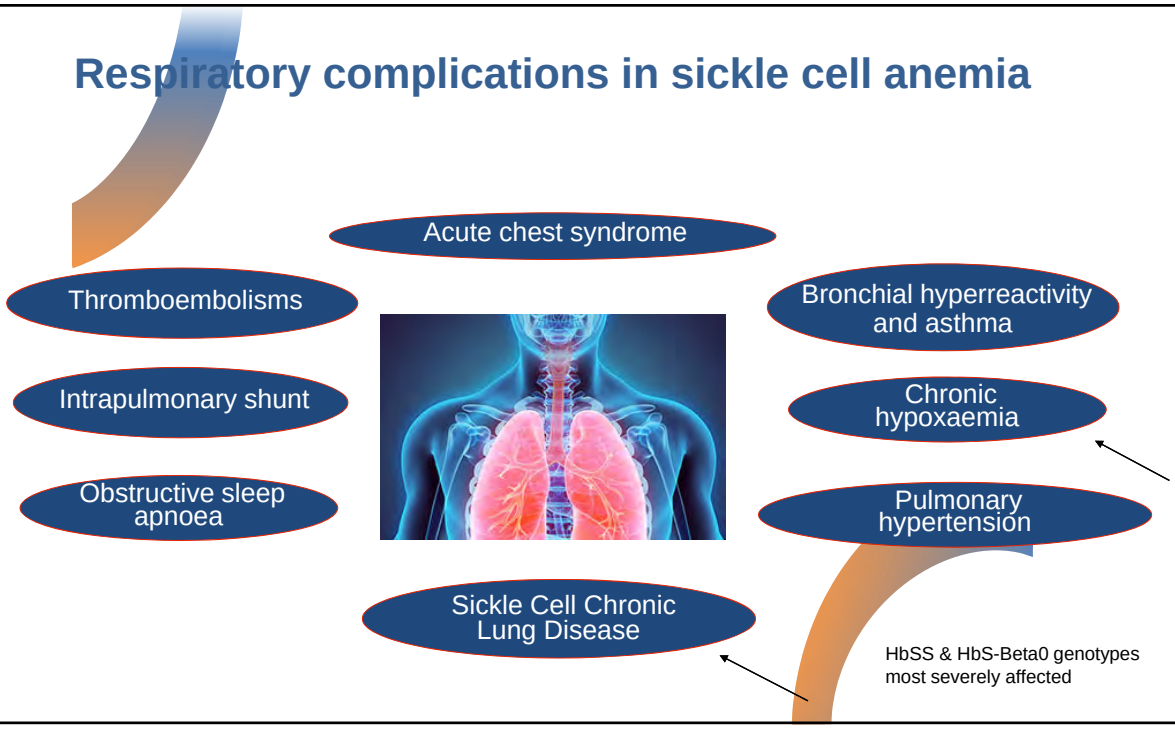
Dr Michele Arigliani
Paediatric Respiratory Fellow
Royal Brompton Hospital, London

No conflict of interest to disclose

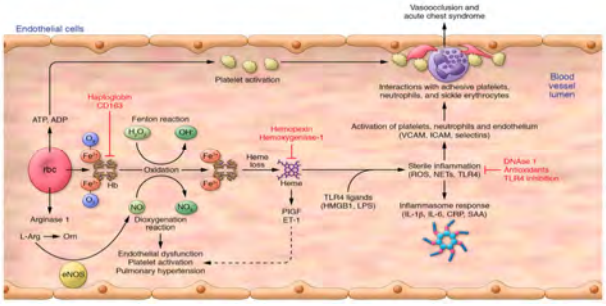


Galdwin et al N Engl J Med 2008;359:2254-65

Respiratory complications in sickle cell anemia



Respiratory pathophysiology in SCA



Kato et al J Clin Invest. 2017 Mar 1;127(3):750-760

Hypoxia, intravascular hemolysis & vaso-occlusion

→ Multiple inflammatory & non-inflammatory pathways (including NO depletion)

→ Increased endothelial cell adhesion & vasocclusion

→ Vascular remodelling

→ Ischemia-riperfusion

→ 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

Sickle Cell Chronic Lung Disease: Prior Morbidity and the Risk of Pulmonary Failure

DARLEEN POWARS,[1] JAMES A. WEIDMAN,[1] TAMARA ODOM-MARYON,[2] JOYCE C. NILAND,[2] AND CAGE JOHNSON[3]

Medicine (Baltimore) 1988 Jan;67(1):66-76

TABLE 3. Sickle chronic lung disease: Staging criteria

Clinical Markers	Stage 1	Stage 2	Stage 3	Stage 4
Chest pain	Recurrent substernal pain and chronic cough	Increased pain over Stage 1	Severe midline crushing chest pain	Severe and prolonged pain with dyspnea at rest
Blood gases	Normal oxygen saturation	Normal oxygen saturation	Hypoxia with partial pressure oxygen (70 mm Hg) during stable periods	Partial pressure oxygen (60 mm Hg) during stable periods
X-ray	Decreased distal pulmonary vascularity, hyperexpansion, evidence suggestive of increased interstitial markings	Diffuse, fine interstitial fibrosis involving all lobes of the lung	Pulmonary fibrosis	Severe pulmonary fibrosis
Pulmonary function tests*	Decreased FVC, TLC, FEV_1, and FEV_1/FVC ratio (mild, 80% of predicted normal, or 1 S.D. below normal)	Decreased FVC, FEV_1, TLC, DCD and FEV_1/FVC ratio (moderate, 60% of predicted, or 2 S.D. below normal)	Decreased FVC, FEV_1, TLC, DCO, and FEV_1/FVC ratio (severe, 40% of predicted, or 3 S.D. below normal)	Patient frequently unable to complete testing due to degree of hypoxia
ECG and ECHO	Left ventricular preponderance persists	Balanced ventricular hypertrophy	Right ventricular hypertrophy and right atrial enlargement. Progressive increase in heart size	Severe right ventricular and right atrial hypertrophy. Ischemic T waves in V1 and V2, and p pulmonale
Pulmonary artery pressure	Normal	Normal	Borderline elevation or normal	Markedly elevated with pulmonary hypertension

Abbreviations: FVC = forced vital capacity, TLC = total lung capacity, FEV_1 = forced expiratory flow rate
* These measurements are based upon common methods for comparison of reference values (66).

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 J AJRCCM 2006 173. 1264–1269

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

	All Patients ($n = 310$)
Summary of PFT results	
FEV_1	
Median	82.80
Mean ± SD	83.03 ± 16.06
FVC	
Median	83.62
Mean ± SD	84.37 ± 16.01
FEV_1/FVC, %	
Median	98.61
Mean ± SD	98.36 ± 9.15
TLC	
Median	69.79
Mean ± SD	70.20 ± 14.69
RV	
Median	78.04
Mean ± SD	88.60 ± 60.88
DL_{CO}	
Median	53.74
Mean ± SD	56.57 ± 20.11
Adjusted DL_{CO}*	
Median	61.74
Mean ± SD	64.54 ± 19.93

TABLE 3. COMPARISON OF PULMONARY FUNCTION TEST RESULTS ACCORDING TO HISTORY OF ACUTE TEST SYNDROME

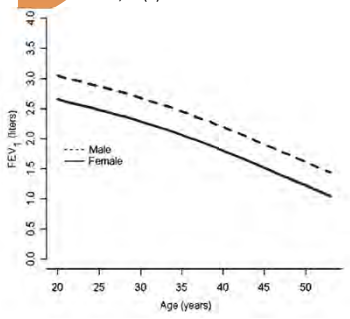
	History of ACS ($n = 221$)	No History of ACS ($n = 89$)	p Value
PFT results*			
TLC, %	69.17 ± 1.01	72.83 ± 1.62	0.06
DL_{CO}, %	55.32 ± 1.43	59.94 ± 2.36	0.10
Adjusted DL_{CO}, %	63.32 ± 1.43	67.81 ± 2.34	0.10
Subclassification based on PFTs			
Normal, n (%)	20 (9)	11 (12)	(0.6073)
Isolated low DL_{CO}, n (%)	27 (12)	13 (15)	
Mixed O/R, n (%)	3 (1)	2 (2)	
Obstructive, n (%)	2 (1)	2 (2)	
Restrictive, n (%)	169 (77)	61 (69)	

No differences between pts with or without h/o ACS

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

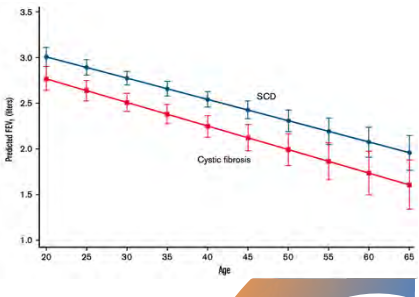
Lung function decline in adults with SCA

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



- 49 adults with SCA - mean follow-up 13 years
- Rate of FEV_1 decline (49 cc/year) twice that of non-smoking, healthy adults (20–26 cc/year)

***Hodges et. al*, Blood advances 2022** Mar 22;6(6):1937-1940



- Retrospective analysis of longitudinal FEV_1 data
- 192 adult with SCA and 309 with cystic fibrosis
- Rate annual FEV_1 decline similar in SCA vs CF pts

Low lung function & mortality in adults with SCA

***Kassim et al* Bloods 2015;**
126 (13): 1544–1550

- 430 SCA adults, mean age 32± 9 yrs (21-67)
- Median follow-up of 5.5 years

Table 3. Final Cox regression model for death after lung function testing with reduced set of covariates (n = 404)

Covariate	B	Hazard ratio (95% CI)	P
Age at PFT	0.07	1.07 (1.04-1.10)	<.001
Male	0.74	2.09 (1.20-3.65)	.010
White blood cell count (10^9/L)	0.08	1.09 (0.98-1.20)	.096
ACS rate post-PFT (no./y)	2.34	10.39 (3.11-34.78)	<.001
Pain rate post-PFT (no./y)	0.14	1.15 (0.98-1.36)	.095
Lactic dehydrogenase (mg/dL)	0.002	1.002 (1.00-1.003)	.015
FEV_1% predicted*	0.021	1.02 (1.00-1.04)	.037

*FEV_1% predicted is reverse-coded so that lower values are associated with hazard ratios >1.

FEV_1 1% lower -> 2% increased mortality risk

***Chaturvedi et al*, AJH 2015;**
2017 Feb;92(2):125-130

- 189 SCA adults, median age 28 (IQR 23, 36)
- Median follow-up 7 years (IQR 2.41, 9.50)

Covariate	Hazard Ratio (95% CI)	P
Age at echocardiograph	1.04 (1.00, 1.09)	0.051
Male sex	2.78 (0.87, 8.91)	0.084
Nephropathy	2.78 (0.95, 8.10)	0.062
$FEV_1 \leq 70\%$ predicted and TRJV < 2.5 m/sec[b]	1.09 (0.22, 5.15)	0.915
$FEV_1 > 70\%$ predicted and TRJV ≥2.5 m/sec	3.78 (0.79, 17.61)	0.094
$FEV_1 \leq 70\%$ predicted and TRJV ≥ 2.5 m/sec	4.97 (1.30, 18.91)	0.019

Suspected PH at echo (TRJV >2.5 m/sec) + FEV_1 <70% -> 5 times higher mortality risk

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

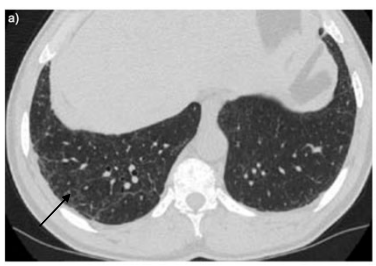
TABLE 2 High-resolution computed tomography (HRCT) data

HRCT pattern	Prevalence % of tot
Lobar volume loss	67
Central vessels	70
Peripheral vessels	52
Irregular linear opacities	42
Reticular pattern	82
Ground-glass opacification	58
Traction bronchiectasis	9
Interlobular septa	18
Nodules	9

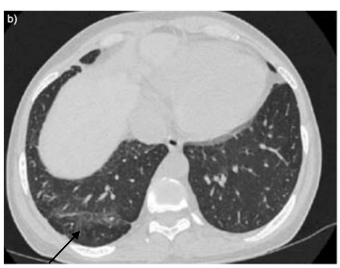
TABLE 4 Relationships between pulmonary function and high-resolution computed tomography (HRCT) abnormalities on stepwise regression

Lung function	r^2 value	HRCT	Coefficient (95% CI)	p-value
FEV1	0.32	Lobar volume loss	-3.6 (-6.0- -1.1)	0.006
		Prominent central vessels	-1.0 (-1.8- -0.2)	0.02
FVC	0.43	Lobar volume loss	-3.3 (-5.2- -1.3)	0.002
		Prominent central vessels	-1.1 (-1.6- -0.4)	0.003
TLC	0.21	Lobar volume loss	-2.5 (-4.3- -0.7)	0.006
V_A	0.29	Lobar volume loss	-2.3 (-3.6- -1.0)	0.001
D_LCO	0.16	Lobar volume loss	-2.5 (-4.8- -0.4)	0.03

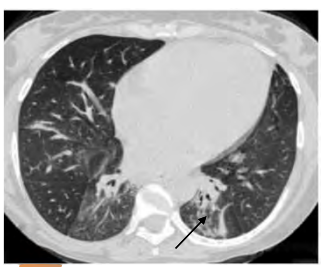
Restrictive lung function associated with lobar volume loss



Fine interstitial reticular pattern at lung bases



Ground glass changes

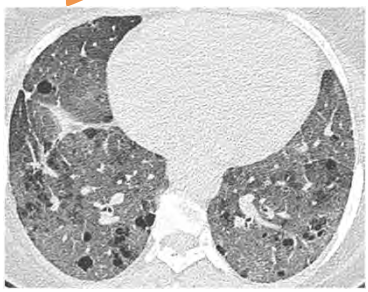

Volume loss

Sickle cell chronic lung disease: chest CT findings

Brief communication

Diffuse cystic lung disease in sickle cell anaemia: a series of 22 cases and a case–control study

Kort et al. Thorax . 2022
Jan;77(1):91-93

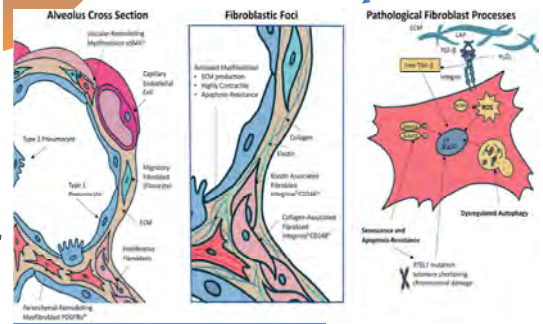


Variable	Number of cases	Results	Number of controls	Results	p value
Age, years, mean±SD	22	37.2±13.4	44	37.1±13.2	Ns
Sex, F/M, n	22	7/15	44	24/20	Ns
Ethnicity	22		43		
Sub-Saharan Africa, n (%)		15 (68.2)		36 (83.2)	Ns
Caribbean, n (%)		7 (32.8)		6 (14)	Ns
Maghreb, n (%)		0 (0)		1 (2.3)	Ns
Tobacco, n (%)	22	4 (18.2)	44	8 (18.2)	Ns
SCD genotype	22		44		
Hemoglobin SS, n (%)		20 (90.9)		39 (88.6)	Ns
Hemoglobin SC, n (%)		2 (9.1)		4 (9.1)	Ns
Hemoglobin Sβ^0-thalassemia, n (%)		0 (0)		1 (2.3)	Ns
Pulmonary hypertension†	22	3 (13.3)	44	1 (2.3)	Ns
FEV_1, L, mean±SD	21	2.23±0.61	40	2.45±0.61	Ns
FEV_1, %, mean±SD*	21	70.2±14.9	40	82.6±15.0	0.003
FVC, L mean±SD	21	2.82±0.75	40	2.93±0.72	Ns
FVC, % mean±SD*	21	74.5±15.7	40	84±16.8	0.01
FEV_1/FVC, %, mean±SD*	21	78.8±5.5	40	83.7±7.4	0.009
FEF 25–75, %, mean±SD*	21	62.6±27.4	40	82.6±27.7	0.006
FEF 25–75<70%, n (%)*	21	13 (61.9)	40	12 (30)	0.03
cDLCO, %, mean±SD	12	64.5±18.5	26	76.6±15.0	Ns

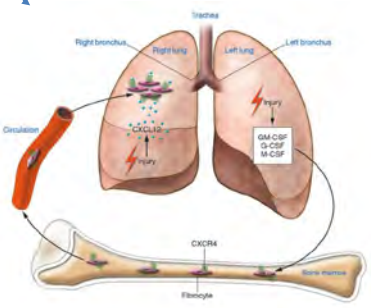
- 22 SCA patients (mean±sd 37±13 yrs) 2006-2019
- 11/22 pts with shortness of breath
- On HRCT, several lungs cysts (up to >1000), ground glass, reticulations, emphysema

Sickle cell chronic lung disease: pathophysiology

Chronic lung injury, hypoxia & inflammation



Wu B. et al Semin Arthritis Rheum 2021 Feb;51(1):310-317.



Strieter RM J. Clin. Invest. **117**:549–556 (2007)

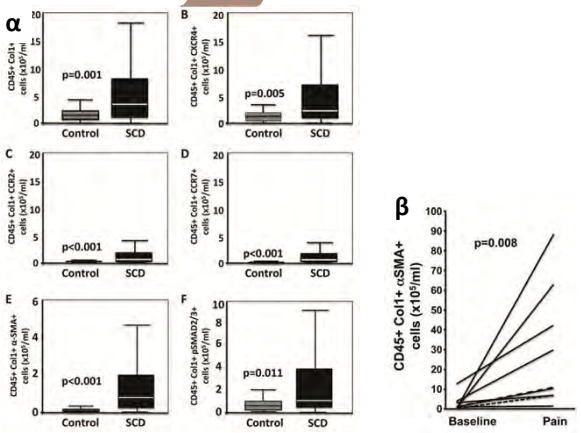
Proliferation of interstitial fibroblast ← Migration of fibrocytes in the lung

Increased extracellular matrix production

Interstitial fibrosis with disruption of the alveolar-capillary membrane and vascular remodeling

Field JJ et al. PLoS One. 2012;7(3):e33702

Sickle cell chronic lung disease: pathophysiology



Circulating fibrocytes higher in SCA pts (n.114) than controls (n.19) **(α) & they** increase during pain crises **(β).**

Field et al J PlosOne PLoS ONE 7(3): e33702 2012

Table 3. Bivariate and multivariable models to demonstrate the association between high fibrocytes and abnormal FEV_1 and FVC

Variable	Odds ratio (95% CI)	χ^2	P
FEV_1			
Univariate			
Fibrocytes	4.408 (1.441-13.484)	6.763	.009
Age	0.960 (0.908-1.016)	2.015	.156
Transfusion in last 120 d	4.278 (1.209-15.134)	5.083	.024
Hemoglobin	0.715 (0.496-1.030)	3.242	.072
WBC	1.142 (0.980-1.332)	2.880	.090
No. of hospitalizations	1.042 (0.949-1.144)	0.750	.386
Smoking history	0.970 (0.332-2.833)	0.032	.955
Fetal hemoglobin	0.990 (0.924-1.060)	0.082	.775
Sex	1.412 (0.478-4.168)	0.390	.532
Asthma	1.747 (0.597-5.114)	1.037	.309
Multivariable			
Fibrocytes	4.462 (1.385-14.376)	6.276	.012
Transfusion in last 120 d	4.352 (1.125-16.837)	4.537	.033
FVC			
Univariate			
Fibrocytes	5.573 (1.655-18.771)	7.688	.006
Age	0.942 (0.882-1.006)	3.212	.073
Hemoglobin	0.713 (0.484-1.051)	2.927	.087
WBC	1.128 (0.967-1.317)	2.344	.126
No. of hospitalizations	0.977 (0.873-1.093)	0.169	.684
Fetal hemoglobin	1.016 (0.947-1.091)	0.204	.652
Smoking	0.530 (0.161-1.742)	1.093	.296
Transfusion in last 120 d	2.557 (0.699-9.357)	2.011	.156
Asthma	1.392 (0.447-4.335)	0.325	.568
Multivariable			
Fibrocytes	5.573 (1.655-18.771)	7.688	.006

High levels circulating fibrocytes (>1.5 cells/ml) associated with 5 times higher risk of FEV_1 & FVC <5th pc in SCA adults (n. 71)

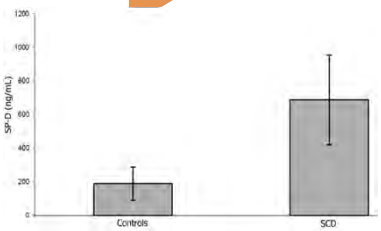
Mehord et al Blood Adv. 2017 Nov 14; 1(24): 2217–2224.

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

Egypt

***Tantawy et al. Pediatr Pulmonol** .2019 May;54(5):610-619*

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



HRCT (Interstitial lung disease grades), *n* (%)	
Grade 0	17 (34)
Grade 1	16 (32)
Grade 2	10 (20)
Grade 3	7 (14)
Pulmonary function tests	
FEV_1	
Mean ± SD	80.3 ± 17.3
Range	55.2-135.8
FVC	
Mean ± SD	83 ± 16.2

Variable	SP-D (ng/mL) Mean ± SD
HRCT (Interstitial lung disease grades)	
Grade 0	506 ± 202.9
Grade 1	612.1 ± 188.7
Grade 2	695.3 ± 201.4
Grade 3	778.8 ± 213.2
Pulmonary function tests	
Normal	592 ± 306.3
Abnormal	781.8 ± 224.9
Type of lung disease, *n* (%)	
Obstructive	547.5 ± 271
Restrictive	996.7 ± 233.8
Mixed	693.6 ± 325.4

Surfactant protein D (SP-D) blood levels associated with restrictive spirometry and ILD features on chest CT

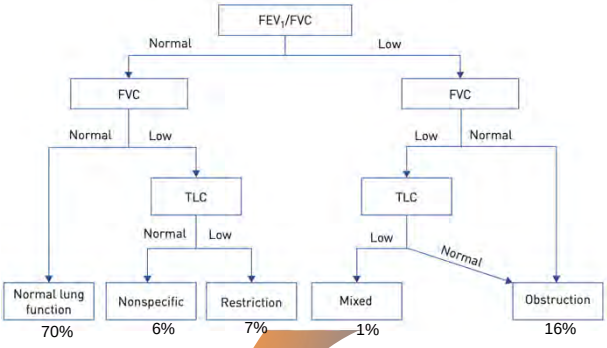
Lung function in children with SCA: high-income countries

***Cohen et al, Annal ATS* 2016** Aug;13(8):1314-23

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

Lung Function Parameter	All (N = 147)	Normal (n = 104)	Obstruction (n = 24)	Restriction (n = 10)	Nonspecific (n = 9)
FEV_1 % predicted	88.3 ± 13.4	93.1 ± 10.4	80.9 ± 13.5	67.0 ± 7.9	75.3 ± 8.5
FVC % predicted	92.8 ± 14.1	96 4 ± 10.9	94.8 ± 14.6	67.2 ± 8.0	74.1 ± 5.2
FEV_1/FVC, actual	0.84 ± 0.06	0.85 ± 0.04	0.76 ± 03	0.88 ± 0.04	0.90 ± 0.06
FEV_1/FVC % predicted	94.9 ± 6.5	96.2 ± 4.7	84.9 ± 3.0	99.5 ± 5.4	101.0 ± 6.2
$FEF_{25-75\%}$ predicted	73.2 ± 21.1	79.6 ± 20.0	49.2 ± 26.7	67.3 ± 15.6	71.5 ± 26.7
BD response ≥ 12.0, n = 143, %	19.6	11.9	41.7	20.0	50.0
RV/TLC ratio	0.33 ± 0.07	0.31 ± 0.07	0.36 ± 0.07	0.34 ± 0.10	0.38 ± 0.06
RV/TLC ratio Z-score††	0.76 ± 1.23	0.56 ± 1.17	1.26 ± 1.14	1.08 ± 1.63	1.84 ± 0.86

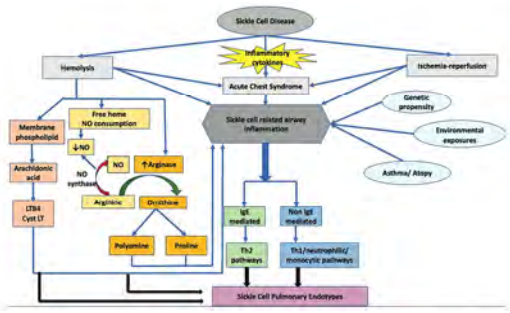
UK - USA



- 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

Why an obstructive LF pattern in SCA?

Airway inflammation



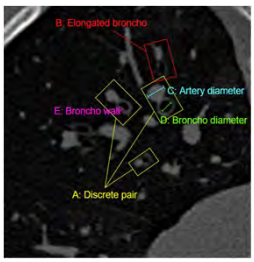
***De et al, Ped Pulmonol*. 2018** Apr;53(4):400-411

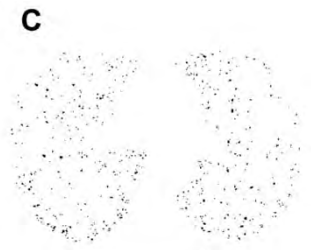
- Asthma in 17-28% of children with SCA *(Boyd, Blood 2006; Strunk, Journ of Ped 2014)*
- Up to 50% of SCA pts with an obstructive LF pattern: no h/o asthma (Arteta et al, *J Pediatr Hematol Oncol* 2013)

Airway compression?

Lunt et al, Thorax 2014; *Aug;69(8):746-51*

- 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)

Anaemia -> hyperdynamic status -> Prominent central vessels & peripheral vascular engorgement -> airways compression?

Lung function in children with SCA: low-middle income countries

Arigliani et al, Thorax 2019. 74 (12):604–606

Arigliani et al, Thorax 2019. 74(12):1154-1160

Sub-Saharan Africa

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

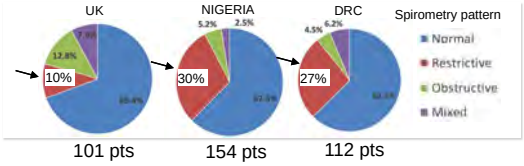
Table 2 Anthropometric and spirometry z-scores in patients aged 6–18 years with sickle cell anaemia (SCA) from the UK and Nigeria (NIG)

	SCA UK	SCA NIG	Mean difference UK–NIG (95% CI; p value)	Controls NIG
N (% male)	101 (51%)	154 (54%)		364 (52%)
Age, years	11.7 (2.7)	11.4 (3.2)	0.3 (−0.5 to 1.0; 0.12)	10.4 (2.4)
zHeight	0.23 (1.25)	−1.77 (1.21)	2.00 (1.68 to 2.30; <0.001)	−0.75 (1.51)
zBMI	0.12 (1.23)	−1.49 (1.08)	1.61 (1.32 to 1.90; <0.001)	−0.62 (1.32)
zFEV$_1$	−0.97 (1.06)	−1.38 (0.96)	0.41 (0.15 to 0.66; 0.01)	−0.35 (0.99)
FEV$_1$%	87.1 (14.2)	81.9 (13.3)	5.1 (1.7 to 8.6; 0.003)	95.2 (13.0)
zFVC	−0.68 (1.06)	−1.21 (0.96)	0.53 (0.28 to 0.78; <0.001)	−0.31 (0.97)
FVC%	91.1 (13.5)	84.3 (12.7)	6.8 (3.3 to 9.8; <0.001)	95.9 (12.4)
zFEV$_1$/FVC	−0.68 (0.97)	−0.47 (0.83)	−0.20 (−0.42 to 0.02; 0.07)	−0.08 (0.88)

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

Table 1 Anthropometric and spirometric z-scores in patients with sickle cell anaemia (SCA) aged 6–18 years from the DR Congo and local controls aged 6–12 years

Index	SCA group DRC	Controls	Mean difference (95% CI) SCA–controls
N (% male)	112 (57 %)	377 (55%)	
Age (years)	11.2 (3.3)	9.5 (1.6)	1.6* (1.2 to 2.1)
Height z-score	−1.16 (1.41)	0.33 (1.11)	−1.50* (−1.75 to −1.25)
BMI z-score	−1.47 (1.07)	−0.20 (1.10)	−1.28* (−1.51 to −1.04)
FEV$_1$ z-score	−1.48 (1.01)	−0.16 (0.79)	−1.33* (−1.51 to −1.15)
FEV$_1$% predicted	80.2 (13.1)	97.9 (10.2)	−17.7%* (−20.0 to −15.3)
FVC z-score	−1.35 (1.03)	−0.09 (0.83)	−1.26* (−1.44 to −1.07)
FVC% predicted	83.0 (13)	98.8 (10.7)	−15.8* (−18.3 to −13.5)
FEV$_1$/FVC z-score	−0.50 (0.80)	−0.17 (0.71)	−0.33** (−0.48 to −0.18)



- Restrictive spirometry: 27-30% of pts in sub-Saharan Africa vs 10% in the UK (p<0.05)
- Malnutrition (zBMI <-2) associated with restrictive spirometry in both Nigerian (adjusted OR 2.3; p 0.03) & Congolese pts (adjusted OR 5.4, p 0.06)

Lung function in children with SCA: low-middle income countries

Al Bitagi et al, Pediatr Pulmonol. 2020 Aug;55(8):2055-2063.

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

	Patient group, n = 139	Control group, n = 123
Age	11.9 ± 4.1	12.1 ± 4
Gender (male %)	84 (60.4%)	71 (57.7%)
Standing height, cm	138 ± 14	143 ± 16
Body weight, kg	31 ± 11.5	42 ± 15
Hemoglobin, g/dL	8.2 ± 2.5	12.8 ± 1.7
Induced sputum IL-6, pg/mL	43.31 ± 4.16	20.4 ± 4.1
FEV1	85.9 ± 13.4	101.4 ± 7.9
FVC	87 ± 12.2	100.6 ± 7.03
FEV1/FVC	91.21 ± 9.28	96.7 ± 2.27
TLC	76.6 ± 18.1	99.4 ± 6.82

Classification based on PFTs	Normal, n (%)	71 (51.1%)
	Obstructive, n (%)	17 (12.2%)
n. 120	Restrictive, n (%)	21 (15.1%)
	Mixed O/R, n (%)	11 (7.9%)

Purohit et al, Indian J Pediatr. 2016 Aug; 83(8):783–786

India

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

Parameter	Cases (n = 99)	Controls (n = 99)	Mean difference (95 % CI)	P value
FEV1 [mean (SD)]	86.79 (11.6)	94.83 (16.1)	−8.04 (−11.97 to −4.10)	<0.001
FVC [mean (SD)]	84.4 (11.5)	91.75 (15.2)	−7.3 (−11.07 to −3.52)	<0.001
FEV1/FVC [mean (SD)]	101.77 (7.6)	99.65 (8.5)	2.12 (−0.13 to 4.38)	0.06

Lung function decline in children with SCA

PRE-HYDROXYUREA

MacLean et al, AJRCCM 2008.
Nov 15;178(10):1055-9

- 312 SCA pts 8-18 years, retrospective data before 1989
- Annual decline in FEV_1 3% pred. & TLC 2.1-2.4% pred.

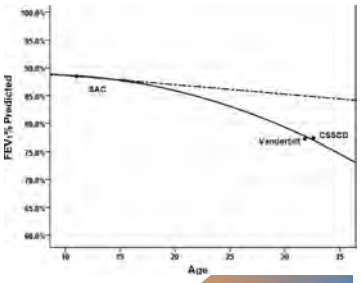
***Lunt et al Ped Pulmonol,* 2016**
Jul;51(7):717-23

- 47 preschool and school-age SCA pts; Prospective FU 10 yrs
- Frequency of Restrictive lung function: baseline 24% -> End of FU: 44%

	Baseline	Follow-up	*P*
SCD children			
FEV_1	90.7 (64.0–117.2)	81.2 (66.4–106.7)	0.0002
VC	97.6 (62.6–116.7)	85.4 (68.7–109.6)	0.0003
$FEF_{25–75}$	91.8 (45.9–144.9)	74.5 (28.9–122.7)	<0.0001
FEV_1/VC	96.2 (69.7–109.4)	95.4 (64.4–108.1)	0.7648
TLC	92.5 (67.6–127.1)	81.6 (61.0–108.3)	<0.0001
RV	101.2 (37.7–212.0)	88.9 (54.8–149.2)	0.0300
RV/TLC	121.2 (73.4–194.3)	113.2 (67.5–221.5)	0.0692

HYDROXYUREA ERA

Willen et al, AJH 2017;
Mar;93(3):408-415



- UK-USA: 194 SCA pts 4-19 years; 2005-2011;
- 33% of pts on hydroxyurea
- Average FU 4 yrs (1.1-6 yrs)
- Annual FEV_1 decline 0.3% pred. (95% CI -0.56 to -0.05)

Hydroxyurea & lung function decline in SCA

Canada

McLaren et al, AJRCCM 2017
Mar 1;195(5):689-691

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

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

	Rate of Change per Year (%)			
	Control (*n* = 75)	Before HU (*n* = 56)	After HU (*n* = 56)	*P* Value
FVC	−0.77 (−0.99 to −0.54)	1.12 (−1.66 to −0.59)	−0.19 (−0.90 to 0.52)	0.04
FEV_1	−1.33 (−1.56 to −1.09)	−1.73 (−2.31 to −1.15)*	−0.60 (−1.21 to 0.01)	0.06
FEV_1/FVC	−0.50 (−0.60 to −0.39)	0.15 (0.05 to 0.26)*	−0.22 (−0.29 to −0.15)*	0.12
$FEF_{25–75\%}$	−2.37 (−2.84 to −1.91)	−3.66 (−4.50 to −2.83)*	−1.47 (−2.41 to −0.53)*	0.06
TLC	−1.13 (−1.33 to −0.92)	−1.38 (−1.88 to −0.87)	−0.42 (−1.06 to 0.23)	0.33
FRC	−1.63 (−1.96 to −1.29)	−1.53 (−2.36 to −0.70)*	−0.72 (−1.69 to 0.26)	0.15

- Slower annual FEV_1 and FVC decline after starting HU

USA

Kotwal et al, Journ Paed Haem Onc, 2022
Aug 1;44(6):e923-e925.

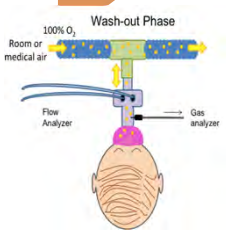
- 62 SCA children on HU vs 30 SCA children without HU
- Spirometry pre & post starting HU (variable interval)

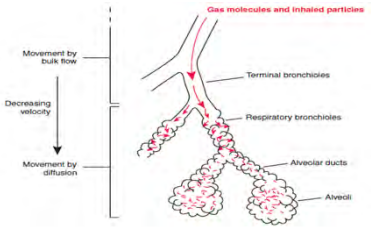
	Hydroxyurea Group (N = 62)	Control Group (N = 30)	*P*
FVC (%predicted)			
First test	90.4 ± 19.7	96.5 ± 19.4	0.16
Second test	97.6 ± 16.5	93.1 ± 19.3	0.26
FVC % change between first and last test	7.2 ± 17.1	−3.4 ± 18.2	0.01
FEV_1 (%predicted)			
First test	88.8 ± 19.0	92.4 ± 18.5	0.39
Second test	93.4 ± 17.1	89.5 ± 17.5	0.30
FEV_1% change between first and last test	4.6 ± 17.0	−3.0 ± 19.2	0.07
FEV_1/FVC ratio			
First test	0.98 ± 0.07	0.96 ± 0.08	0.16
Second test	0.95 ± 0.06	0.96 ± 0.07	0.62
FEV_1/FVC ratio change between first and last test	−0.03 ± 0.08	0.003 ± 0.06	0.06

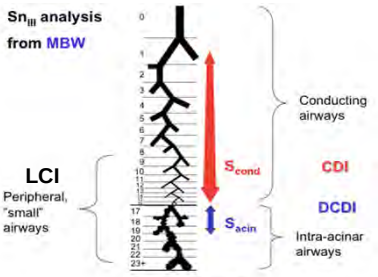
- Spirometry improved in the SCA group on HU (+7% pred.) & declined in the control SCA group (-3%)

How to detect early sickle chronic lung disease?

N_2 Multiple Breath Washout (MBW)







MBW measures ventilation inhomogeneity in the lung depending on:

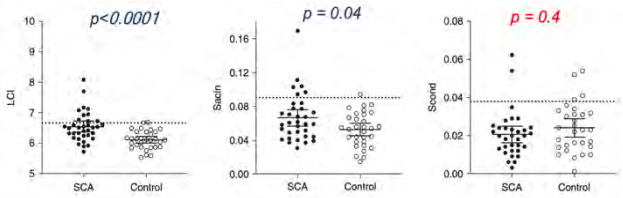
1) Patchy conductive airway disease (*e.g.* early CF): S_{cond} and Lung Clearance Index (LCI)

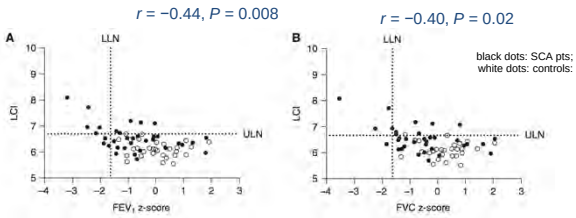
2) Patchy changes in lung compliance or in peripheral lung architecture: S_{acin} and LCI

How to detect early sickle chronic lung disease?

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_{acin} significantly higher in SCA patients than controls
- LCI abnormal in 29% (10/35) of SCA pts

- LCI -> tends to increase for decreasing FEV_1 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 daytime 96.3±3%
- 33% of pts SpO2% <96% & 2.8% <90%

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*

***Halphen et al* 2014** PLoS ONE 2014. 9(5): e97462

- 30 Unselected SCA pts (median age 10.8 – 5 to 17 yrs)
- 50% (15), mean night SpO_2 ≤93%
- Night hypoxemia associated with lower Hb & lung function

	>93% (n = 15)	≤93% (n = 15)	*P* value
Medical history			
Age (yrs)	10.1 (5.7–17.0)	9.1 (6.3–16.8)	0.65
Male gender	3 (20%)	7 (46.7%)	0.12
BMI (Kg/m²)	16.3 (13.3–19.6)	15.7 (13.9–21.4)	0.60
Enlarged tonsils	6 (42.9%)	7 (46.7%)	0.84
N of VOC in the past year	0 (0–7)	0 (0–2)	0.75
Hydroxycarbamide treatment	4 (26.7%)	2 (13.3%)	0.65
History of at least one ACS episode	5 (33.3%)	6 (40%)	0.70
Abnormal lung function test	**2 (13.3%)**	**10 (66.7%)**	**0.003**
SpO_2 values			
Daytime SpO_2	**98 (89–100)**	**95 (92–99)**	**0.03**
Postexercise SpO_2	**97 (79–100)**	**92 (72–100)**	**0.04**
>10% of sleep time with SpO_2<90%	**1 (6.7%)**	**10 (66.7%)**	**0.0007**
Laboratory tests			
Hemoglobin (g/dL)	**8.4 (6.9–10.6)**	**7.5 (5.2–9.5)**	**0.006**
Leukocytes(Giga/L)	9.4 (5.8–16)	10.8 (5.7–21.5)	0.19
Reticulocyte count (Giga/L)	220 (43–276)	246 (121–443)	0.07
Lactate dehydrogenase (IU/L)	1196 (901–1683)	1456 (849–1893)	0.66
Total bilirubin (µmol/L)	36(17–130)	55 (22–163)	0.12
Aspartate aminotransferase (IU/L)	51 (39–132)	63 (48–93)	0.10
Fetal hemoglobin (%)	**12.4 (2.6–28)**	**5.4 (0.8–11.7)**	**0.01**
Creatinine (µmol/L)	36 (20–43)	36 (22–51)	0.91
6 MWT distance (% predicted distance)	86 (46–120)	87 (50–119)	0.66

Chronic hypoxaemia in children with SCA

- Pulse oximeter can over-estimate arterial oxygen saturation in black people with SCA ***Caboot,* Paediatr Respir Rev 2014** Mar;15(1):17-23

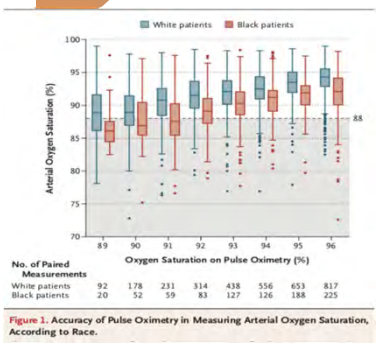


Figure 1. Accuracy of Pulse Oximetry in Measuring Arterial Oxygen Saturation, According to Race.

***Sjoding M et al NEJM 2020** Dec 383;25*

>10,000 adults in-patients on O_2 - ITU

- 11.7% of Black individuals with SpO2 92-96% had arterial SaO_2 <88% vs 3.6% Whites

Arterial gas or arterialized earlobe gas with CO-oximetry if 'surprisingly' normal/mildly low SpO_2 (***Arigliani et al*, BMJ Paediatr Open. 2020** *4(1): e000690*)

Chronic hypoxaemia in SCA: why?

Mechanism of hypoxia	Causes in SCD
Hypoventilation	SDB (OSA, upper airway obstruction) Thoracic splinting due to chronic pain Restrictive pulmonary disease Reduced chest excursion due to hepatomegaly Central hypoventilation (eg, due to excessive use of narcotics)
Diffusion impairment	SCD-associated interstitial lung fibrosis PH Pulmonary vascular disease
Shunt	Intracardiac shunt (eg, ventriculoseptal defect) Extracardiac shunt Arterial-venous malformations Intrapulmonary shunt (eg, due to consolidation or atelectasis resulting in decreased perfusion to affected area)
Ventilation-perfusion inequality	Chronic VTE ACS Plastic bronchitis Obstructive lung disease without asthma Chronic airway inflammation due to asthma

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;

- **Chronic VTE**: 17-25% prevalence in adult studies *(Naik, Am J Med 2013; Brunson, BJH 2013)*

Intrapulmonary shunt

***Hambley et al* Haematologica 2019**;104(1):e1–3.

- 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 SpO_2 <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)

Table II. Prevalence of potential right-to-left shunt detected in SCA + stroke and control subjects.

Method of shunt detection	SCA+Stroke *n*/*N* (%)	Control *n*/*N* (%)	P value*
2D Imaging	3/139 (2·2%)	0/122 (0%)	0·250†
Colour doppler	9/139 (6·5%)	8/122 (6·6%)	0·978
Contrast injection without Valsalva	22/146 (15·1%)	19/122 (15·6%)	0·969
Contrast injection with Valsalva	24/145 (16·6%)	19/118 (16·1%)	0·922
Potential intracardiac shunting:	32/147 (21·8%)	23/123 (18·7%)	0·533
Potential intrapulmonary shunting	35/147 (23·8%)	7/123 (5·7%)	<0·001
'Late Bubbles' only			
Any Potential Shunting (Intracardiac or Intrapulmonary)	67/147 (45·6%)	29/123 (23·6%)	<0·001

- Intrapulmonary shunt more frequent in SCA pts with stroke

Chronic hypoxaemia in SCA: diagnostic work-up

Mechanism of hypoxia	Causes in SCD
Hypoventilation	SDB (OSA, upper airway obstruction) Thoracic splinting due to chronic pain Restrictive pulmonary disease Reduced chest excursion due to hepatomegaly Central hypoventilation (eg, due to excessive use of narcotics)
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Shunt	Intracardiac shunt (eg, ventriculoseptal defect) Extracardiac shunt Arterial-venous malformations Intrapulmonary shunt (eg, due to consolidation or atelectasis resulting in decreased perfusion to affected area)
Ventilation-perfusion inequality	Chronic VTE ACS Plastic bronchitis Obstructive lung disease without asthma Chronic airway inflammation due to asthma

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

→ CR poly (or night oximetry) if daytime SpO_2 <95% of SDB symptoms

→ Lung function:
- If restrictive spirometry -> body pleth & TLco (be mindful of refence 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

Arigliani et al, Eur Respir Rev 2020; 29: 200054

Chronic hypoxaemia in SCA: management

Hydroxyurea

Guidelines for the use of hydroxycarbamide in children and adults with sickle cell disease ***Qureshi et al BJH 2018****, 181, 460–475*

A British Society for Haematology Guideline

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

Van Geyzel, Arigliani et al Arch Dis Child 2020 *Jun;105(6):575-579*

- 21 SCA patients – Median age 9 (range 1-18) daytime SpO_2 & night oximetry pre & after starting HU (median 9 months later, IQR 3.5 – 15 m.)

Table 1 Changes in oxygen saturation parameters and haematological indices with hydroxyurea

	Patients with comparable data (n)	Before HU median (IQR)	After HU median (IQR)	P value
Mean overnight SpO_2 (%)	21	93 (88–97)	95 (93–98)	0.01
Nadir overnight SpO_2 (%)	21	84 (77–89)	87 (83–91)	0.009
3% ODI overnight (events/hour)	18	3.0 (1.5–5.2)	2.8 (1.1–4.6)	0.08
Spot daytime SpO_2 (%)	32	93 (91–97)	96 (94–98)	0.001
Haemoglobin (g/L)	42	76.0 (69.5–86.5)	83.0 (72.7–87.7)	0.04
Fetal haemoglobin (%)	37	6.1 (3.7–12.9)	8.8 (6.0–16.0)	<0.001
Neutrophil count (10^9/L)	42	5.7 (4.3–6.8)	5.4 (3.9–6.2)	0.1

Home oxygen

Home Oxygen Therapy for Children
An Official American Thoracic Society Clinical Practice Guideline
Hayes et al AJRCCM 2019 Feb 1;199(3):e5-e23

Home-O2 therapy (HOT) recommended for SCA children if:

- 3 separate daytime SpO_2 <90%

- >5% TST SpO_2 <90%

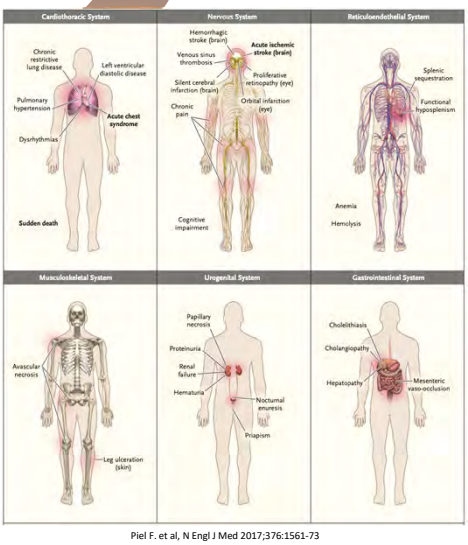
***Liguoro , Arigliani et al Arch Dis Child* 2021**; **106**:258–262.

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

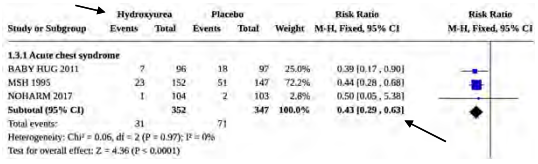
At 1 yr FU:

- Home O_2 safe
- sleep study on O_2 supplementation normalized
- Trend to lower rate of hospital admissions for pain crises
- Improvements in AST & LDH (haemolysis markers)

Future perspective: new drugs and SCA chronic lung disease



Piel F. et al, N Engl J Med 2017;376:1561-73



A.E. Rankine-Mullings et al Cochrane Database Syst Re. 2022 Sep 1;9(9):CD002202.

Medication	Mechanism of Action	Early Stages	Phase 2	Phase 3	Standard of care
Hydroxyurea	Targeting Hb S polymerization: increasing Hb F				
*L-Glutamine (Endari) – FDA approved July 2017	Targeting vasoocclusion: Increase NAD and NADH and decrease adhesion				
**Crizanlizumab (Adakveo) – FDA approved November 2019	Targeting vasoocclusion: P-selectin inhibition				
**Voxelotor/ GBT440 (Oxbryta) – FDA approved November 2019	Targeting Hb S polymerization: increasing oxygen affinity				
HLA-matched transplant	Modify the genotype				
Haploidentical transplant	Modify the genotype				
***Rivipansel	Targeting vasoocclusion: Pan-selectin inhibition				
Sevuparin	Targeting vasoocclusion: Pan-selectin inhibition				
N-Acetylcisteine	Targeting inflammation: Antioxidant effect				
IMR-687	Targeting Hb S polymerization: inhibiting PDE9				
Sanguinate	Targeting Hb S polymerization: carbon monoxide delivery				
CRISPR-Cas9 modified CD34+	Modify the genotype				
Gamma-globin gene transfer	Modify the genotype				
Lentiglobin bb305	Modify the genotype				
Lentivirus shRNA targeting BCL11a	Modify the genotype				

U S A

U K

Salinas-Cisneros et al Front. Physiol. 11:435. doi: 10.3389/fphys.2020.00435

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)*