Improving Lung Health of Patients with Sickle Cell Disease (SCD): Alabama Perspective

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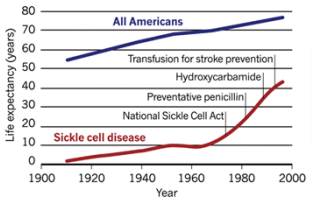
- No conflict of interest related to the presentation

Objectives

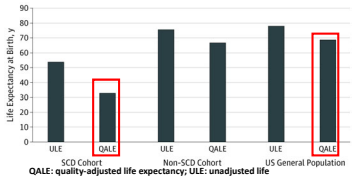
- Review the pulmonary complications of sickle cell disease (SCD)
- Discuss the current state of clinical care and research of SCD related lung diseases in the state of Alabama
- Listen to personal perspective of living with SCD and its pulmonary complications
- Illustrate the role of pulmonary service in SCD care

Sickle Cell Disease (SCD)

- SCD most common life-shortening genetic blood disease
- Point mutation of globin gene (GAG to GTG → glutamine to valine → HbA to HbS)
- SCD >100,000 Americans, 20 million worldwide
- 1/365 African Americans have SCD and 1/13 have SC Trait
- SCD is diagnosed at birth with newborn screening



Pathology (January 2017) 49(1)

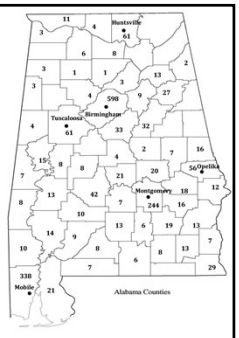


QALE: quality-adjusted life expectancy; ULE: unadjusted life expectancy.

JAMA Netw Open. 2019;2(11)

SCD in Alabama

States	Decade 1 (Jan 1, 1991–Dec 31, 2000) Births	S/S	S/C	S/A	Decade 2 (Jan 1 2001–Dec 31, 2010) Births	S/S	S/C	S/A	Totals (Jan 1, 1991–Dec 31, 2010) Births	S/S	S/C	S/A
Alabama	608,658	0.672	0.327	0.089	603,370	0.502	0.267	0.076	1,212,028	0.587	0.297	0.083
Alaska					78,881	0.076	0.013	0.000	78,881	0.076	0.013	0.000
Arizona	744,355	0.079	0.028	0.003	942,747	0.088	0.029	0.010	1,687,102	0.084	0.028	0.007
Arkansas	347,456	0.426	0.256	0.032	382,133	0.398	0.217	0.010	729,589	0.411	0.236	0.021
California	5,556,877	0.124	0.058	0.017	5,417,932	0.088	0.049	0.028	10,974,809	0.107	0.053	0.022
Colorado	572,543	0.042	0.028	0.016	691,931	0.087	0.030	0.012	1,264,474	0.066	0.029	0.013
Connecticut	450,760	0.253	0.142	0.029	417,425	0.283	0.184	0.067	868,185	0.267	0.162	0.047
Delaware	111,542	0.403	0.251	0.027	120,710	0.480	0.257	0.066	232,252	0.443	0.254	0.047
District of Columbia[1]	169,169	1.413	0.786	0.142	103,183	1.318	0.775	0.107	272,352	1.377	0.782	0.129
Florida[2]	1,598,549	0.525	0.279	0.115	2,213,751	0.545	0.340	0.079	4,152,300	0.535	0.322	0.094
Georgia[3]	291,967	0.596	0.240	0.021	1,417,732	0.667	0.339	0.095	1,709,699	0.655	0.322	0.092
Hawaii[4]	52,360	0.038	0.038	0.000	184,422	0.022	0.016	0.000	236,782	0.025	0.021	0.000
Idaho[5]					155,124	0.000	0.006	0.006	155,124	0.000	0.006	0.006
Illinois	1,833,397	0.463	0.238	0.055	1,748,391	0.313	0.152	0.032	3,581,788	0.390	0.196	0.044
Indiana	843,890	0.211	0.108	0.024	876,526	0.224	0.103	0.031	1,720,416	0.217	0.105	0.027
Iowa	378,283	0.048	0.029	0.021	391,943	0.056	0.015	0.020	770,226	0.052	0.022	0.021
Kansas[6]	275,589	0.138	0.073	0.083	411,781	0.124	0.068	0.010	687,370	0.129	0.070	0.039
Kentucky[7]	313,795	0.115	0.041	0.003	541,304	0.087	0.063	0.000	855,095	0.097	0.055	0.001
Louisiana[8]	608,570	0.817	0.391	0.048	644,606	0.683	0.360	0.127	1,253,176	0.748	0.375	0.089
Maine[9]					129,178	0.023	0.008	0.000	129,178	0.023	0.008	0.000
Maryland	689,363	0.628	0.315	0.087	718,002	0.721	0.354	0.113	1,407,365	0.674	0.335	0.100
Massachusetts	840,895	0.222	0.130	0.013	785,953	0.332	0.146	0.003	1,626,848	0.275	0.138	0.008
Michigan	1,343,489	0.387	0.218	0.022	1,246,254	0.260	0.140	0.059	2,609,743	0.326	0.180	0.040
Minnesota	650,602	0.092	0.043	0.000	705,026	0.159	0.057	0.009	1,355,628	0.127	0.050	0.004
Mississippi	416,095	0.865	0.476	0.142	421,378	0.752	0.498	0.195	837,473	0.808	0.487	0.168
Missouri	776,669	0.349	0.174	0.035	793,604	0.296	0.174	0.030	1,570,273	0.322	0.174	0.032
Montana[10]					90,496	0.022	0.000	0.000	90,496	0.022	0.000	0.000
Nebraska[11]	116,286	0.086	0.026	0.000	264,034	0.098	0.061	0.015	380,320	0.095	0.050	0.011
Nevada	252,212	0.222	0.063	0.004	360,734	0.166	0.091	0.003	612,946	0.189	0.080	0.003
New Hampshire[12]					63,368	0.000	0.032	0.000	63,368	0.000	0.032	0.000
New Jersey	1,132,035	0.433	0.216	0.049	1,106,869	0.380	0.211	0.051	2,238,904	0.407	0.213	0.050
New Mexico[13]	139,360	0.014	0.000	0.000	281,724	0.018	0.000	0.000	421,084	0.017	0.000	0.000

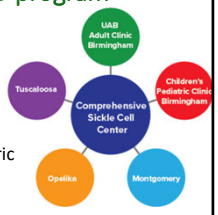


Semin Perinatol. 2015;39(3):238-251

J Health Care Poor Underserved. 2016 ; 27(1): 280–292

UAB/Children's of Alabama (CoA) SCD program

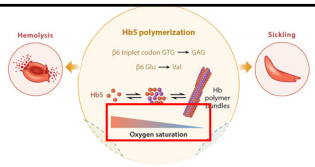
- UAB Comprehensive Sickle Cell Center
- Established in 1995
- Within 5 years, number of patients doubled, and mortality decreased by 90%
- There are >1,200 children followed by the pediatric program



https://www.uab.edu/medicine/sicklecell/about

UAB/CoA Pediatric SCD Pulmonary Program

- Established in 2017
- **Clinical:**
  - Pulmonary SCD clinic 2/month
  - Inpatient consult for (Acute Chest Syndrome (ACS)
  - ACS clinical protocol
  - Pediatric Pulmonary Hypertension (PHTN) program
- **Research:**
  - Clinical (collaboration with MS, GA, LA, FL, and NC)
  - Laboratory (basic and translational)



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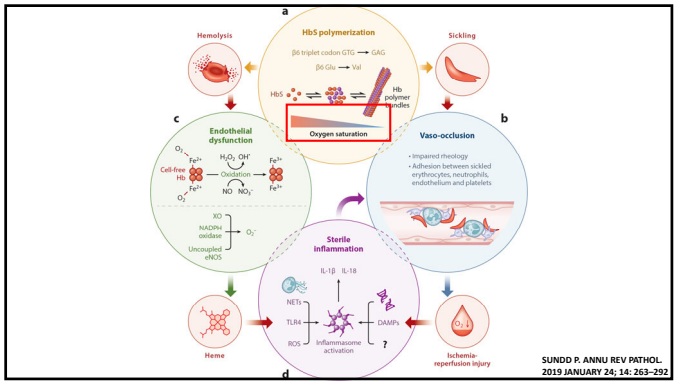

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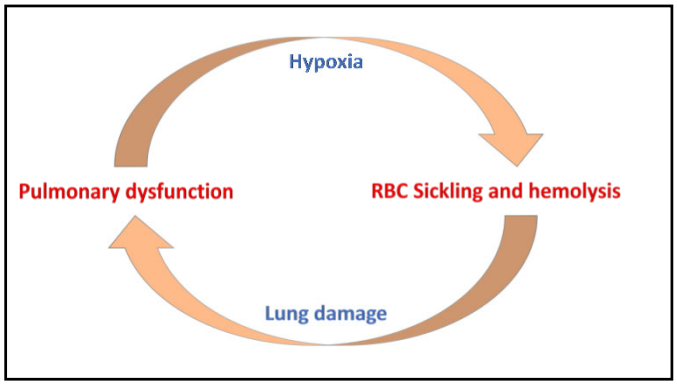
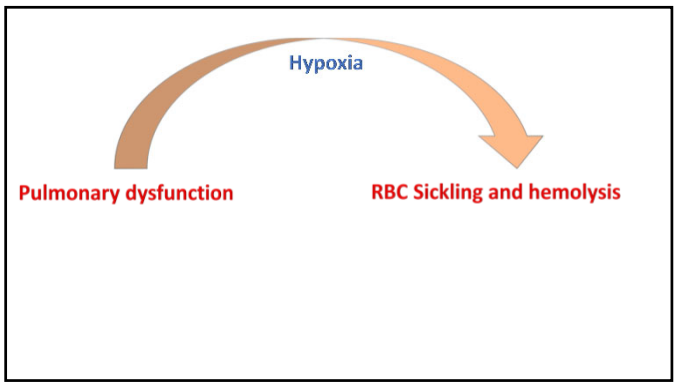
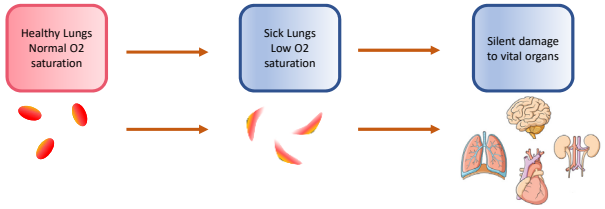


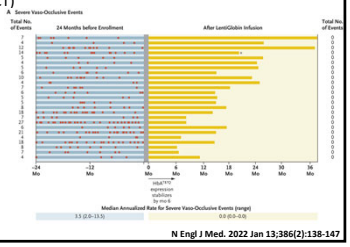


Effects of lung health on SCD

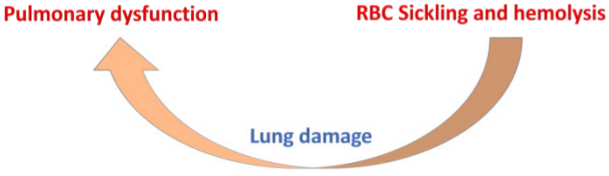
- Pulmonary dysfunction → impaired oxygenation → worse sickling and hemolysis → progressive end organ injury (lung, kidney, pain, CNS, etc)



- Curative therapies:
  - Hematopoietic stem cell transplant (HSCT)
  - Gene therapy
- Goal → to preserve life & organ function

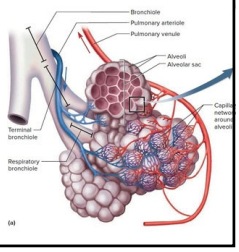


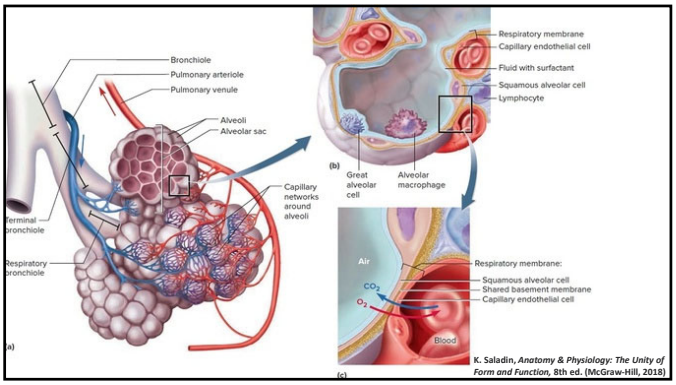
N Engl J Med. 2022 Jan 13;386(2):138-147



Effects of SCD on lung health

- Lungs get 100%+ of Cardiac Output (5-6L/min at rest, and up to 35L/min during exercise)
- Gas exchange surface area is 140 m^2 and extremely thin (0.2-0.6 µm)
- Sickled RBCs and hemolysis toxic products continuously affects pulmonary endothelium, interstitial tissues, and epithelium





K. Saladin, *Anatomy & Physiology: The Unity of Form and Function*, 8th ed. (McGraw-Hill, 2018)

State of research of SCD pulm complications

CLINICAL GUIDELINES

blood advances

Conclusions: Most recommendations were conditional due to a paucity of direct, high-quality evidence for outcomes of interest. Future research was identified, including the need for prospective studies to better understand the natural history of cardiopulmonary and renal disease, their relationship to patient-important outcomes, and optimal management.

An Official American Thoracic Society Clinical Practice Guideline: Diagnosis, Risk Stratification, and Management of Pulmonary Hypertension of Sickle Cell Disease

(weak recommendation, low-quality evidence).

Table. Comparison of the Financial Support vs Need of 3 Prevalent Rare Genetic Diseases in the US

Genetic disease	No. of persons affected	No. of specialty centers	National registry and surveillance system status	Federal funding and expenditures per year
Sickle cell disease	100 000	30 Recognized by the NASCC[a]	To date, no national registry. In 2021, the Sickle Cell Data Collection program, a CDC-funded surveillance system, was established in 11 states.	Federal funding for research: $812 per patient.[9] Foundations/nonprofit expenditures: $102 per person.[b]
Cystic fibrosis	30 000	280 Accredited by the CFF	In 1986, a national CFF patient registry was established with records for 81%-84% of patients.[10] To date, no national surveillance system.	Federal funding for research: $2807 per person.[9] CFF expenditures: $7690 per person.[b]
Hemophilia	30 000	140 Federally recognized HTCs	In 2011, Community Counts, a combined registry and surveillance system, was established with federal and private funding and includes HTC population profiles and the RBDSMR.	Federal funding for clinical care[c]: $35 000 per center. The 340B program also supports >90% of HTC staff.[11]

- **Underrepresentation of pediatric pulmonologists in care and research of SCD pulmonary complications**
- **Supporting SCD research and clinical care can improve health and racial equity**

JAMA Health Forum. 2021;2(10):e213467

Pulmonary complications of SCD

- **Acute Chest Syndrome (ACS)**
- **Sleep-disordered breathing (SDB) and hypoxemia**
- **Asthma and pulmonary function abnormalities**
- **Pulmonary hypertension (PHTN)**

Pulmonary complications of SCD

- **Acute Chest Syndrome (ACS)**
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- **Pulmonary hypertension (PHTN)**

Acute Chest Syndrome

- Most common cause of death in children with SCD
- Peaks 2-4 years
- Half of SCD patients have at least 1 episode of ACS, and most of them develop further episodes
- Children with Hb-SS and S-beta^0 admitted for ACS <4 years have 90% risk of recurrence of ACS
- Half of ACS cases develop during the admission for vaso-occlusive crisis (VOC)

N Engl J Med. 2000;342(25):1855
Pediatr Allergy Immunol Pulmonol. 2017 Dec 1; 30(4): 191–201
UpToDate, Post TW (Ed), UpToDate, Waltham, MA
Am J Hematol. 2015 May;90(5):371-5

ACS diagnosis

- High level of suspicion in the ED and after admission
- Definition: New lung infiltrate on CXR (OR Hypoxemia SpO_2 <95% or 3% below the patient's baseline) + any of the acute respiratory symptoms (fever, cough, wheezing, chest pain, tachypnea)
- Physical exam: vital signs, O_2 saturation (continuous pulse oximetry), sites of pain, cardiac and respiratory exam
- Workup: CXR (**AP and Lateral**), CBC, type and cross match, HbS%, cultures, metabolic panel, and others (COVID, CRP, ABG, VRP, CTA, EKG, etc..)

Acute Chest Syndrome

- LS is a 9 yo F with HbSS, h/o recurrent ACS, and asthma
- 2 days of cough, congestion, SOB, low grade fever, and chest pain

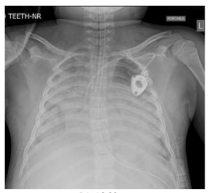

D-90


D0: 12:00


D1: 10:00


D1: 14:00

Acute Chest Syndrome



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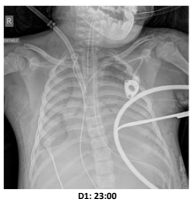
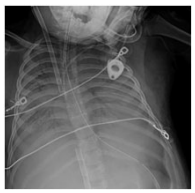

D1: 23:00


D25: 02:00

Risk factors for ACS

- Low **HbF** and high **HbS** concentration
- Severe genotypes (**Hb-SS and S-beta^0**) and less frequent in HbSC and S-beta$^+$
- High steady state **WBC** count
- History of **asthma** (RR 1.60; 95% CI 1.03-2.74)
- **Tobacco smoke** exposure (RR 1.73, 95% CI 1.09-2.74)
- Other factors:
  - Surgery
  - Chronic hypoxemia
  - Previous ACS
  - Winter months
  - Opioid use → hypoventilation

Blood 1994; 84:643
Clin Pulm Med 2004; 11:369
Acad Emerg Med 2012; 19:664

ACS Triggers

- National Acute Chest Syndrome Study Group (NACSSG) 517 episodes of ACS in children:
- **46% → unknown**
- 35% due to infections: (11% viral, 9% mycoplasma, 9% chlamydia, and 4% bacterial)
- Asthma
- Fat embolism and pulmonary embolism

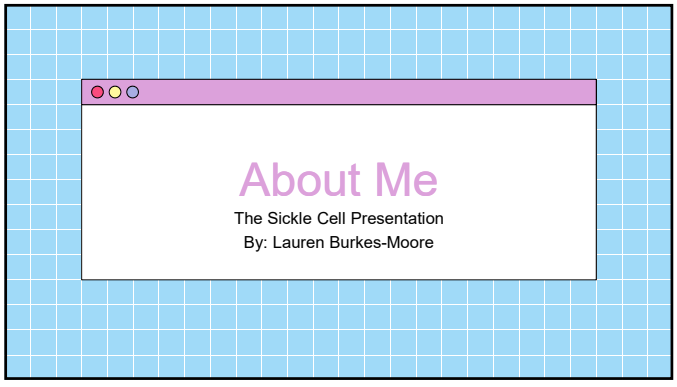
N Engl J Med. 2000;342(25):1855

ACS presentation

- NACSSG:
  - **Chest pain – 41%**
  - **Shortness of breath – 36%**
  - **Pain in arms and legs – 30%**
  - **Rib and sternal pain – 18 %**
  - Neurologic findings – 8%
- Cooperative Study of Sickle Cell Disease (CSSCD):
  - Fever – 85%
  - **Chest pain – 41%**
  - Multilobe infiltrates – 24%
  - **Shortness of breath – 20%**

N Engl J Med. 2000;342(25):1855
Blood 1994; 84:643.

Living with SCD



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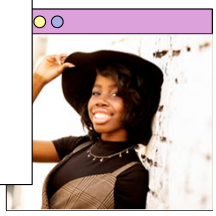
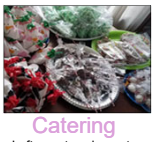
ABOUT ME

Hello, my name is Lauren, and I am 19 year old that loves to bake, cook, draw, anything that involves my hands really. Currently I attend the University of Montevallo with a Nutrition Major.



ABOUT ME



Catering

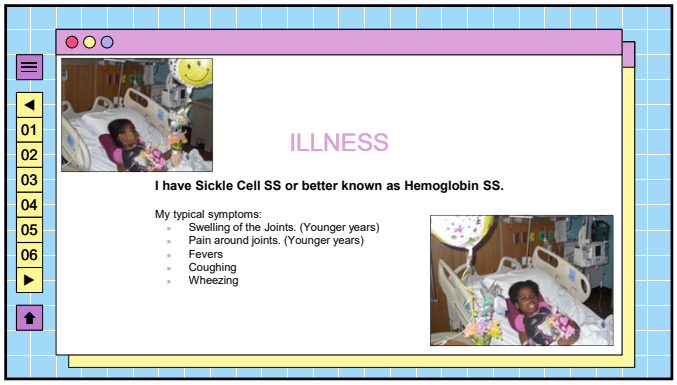
I often catered events and parties ever since I was young.

Baking

Sweets were definitely my specialty, like cakes and cookies.

Culinary

I took multiple baking and pastry classes as well.


01
02
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06
ILLNESS
I have Sickle Cell SS or better known as Hemoglobin SS.
My typical symptoms:
Swelling of the Joints. (Younger years)
Pain around joints. (Younger years)
Fevers
Coughing
Wheezing


01
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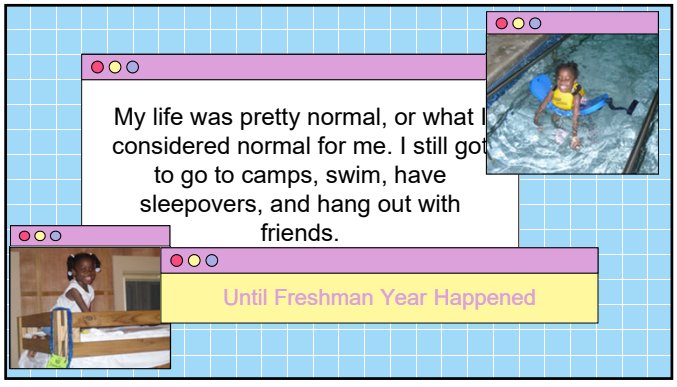
MY LIFE WITH SCD


My life was pretty normal, or what I considered normal for me. I still got to go to camps, swim, have sleepovers, and hang out with friends.
Until Freshman Year Happened

YOUTH & CURRENT LIFE WITH SCD

Fall 2017
Freshman year of highschool

Thanksgiving
Thanksgiving Break, and then a list of things happened.

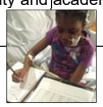
Next 72 Hrs
I was in a medically induced coma and was put on a ventilator.

Learning Steps

I basically had to learn everything over again. Walking, talking, doing math, even drawing had became significantly difficult for me.

YOUTH & CURRENT LIFE WITH SCD

Early 2018
I was in the hospital for a total of three months. I worked on regaining my mobility and academics.



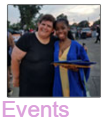
Fall 2018
By fall of 2018 my trach was removed but I had received a port and started to receive monthly transfusions.

MOVING FORWARD

School

I graduated from high school and received multiple leadership and academic scholarships.

01



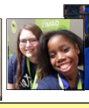
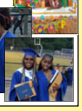



02

Events

Through Magic Moments I was able to go to New York City for week.



03

Friends

Throughout, all of that experience I made friends that stayed by my side.

MY GOALS

Main Goal

- My own culinary business.
- Becoming a Nutritionist

Minor Goals

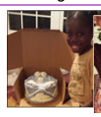
- Achieving a few Internships




Interests



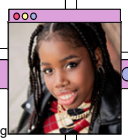
Baking Piano Art



THANK YOU NOTE

MOM

Thank you Mom for always supporting me and being there when I needed you the most.



DOC'S & NURSES

Thank you for aiding me and helping me get this far in life when many thought I wouldn't make it.

DR. SAADOON

Thank you Dr. Saadoon for giving me this GREAT opportunity!

AUDIENCE

Thank you for taking the time to listen to my story and here my situation with SCD.

THANK YOU!

By: Lauren Burkes-Moore

ACS management

- **Analgesia:** early adequate pain control may reduce hypoventilation
- **Respiratory support:**
  - O_2 to maintain saturation ≥95%
  - Incentive spirometry and other RT interventions (positive expiratory pressure (PEP), bubbles, VEST, etc)
  - Bronchodilators (scheduled albuterol): in patients with wheezing, h/o asthma (reduces LOS by 18%), and progressive ACS — Clin Pediatr (Phila). 2018;57(14):1630
  - In severe cases → non-invasive ventilation, invasive ventilation, and ECMO — Blood. 1993;81(12):3422
- **Antibiotics:** empiric coverage including atypical bacteria (ceftriaxone and azithromycin). Vancomycin for severe ACS — Pediatrics. 2003;112(1 Pt 1):87

Blood Adv. 2019 Dec 10;3(23):3867-3897

ACS management

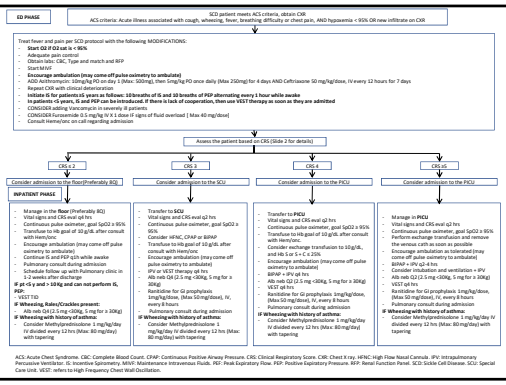
- **Fluids:** dehydration → hyperviscosity. Hypervolemia → pulmonary edema → prolonged hospitalization. Hypotonic fluid of 1-1.5 MIVF first 24-48 hrs — Br J Haematol. 2021;194(5):899
- **Transfusion:** Simple Tx: mild ACS and hypoxemia, low Hgb and declining, and while preparing for exchange transfusion. Exchange Tx: Severe ACS, h/o severe ACS with progression, significant hypoxemia (sat ≤85%), and progressive ACS. — Pediatr Blood Cancer. 2009;53(6):1060
- **No targeted therapy**

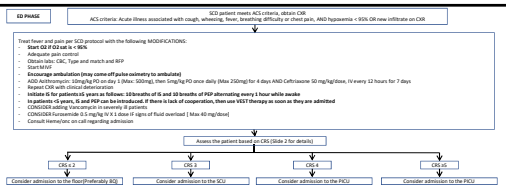
Blood Adv. 2019 Dec 10;3(23):3867-3897

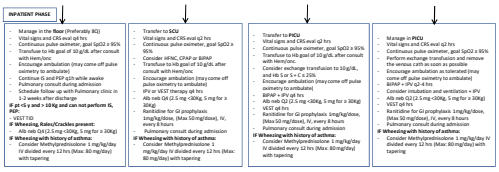
ACS clinical pathway

- Standardized protocol → improved the outcomes of ACS (LOS, exchange transfusion, cost per admission, less progression to severe ACS, etc)
  - Broad definition of ACS to include hypoxia as a major criterion (in addition to new lung infiltrate)
  - Early initiation of respiratory therapy and hematology interventions
  - Respiratory score-based escalation of care

Pediatrics. 2011;127(2):e480
Pediatr Blood Cancer. 2011;56(2):262.

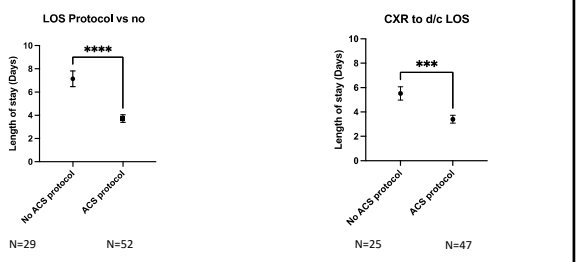






Assess	Clinical Respiratory Score (CRS)		
	0	1	2
Respiratory rate	RR: Age < 1 year: LESS than 40 RR: Age 1-4 years: LESS than 35 RR: Age 5-8 years: LESS than 30 RR: Age 9-12 years: LESS than 26 RR: Age 13 years or older: LESS than 23	RR: Age < 1 year: 40-49 RR: Age 1-4 years: 35-39 RR: Age 5-8 years: 31-35 RR: Age 9-12 years: 26-30 RR: Age 13+ years: 24-27	RR: Age < 1 year: greater than 50 RR: Age 1-4 years: greater than 40 RR: Age 5-8 years: greater than 36 RR: Age 9-12 years: greater than 30 RR: Age 13+ years: greater than 28
Auscultation	Good air movement, scattered wheezing (only expiratory), loose crackles	Decreased air movement, inspiratory and expiratory wheezes	Diminished or absent breath sounds, severe wheezing, or marked prolonged expiration
Use of accessory muscles	none	Mild - moderate intercostal retractions	Severe intercostal and substernal retractions, suprasternal retractions and nasal flaring
Mental status	Normal to mildly irritable	Irritable, agitated, restless	Lethargic
RA oxygen saturation, %	>95	90–95	<90

Add the CRS score from each of the five assessments to obtain the overall CRS score for the patient which is between 0-10



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Cl_2 induced ACS (Model 1)

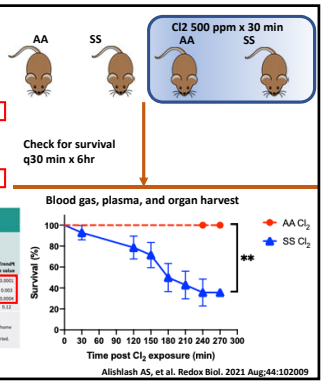


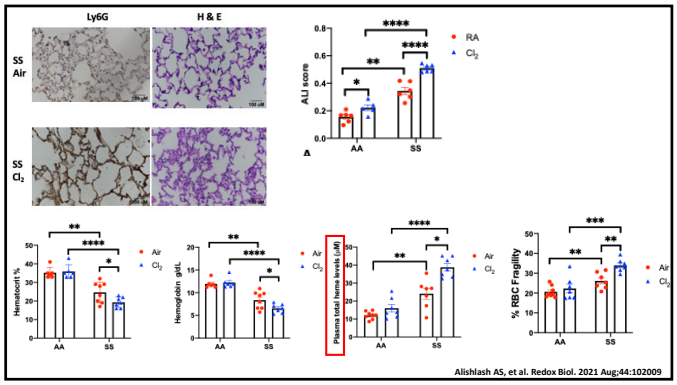
Table 3: Health outcomes in children at 3 years of age per interquartile range increase in the Frequency of Use Score for household use of cleaning products*†

	OR (95% CI)							
	Overall sample population (IQR = 13 points) n = 3922		Boys (IQR = 14 points) n = 1947		Girls (IQR = 13 points) n = 975		Sex‡ FUS p value	
Outcome phenotype	Unadj.	Adj.	Unadj.	Adj.	Unadj.	Adj.	Unadj.	Adj.
Recurrent wheeze	1.40 (1.20–1.73)	1.35 (1.11–1.64)	1.27 (0.97–1.66)	1.17 (0.89–1.55)	1.78 (1.33–2.38)	1.66 (1.22–2.25)	0.07	0.03
Recurrent wheeze and atopy	1.65 (1.15–2.35)	1.49 (1.02–2.16)	1.37 (0.81–2.29)	1.19 (0.96–1.95)	2.18 (1.26–3.66)	2.14 (1.17–3.86)	0.18	0.003
Asthma diagnosis	1.44 (1.16–1.78)	1.37 (1.09–1.70)	1.36 (1.00–1.85)	1.32 (0.96–1.81)	1.60 (1.14–2.23)	1.48 (1.03–2.09)	0.40	0.52
Atopy	1.33 (0.96–1.85)	1.14 (0.90–1.35)	1.33 (0.82–1.29)	1.11 (0.87–1.41)	1.33 (0.94–1.92)	1.17 (0.90–1.50)	0.34	0.29

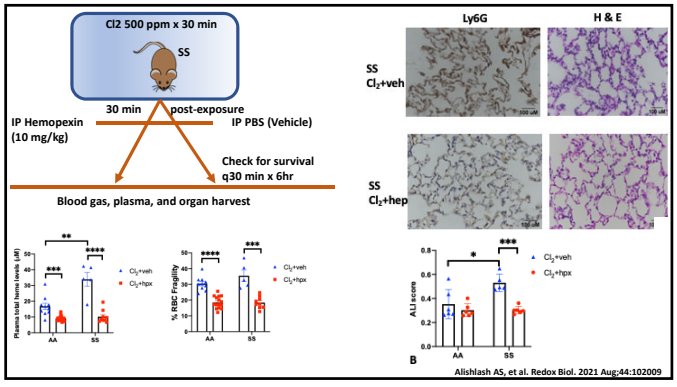
Note: Adj. = adjusted, CI = confidence interval, FUS = Frequency of Use Score, IQR = interquartile range increase, OR = odds ratio, Unadj. = unadjusted.
*As derived all values using multivariable logistic regression models.
†Models were adjusted for prenatal or early-life exposure to tobacco smoke, sex, child's ethnicity, parental asthma history, household income, city/location, visible mould in the home and pet ownership.
‡For the sex stratified analysis, we adjusted for all covariates except sex. The p value of the interaction term when included in the regression model for the overall sample is reported.
§We used a 1-sided Cochran-Armitage test (unadjusted) to evaluate increasing trend, by continuous FUS score for each health outcome.

Am J Respir Crit Care Med Vol 197, Iss 9, pp 1157–1163, May 1, 2018
CMAJ 2020 February 18;192:E154-61

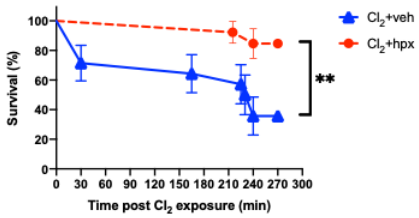
Alishlash AS, et al. Redox Biol. 2021 Aug;44:102009



Alishlash AS, et al. Redox Biol. 2021 Aug;44:102009



Alishlash AS, et al. Redox Biol. 2021 Aug;44:102009



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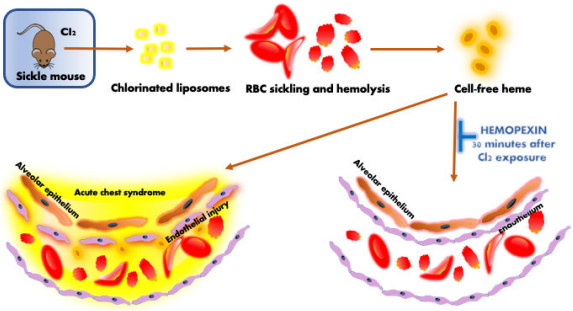

Alishlash AS, et al. Redox Biol. 2021 Aug;44:102009


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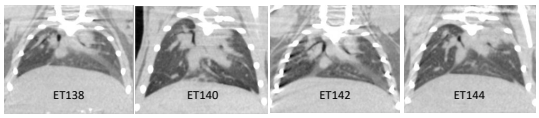
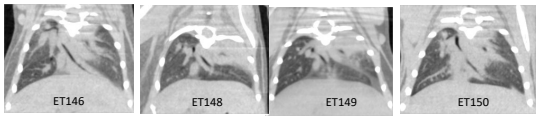
2021 Papers of the year
Previous Article | Next Article
Of 3,942 publications by NIEHS researchers and grantees in 2021, institute leaders selected 35 as Papers of the Year.
BY ROBIN ARNETTE
Promising therapy for fatal sickle cell disease complication
An NIEHS-funded study in mice showed how chlorine exposure leads to acute chest syndrome, a leading cause of death in patients with sickle cell disease (SCD). The results point to a potential lifesaving therapy for SCD patients exposed to chlorine, which is found in some household cleaning products.
The researchers used genetically engineered mice that resembled SCD in humans (sickle mice) and compared them with healthy control mice with human hemoglobin. They exposed both groups to chlorine gas or normal air.
Within six hours of chlorine exposure, 64% of sickle mice died, whereas none of the controls died. Compared with controls, surviving sickle mice experienced lung injury and hemolysis, or the rupture of red blood cells, which releases hemoglobin into the blood. Hemopexin treatment following exposure significantly improved survival and reduced blood heme levels and lung injury.
Citation: Alishlash AS, Saqkota M, Ahmad I, Maclin K, Ahmed NA, Molyvdas A, Doran S, Albert CJ, Agarawal S, Ford DA, Ambalavanan N, Illing T, Matalon S ⟳. 2021. Chlorine inhalation induces acute chest syndrome in humanized sickle cell mouse model and ameliorated by postexposure hemopexin. Redox Biol 44:102009. (Synopsis)

Hypoxia induced ACS in mice (Model 2)

- SS room air (RA)



- SS Hypoxia
  FiO_2 0.07 x3hrs



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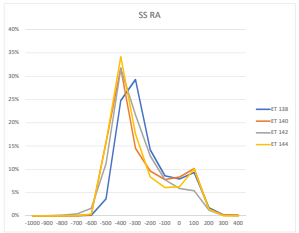
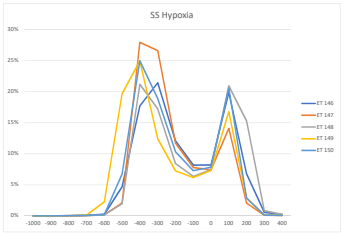
CT data

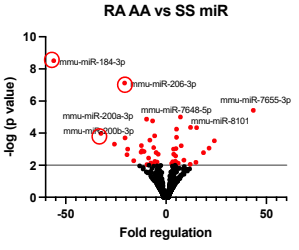


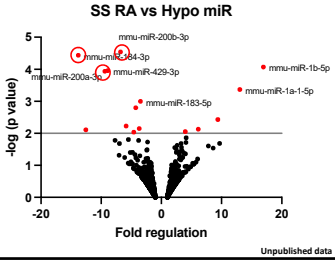


- Hounsfield unit

Unpublished data

ACS biomarker/pathways





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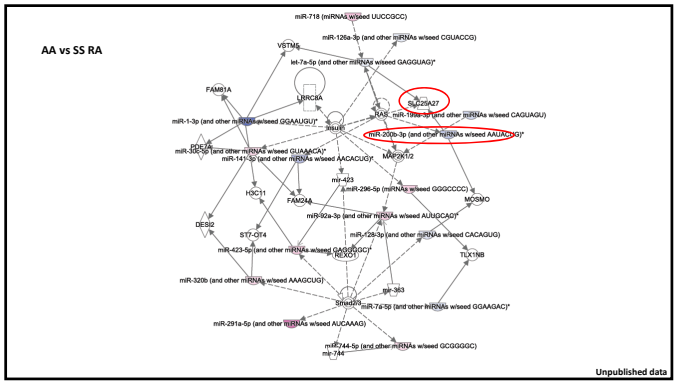
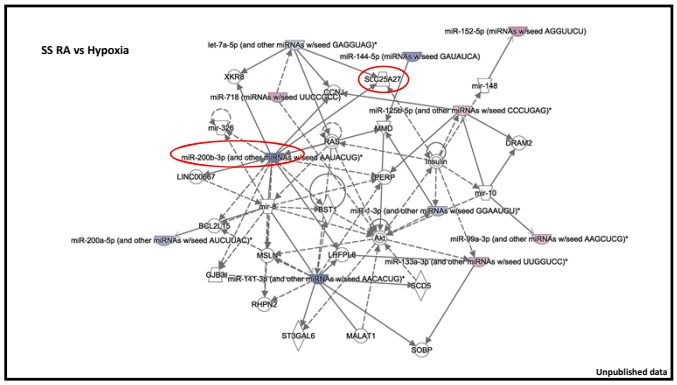




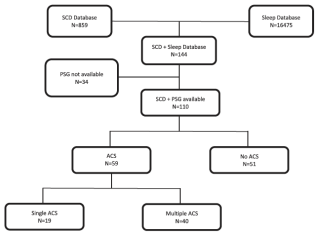
Pulmonary complications of SCD

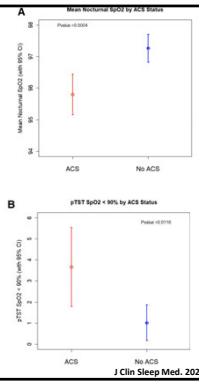
- Acute Chest Syndrome (ACS)
- **Sleep-disordered breathing (SDB) and hypoxemia**
- Asthma and pulmonary function abnormalities
- Pulmonary hypertension (PHTN)

Sleep-disordered breathing and hypoxemia

- The prevalence of obstructive sleep apnea is higher in children with SCD than children with no SCD
- Children with SCD have longer duration of oxygen desaturation, a lower oxygen saturation nadir, and a higher pTST CO_2 >50 mmHg

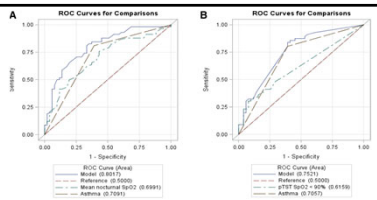
Pediatrics. 2014 Aug; 134(2): 273–281
J Pediatr Hematol Oncol. 2008 Sep;30(9):659-65





- Mean nocturnal O_2 saturation
- % of Total Sleep Time with O_2 sat <90% (pTST SpO_2 < 90%)

J Clin Sleep Med. 2021 Feb 1;17(2):219-226



- **Mean nocturnal O_2 saturation** cutoff value of **97.3%** distinguished between those with ACS vs those with no ACS with **sensitivity of 76%** and specificity of 57% with an AUC-ROC of 0.70.
- With the **pTST SpO_2 < 90%** cut-point of **2.7%** for, we were able to distinguish between those with ACS vs non-ACS with sensitivity of 30% and **specificity of 92%**, corresponding to an AUC-ROC of 0.62

J Clin Sleep Med. 2021 Feb 1;17(2):219-226

Nocturnal hypoxemia and neurocognition

- Nocturnal hypoxemia (Mean O_2 <96%) is associated with increased risk of stroke in SCD

Lancet.2001;357(9269):1656–1659.

- Mean O_2 significantly predicted Verbal Comprehension (VC) (p=0.012)
- pTST O_2< 90% significantly predicted Working Memory (WM) (p=0.003)

- VC decreased by 2.37 standard points for every unit decrease in mean O_2 (β=2.37, p=0.031).
- WM decreased by 1.46 standard points for each 1 percent increase in pTST O_2< 90% (β=-1.46, p=0.030).

Tiffany Tucker. International Neuropsychological Society 2022 Annual Meeting Manuscript under review

Pulmonary complications of SCD

- Acute Chest Syndrome (ACS)
- Sleep-disordered breathing (SDB) and hypoxemia
- **Asthma and pulmonary function abnormalities**
- Pulmonary hypertension (PHTN)

Asthma and pulmonary function abnormalities

- 48% of children with SCD have asthma versus 22% in ethnically matched controls
- Asthma increases the risk of pain and ACS

Thorax. 2005;60(3):206
Curr Opin Pediatr. 2019;31(3):349

Table 2—Multivariate analysis for the association of multiple covariates with ACS.

	Estimated Odds Ratio with 95% CI	*P* Value
Age (for 1-y increase)	1.17 (1.04, 1.33)	<.01
Hemoglobin level (for 1-unit increase)	0.57 (.40,0.82)	<.005
Sickle phenotype, SS vs not SS	1.83 (.55, 6.18)	.3275
Asthma, yes vs n/o	7.52 (2.73, 20.67)	<.0001

J Clin Sleep Med. 2021 Feb 1;17(2):219-226

Effects of SES on ACS

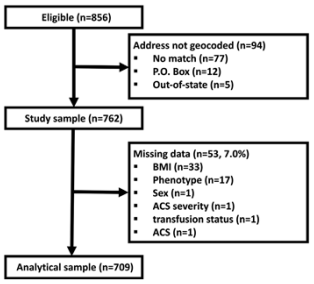


TABLE 3 Multiple regression of recurrent acute chest syndrome (N = 709)

Characteristic	IRR (95% CI)
Residential	
High area deprivation (ADI 7-10)	0.76 (0.58-1.01)
≥90% African American neighborhood	**0.60 (0.39-0.94)***
Nonmetro area (RUCA 4-10)	1.20 (0.87-1.65)
Sociodemographic	
Age	1.01 (0.98-1.04)
Male	**1.86 (1.38-2.50)*****
Public health insurance	0.89 (0.65-1.22)
Clinical	
Chronic transfusions	1.00 (0.73-1.38)
Hydroxyurea	**2.89 (1.74-4.80)*****
Asthma	**2.62 (1.89-3.63)*****
BMI	1.02 (0.99-1.06)
Genotype	
SS	*(reference)* 1.0
SB0	0.81 (0.45-1.45)
SB+	**0.18 (0.04-0.72)***
SC	**0.34 (0.19-0.61)*****

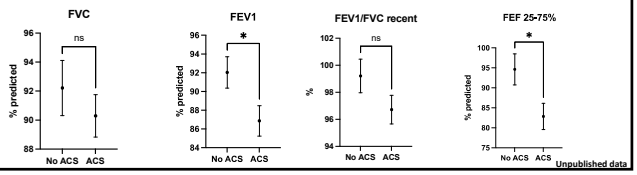
Pediatr Blood Cancer. 2021;68:e28877

Abnormal lung function

- Children with SCD have predominantly obstructive lung disease

Pediatr Hematol Oncol. 2013 Nov;30(8):726-32
J Pediatr Hematol Oncol. 2014;36(3):185
Ann Am Thorac Soc. 2016;13(8):1314

- 150 children with SCD who had at least one spirometry result. Out of those, 94 patients (63%) had at least one episode of ACS



Unpublished data

- 31 patients have at least one full set PFT

Parameters	Mean (SD)
Age at full PFT (n=31)	11.3 (3.76)
Age at spirometry (n=71)	11.04 (3.19)
Males n (%)	37 (52.1%)
Most recent spirometry	
FVC% predicted	94.3% (16.4)
FEV1% predicted	95.1% (15.5)
FEV1/FVC%	102% (5.5)
FEF 25-75% predicted	103.3% (22.2)
Most recent full set PFT	
TLC% predicted	99.3% (27.5)
RV% predicted	**167.5% (111.2)**
RV/TLC%	**153.7% (54.75)**
Growth data	
Weight for age Z-score <2 years	0.24 (1.1)
Length for age Z-score <2 years	**-1.98 (1.34)**
Weight for Length % <2 years	65.5% (31.1)
Weight for height Z-score <2 years	0.55 (1.2)
Weight for age Z-score 2-4 years	-0.07 (1.2)
Height for age Z-score 2-4 years	**-0.35 (1.1)**
BMI % 2-4 years	56.7% (29.1)
BMI Z-score 2-4 years	0.22 (1.0)

Most recent PFT	Correlation coefficient	P-value
TLC		
Weight for age Z-score <2 years	**0.446**	**0.011***
Length for age Z-score <2 years	0.216	0.144
Weight for Length % <2 years	0.318	0.057
Weight for Length Z-score <2 years	0.312	0.060
Weight for age Z-score 2-4 years	**0.345**	**0.036***
Height for age Z-score 2-4 years	**0.451**	**0.008***
BMI% 2-4 years	0.203	0.150
BMI Z-score 2-4 years	0.212	0.139

Am J Respir Crit Care Med 2021;203:A3293

Pulmonary complications of SCD

- Acute Chest Syndrome (ACS)
- Sleep-disordered breathing (SDB) and hypoxemia
- Asthma and pulmonary function abnormalities
- **Pulmonary hypertension (PHTN)**

SCD related PHTN

- PHTN: mean pulmonary artery pressure ≥20 mm Hg
- Group 5: PHTN with unclear or multifactorial mechanisms (hypoxia, thromboembolism, LV diastolic dysfunction, pulmonary vascular injury from sickling and hemolysis, etc)
- 6-11% of adults with SCD

WSPH group
1 – Pulmonary arterial hypertension
2 – Pulmonary hypertension secondary to left heart disease
3 – Pulmonary hypertension from chronic lung diseases and/ or hypoxia
4 – Pulmonary hypertension due to pulmonary artery obstructions
5 – Pulmonary hypertension from unexplained or multifactorial mechanisms

Am J Manag Care. 2021 Mar;27(3 Suppl):S35-541.
Blood Adv. 2019 Dec 10;3(23):3867-3897
Am J Respir Crit Care Med. 2014 Mar 15;189(6):727-40

SCD related PHTN

- Independent risk factor for mortality (median survival time is 6.8 years in adults)
- ASH guidelines: Patients at risk of PHTN (dyspnea at rest, hypoxia, chest pain, exercise limitation, SDB, syncope, loud P2, H failure, PE) need to be screened with **echo** and NT-pro-**BNP**
- **CoA Pediatric PHTN Program**
  - SCD
  - PPHN and CHD
  - BPD

Role of pulmonologists in SCD care

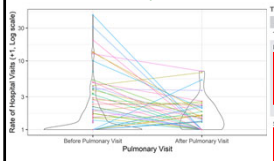


TABLE 2 Details on management of patients with asthma and sickle cell disease

	Total patients	SCD-A-P[a]	SCD-A[c]	p value
Total patients with asthma and sickle cell disease	192	70 (36%)	122 (64%)	
Medications and therapies				
Albuterol or levalbuterol	174 (91%)	69 (99%)	105 (86%)	0.004
Preventative asthma med[c]	108 (56%)	62 (89%)	46 (38%)	<0.001
Hydroxyurea	102 (53%)	46 (66%)	56 (46%)	0.008
Home respiratory support[c]	11 (6%)	10 (14%)	1 (1%)	<0.001
Apheresis	35 (18%)	16 (23%)	19 (16%)	0.21
Standardized asthma care				
Classification of asthma severity	150 (78%)	66 (94%)	44 (69%)	<0.001
Completion of asthma control test	96 (50%)	60 (86%)	36 (30%)	<0.001
Completion of asthma care plan	142 (74%)	68 (97%)	74 (61%)	<0.001
Completion of PFTs[c]	85 (44%)	57 (81%)	28 (23%)	<0.001

- Rate of hospital visits reduced from 3.93 (1.57–6.29) to 0.85 (0.48–1.23) following pulmonary consultation (p = 0.014)
- Evaluation and management of children with SCD and asthma by a pulmonologist were shown to improve outcomes, specifically standardized asthma care and decreased ED/hospitalizations rates for asthma exacerbation and ACS

Pediatric Pulmonology. 2022;1–9.

Moving forward

- Screen children with SCD for symptoms and signs of asthma, SDB, and PHTN
- Multidisciplinary approach to children with SCD and pulmonary complications
- Advocate for improving support to SCD related QI and research efforts
- Collaboration of SCD providers and researchers to establish national registry, and biorepository
- Increase the involvement of pulmonologists in the care and research of patients with SCD

Conclusions

- Pulmonary complications of SCD (that affects>100,000 Americans) include - but not limited to – ACS (leading cause of death in children with SCD), SDB, hypoxia, asthma, abnormal lung function, and PHTN
- Alabama is highly impacted by SCD that is a major personal and public health burden
- The interaction between SCD and the respiratory system is bidirectional and leads to a vicious circle
- Research and evidence-based practice of pulmonary complications of SCD are scarce in comparison to other life-threatening genetic diseases
- Involvement of pulmonary service can improve the outcomes of patients with SCD while waiting for curative therapies
- Increasing research support, collaboration, and multidisciplinary approach to SCD are some ways to improve life quality and expectancy
- Such efforts will ultimately improve lives of people with SCD, and health equity within the SCD population; and between patients with SCD and general population

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- Thanks for listening
- Questions and thoughts