AMERICAN THORACIC SOCIETY DOCUMENTS

Identifying Clinical and Research Priorities in Sickle Cell Lung Disease

An Official American Thoracic Society Workshop Report

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Abstract

Background: Pulmonary complications of sickle cell disease (SCD) are diverse and encompass acute and chronic disease. The understanding of the natural history of pulmonary complications of SCD is limited, no specific therapies exist, and these complications are a primary cause of morbidity and mortality.

Methods: We gathered a multidisciplinary group of pediatric and adult hematologists, pulmonologists, and emergency medicine physicians with expertise in SCD-related lung disease along with an SCD patient advocate for an American Thoracic Society–sponsored workshop to review the literature and identify key unanswered clinical and research questions. Participants were divided into four subcommittees on the basis of expertise: *1*) acute chest syndrome, *2*) lower airways disease and pulmonary function, *3*) sleep-disordered breathing and hypoxia, and *4*) pulmonary vascular complications of SCD. Before the workshop, a comprehensive literature review of each subtopic was conducted. Clinically important questions were developed after literature review and were finalized by group discussion and consensus.

Results: Current knowledge is based on small, predominantly observational studies, few multicenter longitudinal studies, and even fewer high-quality interventional trials specifically targeting the pulmonary complications of SCD. Each subcommittee identified the three or four most important unanswered questions in their topic area for researchers to direct the next steps of clinical investigation.

Conclusions: Important and clinically relevant questions regarding sickle cell lung disease remain unanswered. High-quality, multicenter, longitudinal studies and randomized clinical trials designed and implemented by teams of multidisciplinary clinician-investigators are needed to improve the care of individuals with SCD.

Keywords: sickle cell disease; acute chest syndrome; asthma; sleep disorders; pulmonary hypertension

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Introduction

Sickle cell disease (SCD) is a genetic hemoglobinopathy associated with early mortality that occurs in racial and ethnic groups that are profoundly impacted by social determinants of health and commonly have poor access to health care (1). Although mortality for children living with SCD in high-resource settings has improved, pulmonary-related morbidity remains a high burden across the lifespan. These factors and others have led to significant health disparities and contributed to our limited understanding of disease progression and its complications. In both prospective and retrospective studies, pulmonary complications, implicating nearly every cell type and structure of the lung, continue to be the most common etiology of accelerated morbidity and mortality in individuals living with SCD (2–8). Existing National Heart Lung and Blood Institute (NHLBI) guidelines were developed to aid primary care providers with the management of SCD; however, a lack of high-quality data limited their usefulness in addressing sickle cell lung disease (9). Given that cardiopulmonary complications of SCD are a major risk factor for death in this population, expanding our knowledge of lung disease is crucial to improving patient outcomes.

Fundamental challenges in addressing sickle cell lung disease include a limited understanding of: *1*) the natural history of SCD-associated pulmonary disease, *2*) genetic factors and comorbidities that increase pulmonary risk in SCD, and, consequently, *3*) a lack of SCD-specific therapies. To address these challenges and frame the research agenda for the next 5 to 10 years, we gathered an expert panel for an American Thoracic Society (ATS) workshop to identify key unanswered research questions in the following topics:

1. Acute chest syndrome (ACS)
2. Lower airways disease and pulmonary function
3. Sleep-disordered breathing (SDB) and hypoxemia
4. Pulmonary vascular complications in SCD

This ATS Workshop Report serves to disseminate our findings to the medical community. The key unanswered research questions identified by the Workshop Committee are listed in Table 1.

Methods

Here we describe the methods of the workshop committee composition, literature review, and manuscript preparation (Table 2).

Committee Composition

The committee included SCD experts in adult and pediatric hematology, pulmonology, sleep medicine, and emergency medicine, and one patient advocate. The project chairs, adult (A.P.R. and E.S.K.) and pediatric (S.C.S. and R.T.C.) pulmonologists, selected committee members on the basis of their expertise. The committee consisted of 32 physicians (including the four chairs) from the United States, United Kingdom, Jamaica, and Mali (6 adult pulmonologists, 6 adult hematologists, 12 pediatric pulmonologists, 6 pediatric hematologists and 2 emergency medicine physicians [1 adult and 1 pediatric]), one librarian, and one patient representative with SCD. Two of the pediatric pulmonologists were board certified in sleep medicine. The committee was divided into four subcommittees, each led by a workshop co-chair, to address the key topics. All committee members disclosed their potential conflicts of interest to the ATS and the project chairs, who reviewed them, discussed them with the chair of the Ethics and Conflict of Interest Committee of the ATS, and resolved them with the individual committee members. Committee members were required to refrain from discussing topics related to their conflicts of interest.

Subcommittees

Four subcommittees were formed to focus the workshop on the following topics: *1*) Acute chest syndrome (A.P.R., D.A.D., J.A.G., J.H., J.K.-M., C.R.M., S.L.T., E.V.), *2*) Lower airways disease and pulmonary function (S.C.S., J.J.F., L.M.G., A.G., B.T.K., A.C.K., R.I.L., F.O.O., K.S.-W.), *3*) SDB and hypoxia (J.L.A., A.D.C., T.D.C., E.K.F., C.L.R., D.T., R.T.C.), *4*) Pulmonary vascular complications of SCD (D.P.B., M.T.G., V.R.G., G.J.K., S.M.L., R.F.M., A.M., N.A.W., E.S.K.). Each subcommittee, led by one of the co-chairs, held a conference call before the all-day meeting at the 2018 ATS International Conference for identification of important potential areas of focus for the workshop.

Table 1. Summary of key unanswered research questions

Research Topics	Key Unanswered Clinical and Research Questions
ACS	
ACS severity and subtypes	Which criteria should be used to classify ACS as mild, moderate, or severe? Which tests are best for determining specific etiologies of ACS? Which biomarkers reliably predict ACS severity? What therapies improve ACS outcomes?
Primary and secondary prevention of ACS	Which patients are at increased risk for ACS and may benefit from primary or secondary prevention? Can we identify patients with vaso-occlusive events are at highest risk of ACS? Which interventions are effective in preventing first-time and recurrent ACS?
Management of ACS in low-resource settings	How should patients with acute onset of signs and symptoms concerning for ACS be managed in low-resource settings? Which physical signs/symptoms are most indicative of ACS in settings without chest radiography? Which sustainable interventions decrease ACS-related maternal mortality in low-resource settings where hematologists and transfusion therapy are not uniformly available?
Lower airway disease and pulmonary function	
Lung function across the lifespan	What are the characteristics of lung function in SCD patients across the lifespan? Is there a predominant lung function pattern in SCD? Do lung function patterns evolve in patients with SCD across the lifespan?
Pathophysiology of lower airway disease	What are the features and pathophysiology of lower airway disease in SCD? Which inflammatory pathways contribute to lower airway disease? How do pulmonary vascular abnormalities contribute to lower airway disease?
Impact of lower airway disease on SCD outcomes	Does lower airway disease impact clinical outcomes in SCD? What is the relationship between lower airway disease and SCD outcomes? Is there a role for screening asymptomatic patients with PFTs? Are there modifiable risk factors for lower airway disease?
SDB and hypoxemia in SCD	
Assessment of hypoxemia and SDB	What are the optimal approaches to evaluating hypoxemia, oxygen desaturation, and SDB? Which signs and symptoms are useful to identify individuals who warrant formal evaluation for nocturnal respiratory disorders? Which alternative to full, in-laboratory polysomnography could be used to identify SDB and nocturnal hypoxemia in individuals with SCD?
Consequences of SDB and recurrent oxygen desaturation	How do OSA, sustained versus intermittent oxygen desaturation, and repeated arousals during sleep impact SCD morbidity and mortality? Which oxygen saturation threshold for nocturnal hypoxemia contributes to SCD morbidity and mortality?
Treatment of SDB and recurrent oxygen desaturation	What is the optimal treatment of SDB among individuals with SCD? What is the acceptability of treatment for hypoxemia and SDB? What is the impact of treatment of hypoxemia and SDB on short- and long-term outcomes in SCD?
Pulmonary vascular complications of SCD	
Impact of PH diagnosis on outcomes	Does the early identification and treatment of PH in SCD improve outcomes? In the asymptomatic patient, does evaluation for SCD-PH impact clinical outcomes? What is the best strategy to screen for SCD-PH? What should be the approach to abnormal screening studies or the diagnosis of the symptomatic patient?
Treatment of SCD-related PAH	Do patients with SCD-PAH respond to PAH therapy? Which criteria should be used to determine which patients should receive PAH therapy? Which novel PAH therapeutics hold the most promise for patients with SCD-PAH? What should be the treatment approach for patients with PH related to left-sided heart disease?
DVT prophylaxis in specific cohorts of patients with SCD	How should DVT prophylaxis be approached in pregnant women and children with SCD?
Secondary prevention of DVT, PE, or pulmonary artery thrombosis	If a patient with SCD is diagnosed with a DVT, PE, or pulmonary artery thrombosis, what treatment should be used and for what duration? What are indications for long-term anticoagulation in SCD?

Definition of abbreviations: ACS = acute chest syndrome; DVT = deep venous thrombosis; OSA = obstructive sleep apnea; PAH = pulmonary arterial hypertension; PE = pulmonary embolism; PFT = pulmonary function test; PH = pulmonary hypertension; SCD = sickle cell disease; SDB = sleep-disordered breathing.

Table 2. Summary of workshop methods

Proposed Methods Checklist: for Each, Respond as Yes or No	Yes	No
Panel assembly:		
Included experts from all relevant clinical and nonclinical disciplines	X	
Included individual who represents views of patients and society at large	X	
Included methodologist with appropriate expertise (documented expertise in development of conducting systematic reviews to identify the evidence base and development of evidence-based recommendations).		X
Literature review:		
Performed in collaboration with librarian	X	
Searched multiple electronic databases	X	
Reviewed reference lists of retrieved articles	X	
Evidence synthesis:		
Applied prespecified inclusion and exclusion criteria		X
Evaluated included studies for sources of bias		X
Explicitly summarized benefits and harms	X	
Used GRADE to describe quality of evidence		X

Definition of abbreviation: GRADE = Grading of Recommendations Assessment, Development, and Evaluation.

Literature Review

A comprehensive literature search was performed on each topic before the workshop by a librarian from the National Institutes of Health Library (N.T.) and was updated during the preparation of this report. Common search parameters used for each topic included SCD and human subjects research in both children and adults in the PubMed and Cochrane Library databases from 1970 to January 28th, 2019. Additional literature was cited as it became available.

Workshop Overview

Each chair presented an overview of the current state of knowledge of their respective topic followed by a group discussion with all workshop participants. This was followed by breakout subcommittee meetings, where the most important questions in each topic were identified. The workshop concluded with each subcommittee presenting their findings to the entire group.

Document Preparation

After the workshop, each subcommittee analyzed and synthesized the evidence for their topic, applied it to the broader context of the field, and drafted a section of the document. These drafts were edited by the co-chairs, and the document was distributed for discussion and editing. All committee members had the opportunity to contribute to the document. The key unanswered research questions are listed in Table 1.

Results

Understanding the Natural History of Sickle Cell Lung Disease Is Critical

At the workshop, a common theme unified all discussions: there are significant limitations in our knowledge because of a relatively poor understanding of the natural history of sickle cell lung disease and a lack of data, in most cases, on the clinical significance of pulmonary comorbidities. The current situation is a result of several missed opportunities.

Although every major study of SCD has identified cardiopulmonary disease as the major cause of death (10), current knowledge has been hindered by a lack of prospective data on the natural history of sickle cell lung disease and a lack of a widely accessible standardized SCD registry that would provide these data for both high- and low-resource settings (3).

The Cooperative Study of Sickle Cell Disease, a prospective clinical study conducted between 1978 and 1998 across 23 centers in the United States, was intended to set a framework for understanding SCD and its multisystem complications. Unfortunately, the assessment of chronic cardiopulmonary disease was limited by incomplete collection of longitudinal pulmonary function data and a lack of ascertainment of complications such as pulmonary hypertension (PH) and SDB. Furthermore, patients were enrolled in 1979 to 1981 (11), before the widespread use of penicillin prophylaxis, pneumococcal vaccination, and hydroxyurea, limiting the applicability of findings to the current SCD population. More recently, most pulmonary-focused studies in this underserved and understudied population have been small, retrospective, and focused either on pediatric or adult populations, but not both. There have been no studies on progression of pulmonary disease in the "transition age group" from late adolescence through early adulthood when the care of patients transfers from pediatric to adult providers, patients assume responsibility for their own care, and, importantly, functional capacity and quality of life drop precipitously, with an increase in mortality (12). Consequently, although we understand that children and adolescents in settings with access to preventive SCD care have benefitted from improved mortality over the last several decades, they continue to suffer significant morbidity from sickle cell lung disease, while adults continue to suffer from high mortality even in high-resource settings.

In terms of lung function, we know that individuals with SCD have lower lung function than those without SCD. About 15% to 20% of children and adolescents have obstructive physiology; by adulthood (13, 14), many individuals meet criteria for restrictive disease (15, 16), yet we do not understand the evolution of lung function, the clinical significance of these abnormalities, or how they may be related. Similarly, increased tricuspid regurgitant jet velocity (TRV) observed in 10% to 20% of children and adolescents with SCD has unclear prognostic significance (17, 18), whereas in adults these echocardiographic findings have been repeatedly associated with early mortality (8, 19, 20). The workshop committee strongly advocates for a modern-day, prospective, longitudinal multicenter assessment of the pulmonary complications of SCD encompassing pediatric and adult populations. The workshop committee also strongly acknowledges the need to include high-prevalence areas of SCD, such as sub-

Saharan Africa, the Middle East, India, and Brazil, in clinical research studies (21).

Each of the four subcommittees identified the priority focus areas for their topic. The results of these discussions are presented here.

ACS

ACS is a clinical syndrome consisting of chest pain, fever, tachypnea, wheezing, rales, or cough plus a new infiltrate involving at least one lung segment (22–24) and is a leading acute cause of mortality in this population (24). This nonspecific definition applies to episodes with variable etiologies, severities, and timing of symptom onset (24–26). Diagnosis relies on radiographic abnormalities, which may precede or lag behind symptoms, and radiography may be unavailable in low-resource settings. Although one randomized clinical trial demonstrated that incentive spirometry during vaso-occlusive crisis decreases ACS risk (27), additional preventive approaches are necessary. It is possible that modern informatics and machine learning could use large clinical data sets to identify other preventive therapies, risk factors, or early indicators of ACS, such as a decrease in oxygen saturation (28). The need to perform clinical research in ACS in international areas of high SCD prevalence is pressing, as improved understanding of these populations is vital to advance our ability to diagnose, prevent, and treat ACS in low-resource settings.

A comprehensive understanding of ACS pathogenesis is needed to evaluate the efficacy of existing therapies and develop preventive strategies and targeted treatments (9). Priority areas for research include: *1*) ACS severity and subtypes, *2*) primary and secondary prevention, and *3*) management in low-resource settings.

ACS Severity and Subtypes

***Research question*: Which criteria should be used to classify ACS as mild, moderate, or severe?**

Supporting questions:

- Which tests are best for determining specific etiologies of ACS?
- Which biomarkers reliably predict ACS severity?
- What therapies improve ACS outcomes?

The umbrella term "ACS" describes a clinical syndrome with distinct phenotypes that require better characterization. Rapidly progressive ACS, associated with multiorgan failure and death (2), appears distinct from milder ACS with minimal respiratory signs and symptoms and improves with antibiotics and supportive care. Some ACS episodes are associated with transient or worsening PH (29), whereas others (particularly in children) mimic an asthma exacerbation (30). Designing therapeutic trials targeting ACS is challenging, given the diverse underlying etiologies of this syndrome (i.e., infection, bone marrow/fat embolism, thrombosis) (24).

Development of an ACS risk and severity stratification algorithm is a top research priority for clinical trial development. Currently, the criteria used to define severity are applied after the ACS course has evolved. In comparison, timing of symptom onset was integrated into the 2012 Berlin definition of acute respiratory distress syndrome (ARDS) allowing for risk prediction. A recent retrospective study of 173 children and adults with SCD found that, in adults, thrombocytopenia was the only predictor of rapidly progressive ACS (2). This needs to be confirmed prospectively in a larger cohort, as these patients would require immediate, aggressive therapy if at risk for severe morbidity and mortality (2, 31). Additional biomarkers (32–34) should be evaluated for their potential in predicting ACS development and progression, including: plasma free hemoglobin, soluble phospholipase A_2 (32), and circulating exosomes (33), and also common laboratory tests such as white blood cell count, nucleated red blood cells, or C-reactive protein (34). Other experimental biomarkers, such as soluble phospholipase A_2 in exhaled breath condensate, are currently under study (35). Much like updates providing clarity for definition of ARDS (36), ACS phenotype severity classifications should be explicitly defined and categorized by: *1*) acuity and severity, and *2*) identifiable pathophysiology allowing for targeted therapies.

Primary and Secondary Prevention of ACS

***Research question*: Which patients are at increased risk for ACS and may benefit from primary or secondary prevention?**

Supporting questions:

- Can we identify which patients with vaso-occlusive events (VOEs) are at highest risk of ACS?
- Which interventions are effective in preventing first-time and recurrent ACS?

ACS often occurs 1 to 3 days after hospital admission for VOEs, but patients can also present with ACS independently of a painful episode (24, 37, 38). Hydroxyurea, L-glutamine, and chronic transfusions decrease ACS frequency but do not prevent all episodes (39, 40). Some clinicians use early blood transfusion or noninvasive ventilation (NIV) in patients at high risk for ACS. Ideal timing and type of transfusion (simple vs. exchange) and the efficacy of NIV to decrease ACS progression should be tested in intervention trials. Systemic steroids may reduce the severity and/or duration of an ACS episode, but some studies and anecdotal observations suggest an increased risk of rehospitalization for a VOE (41–45).

Pharmacologic therapy for ACS prevention (inhaled corticosteroids [46, 47] and novel medications including crizanlizumab, a monoclonal antibody targeting P-selectin [48]) should be evaluated in large randomized trials (15). Agents targeting erythrocyte sickling, hemolysis, fat embolism, and thrombosis should be investigated (49). Moreover, preventive measures against ARDS should be evaluated as preventive measures for ACS in patients with SCD, such as low–tidal-volume ventilation, either in the intensive care unit or when undergoing general anesthesia.

Management of ACS in Low-Resource Settings

***Research question*: How should patients with acute onset of signs and symptoms concerning for ACS be managed in low-resource settings?**

Supporting questions:

- Which physical signs/symptoms are most indicative of ACS in settings without chest radiography?
- Which sustainable interventions decrease ACS-related maternal mortality in low-resource settings where hematologists and transfusion therapy are not uniformly available?

ACS is a common cause of hospitalization in SCD in high-resource settings (24, 37), but in many low-resource regions where SCD is highly prevalent, chest radiographs are unavailable or cost

prohibitive, creating diagnostic challenges (50). A diagnostic strategy for ACS independent of imaging could facilitate early identification and intervention allowing for targeted resource use. The role of portable pulse oximetry devices in ACS diagnosis should be evaluated.

Pregnancy and the postpartum period are associated with increased ACS risk. ACS is the most common cause of acute respiratory failure and death in pregnant or postpartum SCD patients in low-resource settings, with ACS responsible for >60% of the deaths in pregnant women with SCD in this population (31, 51). In Ghana, a multidisciplinary approach using a combined obstetric and hematology team was effective in reducing ACS incidence and all-cause maternal mortality (52). This suggests that standardized early identification and management protocols for pregnant and postpartum patients with SCD could improve both maternal and fetal outcomes.

Lower Airway Disease and Pulmonary Function

Many children and adults with SCD have abnormal pulmonary function and/or recurrent respiratory symptoms. NHLBI SCD management guidelines recommend against screening pulmonary function tests (PFTs) (53); however, a better understanding of the pathophysiology and progression of lower airway disease is needed to understand the potential benefits of screening. Priority areas for research include: 1) lung function across the lifespan, 2) pathophysiology of lower airway disease, and 3) the impact of lower airway disease on SCD outcomes.

Lung Function across the Lifespan

Research question: What are the characteristics of lung function in patients with SCD across the lifespan?

Supporting questions:

- Is there a predominant lung function pattern in SCD?
- Do lung function patterns evolve in patients with SCD across the lifespan?

Studies demonstrate PFT abnormalities in infants (54), children (7, 55–58), and adults (15, 16, 59). Children, on average, have reduced lung function compared with control subjects, but most are still within the normal range. Obstructive physiology is the most common abnormality in children (13, 14), whereas many adults have restrictive physiology (15, 16, 60). It is not clear whether the obstructive defects observed in childhood lead to restrictive defects in adulthood (i.e., if there is a progression or trajectory of PFT abnormalities), or whether these abnormalities affect different patient subgroups at different points in their lifespan.

Our understanding of lung function in SCD has been impaired by inconsistent study design, nonuniform interpretation/classification strategies when comparing results across studies, and a lack of longitudinal data (61). Use of spirometry alone overestimates the prevalence of restrictive defects, and obstruction may be underestimated when absolute forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) cutoffs are used. There are few longitudinal lung function studies in SCD, and most were retrospective. One pediatric cohort demonstrated a 2% to 3% annual decline in FVC, FEV_1, and total lung capacity (62); however, this finding has not been replicated in other studies (63, 64).

Beyond the increased mortality risk associated with a reduced FEV_1 (6, 65), the significance of abnormal PFTs in SCD remains unknown. There is no association between abnormal lung function and rates of pain or ACS in children (13), but recurrent ACS episodes may be associated with reduced total lung capacity in adults (60). Future research should examine associations between abnormal lung function, respiratory symptoms, and SCD outcomes beyond rates of VOEs and ACS and, most importantly, how evaluation of lung function can aid providers in optimizing the care of their patients with cardiopulmonary symptoms (66).

Pathophysiology of Lower Airway Disease

Research question: What are the features and pathophysiology of lower airway disease in SCD?

Supporting questions:

- Which inflammatory pathways contribute to lower airway disease?
- How do pulmonary vascular abnormalities contribute to lower airway disease?

The prevalence of physician-diagnosed asthma among children with SCD is approximately 25% (67). However, many more patients exhibit isolated recurrent wheezing (68, 69), lower airway obstruction (13, 14, 70), or airway hyperresponsiveness (AHR) (71–73) without meeting diagnostic criteria for asthma. Distinguishing between wheezing due to comorbid asthma versus SCD-specific mechanisms is important for delineating pathogenesis and guiding therapeutics (74). Activated neutrophils (75) and fibrocytes (76, 77), proinflammatory cytokines (78), exaggerated allergic inflammation (71, 79–82), increased placental growth factor (83, 84), and increased pulmonary vascular congestion have been implicated in the pathogenesis of airway disease in SCD (59, 85, 86). Future research should focus on elucidating these mechanisms further to identify novel therapeutic approaches.

Impact of Lower Airway Disease on SCD Outcomes

Research question: Does lower airway disease impact clinical outcomes in SCD?

Supporting questions:

- What is the relationship between lower airway disease and SCD outcomes?
- Is there a role for screening asymptomatic patients with PFTs?
- Are there modifiable risk factors for lower airway disease?

Childhood asthma is associated with more frequent VOEs, earlier onset of ACS, recurrent ACS, and mortality (67, 87, 88). In one adult cohort, patient-reported "recurrent wheezing" (but not asthma) was associated with increased morbidity and mortality (68). Other features of airway dysfunction, including AHR and lower airway obstruction, have not been consistently associated with SCD morbidity (13, 89). Environmental exposures, including outdoor air pollution (90, 91) and tobacco smoke (92–96), may contribute to SCD morbidity via direct or indirect effects on airways or pulmonary vasculature, but more study is needed.

Little is known about the impact of treating lower airway disease in SCD. Although one retrospective study demonstrated that hydroxyurea was associated with slower longitudinal lung function decline (97), the impact of hydroxyurea on AHR and wheezing is unknown. A randomized pilot trial of inhaled corticosteroids in adults with SCD without asthma with recent respiratory symptoms found decreased soluble vascular cell adhesion molecule-1 levels (suggesting

reduced inflammation and cellular adhesion) and reduced daily pain scores in the inhaled steroid group compared with the placebo group (98). These studies support overlap between lower airway disease and SCD pathobiology.

Determining the impact of anti-inflammatory pulmonary treatment on SCD morbidity and mortality is a priority. Similarly, the impact of SCD disease-modifying therapy on lower airway disease needs further evaluation. Asthma therapy should be studied specifically in patients with SCD, because unique toxicities may be observed in this population. For example, systemic steroids have been shown to be beneficial in numerous acute pulmonary conditions including asthma exacerbations in the general population, but, as described above, steroids may increase the risk of rebound pain or avascular necrosis in SCD (41, 42).

SDB and Hypoxemia

SDB, hypoxemia, and other sleep disturbances appear to be common in SCD and may impact SCD morbidity and mortality (99). SDB includes obstructive sleep apnea (OSA), central sleep apnea, and sleep-related hypoventilation. Individuals may separately have sustained (diurnal), intermittent, or sustained nocturnal hypoxemia. Adults with SCD may be at risk for central sleep apnea secondary to chronic opioid use and/or comorbid congestive heart failure (100).

Insufficient and inconsistent data concerning SDB and hypoxemia in SCD led the NHLBI Guidelines for Management of SCD committee to recommend screening for OSA symptoms only, even though some patients with SCD have SDB without typical symptoms (101, 102). Hydroxyurea and blood transfusions improve oxygen saturation (103), suggesting that increasing hemoglobin concentration can improve tissue oxygen delivery. Priority areas for research include: *1*) assessment of blood and tissue oxygen content and SDB, *2*) consequences of SDB and episodic versus sustained oxygen desaturation, and *3*) impact of treating SDB and oxygen desaturation.

Assessment of Hypoxemia and SDB

***Research question:** What are the optimal approaches to evaluating hypoxemia, oxygen desaturation, and SDB?*

Supporting questions:

- Which signs and symptoms are useful to identify individuals who warrant evaluation for nocturnal respiratory disorders?
- Which alternatives to full, in-laboratory polysomnography (PSG) could be used to identify SDB and nocturnal hypoxemia in individuals with SCD?

The gold standard for measuring blood oxygen content is an arterial blood gas with CO-oximetry that measures carboxyhemoglobin and methemoglobin. CO-oximetry is important in SCD because it accounts for hemolysis-related dyshemoglobinemia (104, 105). Pulse oximetry is a noninvasive modality to measure oxyhemoglobin saturation (106); however, the accuracy of pulse oximetry in patients with SCD, particularly during VOEs and/or severe anemia, has been questioned (107) because of: *1*) rightward shifts of the oxyhemoglobin dissociation curve (Figure 1) (108), and *2*) dyshemoglobins, which absorb light at the two wavelengths analyzed by pulse oximetry and may confound measurements (109). There is controversy concerning the appropriate normal oxygen saturation range in SCD. The rightward shift of the oxyhemoglobin dissociation curve in the setting of severe hemolytic anemia suggests that oxygen saturation targets appropriate for the general population may not be applicable for all individuals with SCD (110). Right-to-left shunting (either intracardiac or intrapulmonary) has recently been identified as a possible etiology for oxygen desaturation in a subset of patients (111, 112). However, data suggest that the normal range of oxygen saturation for patients with SCD should be similar to that of healthy control subjects (28, 113).

Although the gold standard for diagnosis of SDB is overnight, in-laboratory PSG for adults (114) and children (115), it is expensive and burdensome for patients. Unfortunately, there are insufficient data about accuracy of home sleep apnea testing or other modalities in patients with cardiorespiratory comorbidities (116, 117), including SCD. History and physical examination are inadequate for identifying OSA in children (118, 119). Although sleep disruption can be assessed by motion-tracking devices such as actigraphy, accuracy

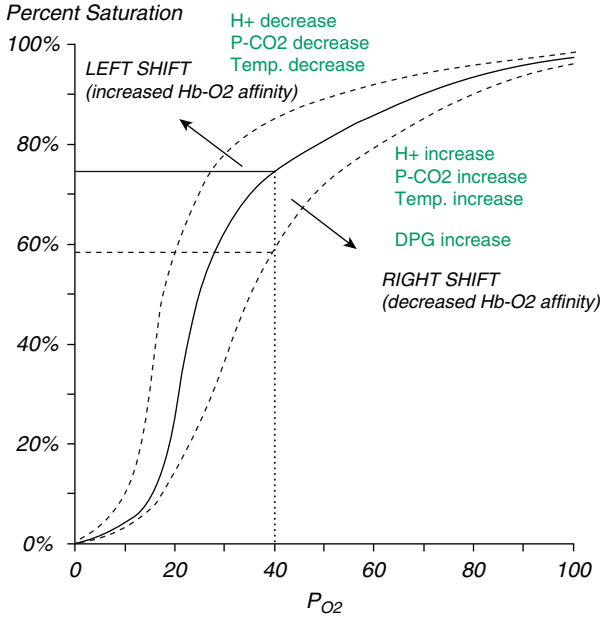

Figure 1. Oxyhemoglobin dissociation curve. Oxyhemoglobin saturation at a given arterial oxygen pressure (Pa_{O_2}) (i.e., 40 mm Hg) is lower in patients with sickle cell disease (SCD) (right dashed line) than would be predicted by a normal oxyhemoglobin dissociation curve (solid line) because of increased 2,3 diphosphoglycerate (2,3 DPG) in sickled erythrocytes, as an adaption to severe anemia to prevent tissue hypoxia, or in the setting of hypoventilation with CO_2 retention from pain, opioid use, and/or sleep-disordered breathing. The oxygen pressure (P_{O_2}) at which hemoglobin (Hb) is 50% saturated is about 27 mm Hg in normal subjects and about 33 mm Hg in patients with SCD. Reprinted by permission from Reference 178.

is reduced in the presence of other sleep disorders (120). Relationships between SCD comorbidities and SDB and/or hypoxemia need further investigation, including poor sleep quality, insomnia, nocturnal enuresis, depression, and pain (121–125).

Areas for investigation include: *1*) identification of oxygen saturation targets at rest and during exertion, sleep, and acute illness; and *2*) evaluation of alternative modalities to improve access to evaluation for SDB (Table 3).

Consequences of SDB and Recurrent Oxygen Desaturation

***Research question:** How do OSA, sustained versus intermittent oxygen desaturation, and repeated arousals during sleep impact SCD morbidity and mortality?*

Supporting question:

- Which oxygen saturation threshold for nocturnal hypoxemia contributes to SCD morbidity?

Relationships between SCD pathophysiology and oxygen delivery to the vasculature and organs are complex and multifactorial. Studies suggest that oxyhemoglobin desaturation may predispose to VOEs (126) and ACS (28), but findings are inconsistent (89, 127). A recent prospective cohort of children failed to demonstrate an association between OSA and pain or ACS. Nocturnal oxygen desaturation increased stroke risk in one study (128) but not another (129). Oxyhemoglobin desaturation may adversely affect neurocognitive function, verbal IQ (130), and executive function (131); however, these findings need confirmation in larger cohorts. Notably, the clinical and pathophysiologic significance of SDB and chronic and/or recurrent oxygen desaturation has not been studied in adults with SCD. Although the ATS guidelines for PH in SCD recommend evaluating suspected OSA with polysomnography (132), there have been no studies evaluating OSA as a potential risk factor for PH, PH-associated mortality, or other adverse cardiac outcomes in SCD.

Studies evaluating associations between SDB and clinical outcomes need to account for the impacts of desaturation severity and sleep quality. Tissue hypoxia promotes endothelial injury and hypoxic pulmonary vasoconstriction. Nocturnal oxygen desaturation has been associated with

Table 3. Available modalities for the diagnosis of sleep disorders and nocturnal oxygen desaturation

Modality	Description	Advantages	Disadvantages
Full polysomnography	Full channel, in-laboratory with audiovisual recording; technician-attended study; measures cardiorespiratory parameters, limb movements, sleep staging, and quality	"Gold standard" physiological measurement of sleep, breathing, and of sleep and breathing; can be used in individuals with complex medical problems	Expensive, burdensome, limited access, often with long wait times
Home sleep apnea testing	Option A: Limited channel unattended study in the home that measures cardiorespiratory parameters: pulse oximetry, chest wall movement, nasal air flow; ±snoring, ECG	Home based, less expensive, more convenient; valid method to diagnose OSA in uncomplicated adult patients, but data in pediatric population sparse and no data for SCD	Not recommended for those with chronic conditions including cardiopulmonary comorbidities (117); does not assess sleep quality; may underestimate disease severity; not recommended for children
	Option B: Devices measuring pulse oximetry, actigraphy and estimating sleep and SDB from arterial tonometry (WatchPAT)	Validated for OSA diagnosis in adults without chronic cardiorespiratory conditions	Not validated in children or SCD populations
History and physical examination	Inquiring about snoring and daytime sleepiness; assessment of tonsil size	Inexpensive, noninvasive	Poor sensitivity and specificity for OSA; individuals may not be aware of snoring; SDB exists in absence of adenotonsillar hypertrophy and may persist A/T
Pulse oximetry	Noninvasive measure of oxyhemoglobin saturation	Low cost, easy to use, well tolerated	Results confounded by dyshemoglobins, questionable reliability in severe anemia and illness, limited by motion artifact
Pulse CO-oximetry	Noninvasive measure of carboxyhemoglobin and methemoglobin via 8 wavelength spectrophotometry	Estimates contribution of carboxyhemoglobin and methemoglobin to decreased Sp_{O_2}; agrees with blood CO-oximetry; easy to use, well-tolerated (179)	Not widely used, may be cost prohibitive, limited by motion artifact
Actigraphy	Wrist device using accelerometer technology to estimate wake–sleep patterns and sleep disruption	Low cost, noninvasive, well tolerated, can be used in the home	Accuracy varies across devices; results confounded by other sleep disorders (OSA, periodic limb movement); estimates sleep, but not SDB

Definition of abbreviations: A/T = adenotonsillectomy; ECG = electrocardiogram; OSA = obstructive sleep apnea; SCD = sickle cell disease; SDB = sleep-disordered breathing; Sp_{O_2} = oxygen saturation as measured by pulse oximetry; WatchPAT = Watch-peripheral arterial tone.

biomarkers of hemolysis (133) and endothelial activation and adhesion (134). Associations between poor sleep quality, SDB, and desaturation with depression and pain are likely multidirectional (125, 126, 135–137) and need further investigation.

Treatment of SDB and Recurrent Oxygen Desaturation

***Research question:* What is the optimal treatment of SDB among individuals with SCD?**

Supporting questions:

- What is the acceptability of treatment for hypoxemia and SDB?
- What is the impact of treatment of hypoxemia and SDB on short and long-term outcomes in SCD?

Acceptability and impact of treating hypoxemia and SDB in SCD are important research priorities. One 6-week pilot trial of auto-adjusting continuous positive airway pressure in 24 children with SCD and OSA demonstrated good adherence and improved sleep parameters, oxygen saturation, and reported pain days (138). No studies have compared adherence among treatment modalities in SCD. Small retrospective cohort studies demonstrate improvements in PSG parameters after adenotonsillectomy for OSA (139–141); however, postoperative complications, including ACS, have been reported (142). Three retrospective studies demonstrate improvements in OSA and nocturnal and daytime oxygen saturation after treatment with hydroxyurea (143–145). No studies to date have evaluated the long-term impact of SDB treatment on VOEs, cardiopulmonary and neurocognitive outcomes, or vascular dysfunction.

Pulmonary Vascular Complications of SCD

The pulmonary vascular complications of SCD include PH, pulmonary artery thrombosis, and venous thromboembolism (VTE). PH is a mortality risk factor, occurs in 6% to 11% of adults with SCD (146–148), and reflects a spectrum of hemodynamics, including precapillary PH (40%) and postcapillary PH (60%) (149); mortality risk increases with worsening hemodynamics and right ventricular dysfunction (150, 151).

Table 4. Risk factors for venous thromboembolism in sickle cell disease

Traditional VTE Risk Factors	SCD-related VTE Risk Factors
Immobilization due to frequent hospitalizations (1)	Coagulation factors
Use of central venous catheters for venous access and red cell exchange/ transfusion therapy (180)	Decreased protein C, protein S, and antithrombin III levels
Surgery	Decreased factor XII levels (181)
Orthopedic surgery (avascular necrosis of hip, shoulder)	Elevated circulating antiphospholipid antibodies (182)
Cholecystectomy	Elevated plasma levels of thrombin–antithrombin complexes, prothrombin fragment 1 + 2 (a marker of thrombin and fibrin generation and platelet activation) (183)
Increased pregnancy-related VTE	During VOE
Splenectomy: functional asplenia and postsurgical splenectomy	Abnormal externalization of phosphatidylserine in erythrocytes and adherence to the vascular endothelium
	Increased tissue factor expression
	Increased circulating fibrinogen, vWF, and factors VII and VIII
	Impaired fibrinolysis
	Upregulation of cellular adhesion molecules

Definition of abbreviations: SCD = sickle cell disease; VOE = vaso-occlusive events; VTE = venous thromboembolism: vWF = Von Willibrand's factor.

SCD is a hypercoagulable state (Table 4); as such, patients have a fourfold increase in VTE compared with the general population (152). Thrombosis risk is hard to predict in individual patients. There are no SCD-specific guidelines or clinical trials of anticoagulant therapies.

Priority areas for research in SCD-PH include: *1*) understanding the impact of early identification of PH on clinical outcomes, and *2*) the best therapeutic strategy for SCD-PH. Priority research areas in patients with VTE in SCD include: *1*) management of thromboprophylaxis in pregnant women and children, and *2*) approach to anticoagulant therapy for a first-time VTE.

Impact of PH Diagnosis on Outcomes

***Research question:* Does the early identification and treatment of PH in SCD improve outcomes?**

Supporting questions:

- In the asymptomatic patient, does evaluation for SCD-PH improve clinical outcomes?
- What is the best strategy to screen for SCD-PH?
- What should be the approach to abnormal screening studies or the diagnosis of the symptomatic patient?

An elevated TRV by echocardiography (defined as ⩾2.5 m/s) occurs in approximately one-third of hemoglobin-SS adults, 10% to 20% of hemoglobin-SC adults, and 10% to 20% of HbSS children and adolescents (8, 132, 153). An elevated TRV on echocardiography can be used to estimate right ventricular or pulmonary artery systolic pressure. Values in adults ⩾2.5 m/s identify 25% to 44% of patients with PH assessed by right heart catheterization, and values ⩾3.0 m/s identify about 75% of patients with pulmonary hypertension (149). In adults, even borderline values (⩾2.5 m/s) are associated with early mortality (8). In contrast, in children and adolescents, an elevated TRV does not increase mortality risk but does predict reduced exercise capacity (18, 132, 154), However, there are no right heart catheterization data in children, which would be needed to better interpret TRV values in this age group. An elevated N-terminal pro-brain natriuretic peptide level or a reduced 6-minute-walk distance increases TRV specificity for PH (124).

An approach to evaluate an elevated TRV in SCD was proposed as part of the ATS Clinical Guidelines for Diagnosis and Treatment of PH in SCD (132). Screening with TRV was proposed to identify patients at high risk of having PH and increased mortality, to intensify hematological therapy with hydroxyurea or chronic transfusion therapy, and also to identify patients with treatable forms of PH, for example group I pulmonary arterial

hypertension (PAH) and group IV chronic thromboembolic PH. A recent retrospective study of 13 HbSS patients with precapillary PH reported that chronic transfusion therapy improved New York Heart Association functional class and hemodynamics, particularly pulmonary vascular resistance ($P = 0.01$) (155). Right heart catheterization is necessary for PH diagnosis and classification, yet inconsistency remains across centers regarding when this is pursued.

Despite the mortality risk and identification of elevated TRV, it is unclear whether interventions in response to abnormal echocardiograms affect clinical outcomes (9, 132). Echocardiography is, however, widely accepted in the evaluation of dyspnea, a commonly reported symptom in adults with SCD (9, 132, 156). Studies demonstrate increased mortality in adults with SCD with PH or an isolated elevated TRV or N-terminal pro-brain natriuretic peptide level (8, 150, 157, 158). Whether increased mortality can be ameliorated with early intervention is unclear, because randomized trials have not been completed.

Two recent guideline documents offer conflicting recommendations (9, 132). The ATS guidelines recommend screening all patients 18 years and older, whereas the NHLBI guidelines for the care of patients with SCD do not. Optimal PH screening tests and frequency of testing have not been determined. Elevated TRV is not associated with mortality among children and adolescents, weakening the argument for screening pediatric age groups (132, 159, 160). However, the association with progressive exercise limitation in children with higher TRV values suggests that studies may be needed to evaluate screening in children for cardiopulmonary complications and then to follow them to adulthood to identify higher-risk groups for intervention. It is unknown whether newer modalities, such as cardiac magnetic resonance imaging, could be more informative than echocardiography (151).

Treatment of SCD-related PAH

***Research question:* Do patients with SCD-PAH respond to PAH therapy?**
Supporting questions:

- Which criteria should be used to determine which patients should receive PAH therapy?
- Which novel PAH therapeutics hold the most promise for patients with SCD-PAH?
- What should be the treatment approach for patients with PH related to left-sided heart disease?

PH in SCD represents a spectrum of hemodynamic and clinical findings; those with precapillary PH similar to PAH are most appropriate to study for efficacy of PAH therapy. The use of U.S. Food and Drug Administration–approved PAH medications for SCD-PAH is controversial, as no randomized trials in SCD have been completed (161, 162). In SCD-PAH, the strongest support for PAH-targeted therapy comes from seven case series, in which 53 patients with SCD and precapillary PH hemodynamics (six with chronic thromboembolic PH) who received targeted PAH therapies had improved 6-minute-walk distance (157, 163–166). Improvements in mean pulmonary arterial pressure, pulmonary vascular resistance, and cardiac index occurred but were only assessed in a subset of patients (164). Three randomized trials of bosentan or sildenafil in SCD were stopped early and were underpowered to address efficacy. Two of the clinical trials evaluating bosentan for pre- and postcapillary PH (ASSET 1 and 2) were terminated by the sponsor because of underenrollment (161). The trial of sildenafil for the treatment of PH in SCD enrolled patients on the basis of an elevated TRV and not by right heart catheterization–proven PAH (162). The sildenafil trial was stopped after enrollment of 72 subjects because of an increased rate of hospitalizations, particularly for vaso-occlusive crises in the sildenafil-treated group. PAH therapy may be most appropriate in those with pre-capillary hemodynamics, similar to Group 1 PAH (132). Despite similarities in hemodynamics, hemoglobinopathy-related complications in these patients emphasize the importance of clinical trials in SCD (167).

Deep Venous Thrombosis Prophylaxis in Specific Cohorts of Patients with SCD

Research question: How should deep venous thrombosis (DVT) prophylaxis be approached in pregnant women and children with SCD? SCD is a risk factor for pregnancy-related VTE (168–170), yet there are no studies of thromboprophylaxis in this population. Standard of care includes thromboprophylaxis for all adult hospitalized patients with SCD (171), and current guidelines recommend the consideration of outpatient VTE prophylaxis in pregnant women with SCD and prior VTE (152, 172). The high risk of VTE in pregnancy in SCD raises the question of whether thromboprophylaxis is warranted in all pregnant patients.

Evidence regarding thromboprophylaxis in the pediatric SCD population is limited. VTE in pediatric patients with SCD appears to be rare, and cases are often catheter related (173). Thromboprophylaxis is generally reserved for children with additional risk factors for thrombosis in addition to SCD alone (174). There may be increased hemorrhagic risk in patients with SCD receiving anticoagulant therapy because of retinal and cerebral vasculopathy, which raises concern for universal use. The epidemiology of pediatric SCD-VTE needs further investigation.

Secondary Prevention of DVT, Pulmonary Embolism, or Pulmonary Artery Thrombosis

Research question: If a patient with SCD is diagnosed with a DVT, pulmonary embolism, or pulmonary artery thrombosis, what treatment should be used and for what duration?
Supporting question:

- What are indications for long-term anticoagulation in SCD?

Patients with SCD with an isolated, first-time DVT or pulmonary embolism currently receive standard American College of Chest Physicians guideline–directed anticoagulation for 3 to 6 months (175). A retrospective study using patient discharge data reported a 31.3% VTE recurrence risk at 5 years, which suggests that this approach may be inadequate (176). For patients with SCD-PH and VTE, consensus guidelines recommend indefinite anticoagulation for those without significant hemorrhagic risk (132). The rate of recurrence of VTE and the impact of PE on cardiopulmonary function should be studied to better understand how different treatment regimens impact clinical outcomes.

FUTURE DIRECTIONS

When assessing the most important questions facing the field of sickle cell lung disease, we must keep an eye toward the future. Curative therapies, including hematopoietic stem-cell transplantation and gene therapy, are currently under investigation in SCD. Although pulmonary comorbidities, including an elevated TRV, are among the inclusion criteria for many of these studies, we do not know whether, or how, the course of pulmonary disease is altered by "curing" the hemoglobinopathy.

It is critical that adult and pediatric pulmonologists take an active role in the design and analyses of these studies. In addition, we must focus on training the future generation of pediatric and, particularly, adult pulmonologists to develop a cadre of experts who can work together to move the field of sickle cell lung disease forward.

Given that diseases affecting underserved populations frequently receive less research funding (177), it will take a concerted effort to develop high-quality clinical research studies of sickle cell lung disease. We advocate for targeted funding initiatives from the U.S. National Institutes of Health and specialty organizations, such as the ATS, the American Society of Hematology, the European Respiratory Society, and the American Society of Human Genetics, for international, multicenter, longitudinal studies that include high-prevalence and low-resource settings as well as training grants targeted toward clinical investigators to promote these efforts in a systematic fashion.

SUMMARY

Important questions relating to sickle cell lung disease remain unanswered. There are multiple barriers to characterizing sickle cell lung disease, including a lack of multicenter prospective studies, inadequate research funding, and inconsistent phenotyping strategies. Patient registries are critical to study the natural history of this disease. High-quality, multicenter, longitudinal cohort studies and randomized clinical trials designed and implemented by multidisciplinary teams are the best way to evaluate the questions outlined in this report and advance the care of patients with pulmonary complications of SCD. ■

This official workshop report was prepared by an *ad hoc* subcommittee of the ATS Assembly on Pediatrics.

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