Identifying Clinical and Research Priorities in Sickle Cell Lung Disease
An Official American Thoracic Society Workshop Report: Executive Summary

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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 a SCD patient advocate for an American Thoracic Society–sponsored workshop to review the literature and identify key unanswered 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 sickle cell disease. 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

*These authors contributed equally to the planning and drafting of this document.

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Introduction

Sickle cell disease (SCD) is a genetic hemoglobinopathy associated with early mortality (1). 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 among individuals living with SCD (2–8). Existing National Heart Lung and Blood Institute (NHLBI) guidelines for the management of SCD included very little about screening and management of pulmonary issues because of a lack of high-quality evidence in this area (9). Given that cardiopulmonary complications of SCD are a major risk factor for death, 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 (SBD) and hypoxemia
4. Pulmonary vascular complications in SCD

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

Methods

A detailed description of workshop committee composition, literature review, and manuscript preparation is reported in the full Workshop Report. The committee included SCD experts in adult and pediatric hematology, pulmonology, sleep medicine, and emergency medicine, and one patient advocate. The committee was divided into four subcommittees, each led by a workshop co-chair, to address the key topics. A National Institutes of Health (NIH) librarian performed a literature search before the workshop with periodic updates thereafter. At the workshop, each co-chair presented an up-to-date topic overview followed by a discussion with all workshop participants. Subcommittees determined the most important research questions in each topic (Table 1), synthesized the evidence, and drafted their section. Sections were edited and combined by the co-chairs, and the final report was reviewed and approved by the committee. The methods used to develop this workshop report are summarized in Table 2.

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 of sickle cell lung disease 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 to provide these data (3).

The multicenter, longitudinal Cooperative Study of Sickle Cell Disease enrolled patients from 1979 to 1981 (11), before the widespread use of penicillin prophylaxis, pneumococcal vaccination, or the use of hydroxyurea. More recent pulmonary-focused studies in this underserved and understudied population have been small, retrospective, and/or focused either on pediatric or adult populations, but not both.

The workshop committee strongly advocates a prospective, longitudinal multicenter assessment of the pulmonary complications of SCD encompassing pediatric and adult populations as well as populations from high-prevalence areas of SCD, such as sub-Saharan Africa, the Middle East, India, and Brazil (12).

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 (13–15). This
| Research Topics | Key Unanswered Clinical and Research Questions |
|-----------------|---------------------------------------------|
| 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 at the 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 | 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?  
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?  
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? |
| 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 | 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?  
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? |
| 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?  
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? |
| 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 | 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? |
| 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.*
nonspecific definition applies to episodes
with variable etiologies, severities, and
timing of symptom onset (15-17). Diagnosis relies on radiographic
abnormalities, which may precede or lag
symptoms, and radiography may be
unavailable in low-resource settings. Study of ACS in international areas with high SCD
prevalence is vital to improve 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, including 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?
- Which therapies improve ACS outcomes?

The umbrella term “ACS” describes a
syndrome with distinct phenotypes that
require better characterization. Although
some episodes are characterized by mild
signs and symptoms and rapid
improvement with antibiotics and
supportive care, other episodes are rapidly
progressive and severe and lead to
multigorgan failure and even death.

Designing therapeutic trials targeting ACS is
challenging, given the diversity of
underlying etiologies (i.e., infection, bone
marrow/fat embolism, thrombosis) (15).

Development of an ACS risk and severity
stratification algorithm is a top clinical trial
research priority. Biomarkers (18-20),
including thrombocytopenia (14, 17), plasma
free hemoglobin, soluble phospholipase A2
(18), circulating exosomes (19), and common
laboratory tests such as white blood cell count,
nucleated red blood cells, or C-reactive
protein (20) should be evaluated for their
potential in predicting ACS development and
progression. Other experimental biomarkers,
such as soluble phospholipase A2 in exhaled
breath condensate, are under study (21).

Much like updates providing clarity for
the acute respiratory distress syndrome
definition (22), 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
admission for VOEs, but patients can
present with ACS independently of a painful
episode (15, 23, 24). Hydroxyurea,
L-glutamine, and chronic transfusions
decrease ACS frequency but do not prevent
all episodes (25, 26). Some clinicians use early
blood transfusion or noninvasive ventilation
in patients at high risk for ACS, but these
have never been tested in intervention trials.

Systemic steroids may reduce the severity
and/or duration of an ACS episode; however,
studies and anecdotal observations suggest an
increased risk of rehospitalization for a VOE
(27, 28). Pharmacologic therapy for ACS
prevention (15), including agents targeting
inflammation, adhesion, erythrocyte sickling,
hemolysis, fat embolism, and thrombosis,
should be evaluated in randomized trials
(29-31).

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?

In many low-resource regions where SCD is
highly prevalent, chest radiographs are
unavailable or cost prohibitive, creating
diagnostic challenges (32). 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
patients with SCD in low-resource settings
(33, 34). Data suggest that standardized
earl identification and multidisciplinary
management protocols for pregnant and
postpartum women with SCD could improve
maternal and fetal outcomes (35).

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) (36); however, a better
understanding of the pathophysiology and
progression of lower airway disease is
needed to evaluate the potential benefits of
screening. Priority areas for research
include: 1) evolution of 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 (37), children (7, 38-41), and
adults (42-44). Children, on average, have
reduced lung function compared with
control subjects, but most remain within the
normal range. It is not clear whether the
Beyond rates of VOEs and ACS (50), respiratory symptoms, and SCD outcomes associations between abnormal lung function, unclear. Future research should examine significance of abnormal PFTs in SCD remains unclear. Future research should examine associations between abnormal lung function, respiratory symptoms, and SCD outcomes beyond rates of VOEs and ACS (50).

### 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% (51); however, many more patients exhibit isolated recurrent wheezing (52, 53), lower airway obstruction (45, 46, 54), or airway hyperresponsiveness (AHR) (55–57) without meeting asthma diagnostic criteria. Distinguishing between wheezing due to comorbid asthma versus SCD-specific mechanisms is important for delineating pathogenesis and guiding therapeutics (58). Future research should focus on elucidating these mechanisms 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?

SCD has been impaired by inconsistent study design, nonuniform interpretation/classification strategies when comparing results across studies, and a lack of longitudinal data (48). There are few longitudinal lung function studies in SCD and none that follow individuals from childhood into adulthood.

Beyond the increased mortality risk associated with a reduced FEV1 (6, 49), the significance of abnormal PFTs in SCD remains unclear. Future research should examine associations between abnormal lung function, respiratory symptoms, and SCD outcomes beyond rates of VOEs and ACS (50).

**SDB and Hypoxemia**

SDB, hypoxemia, and other sleep disturbances appear to be common in SCD and may impact SCD morbidity and mortality (62). 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 (63).

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 (64, 65). 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 hemolysis-related dyshemoglobins (carboxyhemoglobin and methemoglobin) (66, 67). Pulse oximetry is a noninvasive modality to measure oxyhemoglobin saturation (68); however, the accuracy of pulse oximetry in patients with SCD, particularly during VOEs and/or severe anemia, has been questioned (69) because of: 1) rightward shifts of the oxyhemoglobin dissociation curve (70), and 2) dyshemoglobins, which absorb light at the two wavelengths analyzed by pulse oximetry and may confound measurements (71).

Although the gold standard for SDB diagnosis is overnight, in-laboratory PSG (72), (73) 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 (74, 75), including SCD. 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?

### 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 (75); 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 \( \text{SpO}_2 \); agrees with blood CO-oximetry; easy to use, well-tolerated (120) | 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; \( \text{SpO}_2 \) = oxygen saturation as measured by pulse oximetry; WatchPAT = Watch-peripheral arterial tone.
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 (89). No studies have compared adherence and effect of different positive pressure modalities for treatment of SDB in SCD. Although adenotonsillectomy improves PSG parameters in OSA (90–92), postoperative complications, including ACs, have been reported (93). Hydroxyurea has been associated with improvements in OSA, nocturnal, and daytime oxygen saturation (94–96). The long-term impact of SDB treatment on VOEs, cardiopulmonary and neurocognitive outcomes, or vascular dysfunction has not been evaluated.

Pulmonary Vascular Complications of SCD

The pulmonary vascular complications of SCD include pulmonary hypertension (PH), pulmonary artery thrombosis, and venous thromboembolism (VTE). PH is a mortality risk factor (97–99) and reflects a spectrum of hemodynamics, including precapillary and postcapillary PH (100); mortality risk increases with worsening hemodynamics and right ventricular dysfunction (101, 102).

SCD is a hypercoagulable state (Table 4); as such, patients have a fourfold increase in VTE compared with the general population (103). 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 of the impact of early identification of PH on clinical outcomes, and 2) the best therapeutic strategy for SCD-PH. Priority research areas in patients VTE in SCD include: 1) management of thromboprophylaxis in pregnant women and children, and 2) approach to anticoagulation therapy for a first-time VTE.

### 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 (121) | Decreased protein C, protein S, and antithrombin III levels |
| Surgery | Decreased factor XII levels (122) |
| Orthopedic surgery (avascular necrosis of hip, shoulder) | Elevated circulating antiphospholipid antibodies (123) |
| Cholecystectomy | Elevated plasma levels of thrombin–antithrombin complexes, prothrombin fragment 1 + 2 (a marker of thrombin and fibrin generation and platelet activation) (124) |
| 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.

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?

Although an elevated tricuspid regurgitant jet velocity (TRV) on echocardiography (defined as ≥2.5 m/s) is poorly predictive for PH (100), it is present in approximately one-third of hemoglobin-SS adults and has been repeatedly associated with early mortality (8). In contrast, small cohort studies suggest that an elevated TRV is not a mortality risk factor for children and adolescents (104–106). 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 (104). Right heart catheterization is necessary for PH diagnosis, yet inconsistency remains across centers regarding when this is pursued.

Despite the mortality risk, we do not understand whether interventions responding to abnormal echocardiograms impact clinical outcomes (9, 104). Two recent guideline documents offer conflicting recommendations (9, 104). The ATS guidelines recommend screening all patients 18 years and older, whereas the NHLBI guidelines for patients with SCD do not. Optimal PH screening tests and frequency of testing have not been determined. It is unknown whether newer modalities, such as cardiac magnetic resonance imaging, could be more informative than echocardiography (102).

Treatment of SCD-related Pulmonary Arterial Hypertension

Research question: Do patients with SCD-pulmonary arterial hypertension respond to pulmonary arterial hypertension therapy?

Supporting questions:
- Which criteria should be used to determine which patients should receive pulmonary arterial hypertension (PAH) therapy?
- Which novel PAH therapeutics hold the most promise for patients with SCD-PAH?
Deep Venous Thrombosis Prophylaxis in Specific Cohorts of Patients with SCD

**Research question:** How should deep venous thrombosis prophylaxis be approached in pregnant women and children with SCD? SCD is a risk factor for pregnancy-related VTE (110–112), yet there are no studies of thromboprophylaxis in this population. Current guidelines recommend the consideration of outpatient VTE prophylaxis in pregnant women with SCD and prior VTE (103, 113). The high risk of VTE in pregnancy in SCD raises the question of whether thromboprophylaxis is warranted in all pregnant patients.

VTE in pediatric patients with SCD appears to be rare, and cases are often catheter related (114). Thromboprophylaxis is generally reserved for children with additional risk factors for thrombosis in addition to SCD alone (115). The epidemiology of pediatric SCD-VTE needs further investigation. The increased hemorrhagic risk with the use of anticoagulants in the setting of retinal and cerebral vasculopathy raises concern for universal use.

Secondary Prevention of Deep Venous Thrombosis, Pulmonary Embolism, or Pulmonary Artery Thrombosis

**Research question:** If a patient with SCD is diagnosed with a deep venous thrombosis, 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 deep venous thrombosis or pulmonary embolism currently receive standard American College of Chest Physicians guideline-directed anticoagulation for 3 to 6 months (116). 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 (117). The rate of recurrence of VTE and the impact of pulmonary embolism 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. 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 outcome studies of these therapies. 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.

Diseases affecting underserved populations such as SCD frequently receive less research funding (118, 119). We advocate for targeted funding initiatives from the NIH and specialty organizations such as the American Society of Hematology, the ATS, and the European Respiratory Society 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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