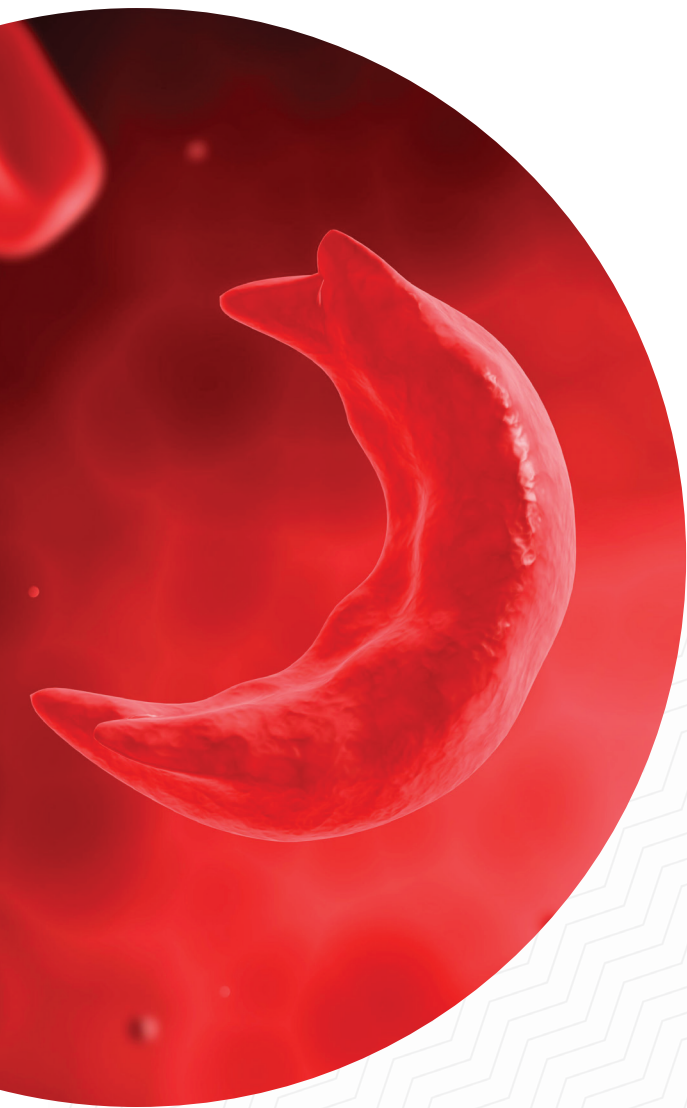




ASH CLINICAL PRACTICE GUIDELINES
SICKLE CELL DISEASE (SCD)

POCKET GUIDE



Cardiopulmonary and Kidney Disease in Sickle Cell Disease: Screening and Management

A POCKET GUIDE FOR THE CLINICIAN
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The recommendations in this guide are based on the American Society of Hematology 2019 Guidelines for Sickle Cell Disease: Cardiopulmonary and Kidney Disease



Context

The management of end organ damage is a major challenge facing individuals living with sickle cell disease (SCD), the majority of whom now survive into adulthood. Prevention and treatment of SCD-related complications linked to cardiopulmonary and kidney disease are especially challenging for providers. The information in this pocket guide is intended to support patients, clinicians, and other health care professionals in making evidence-based decisions about screening, diagnosis, and management of these complications.

Cardiopulmonary Complications: Screening & Management

Providers should understand the importance of educating patients, discussing patient/caregiver priorities and incorporating shared decision making when considering evaluation for cardiopulmonary disease.

PULMONARY HYPERTENSION (PH): SCREENING

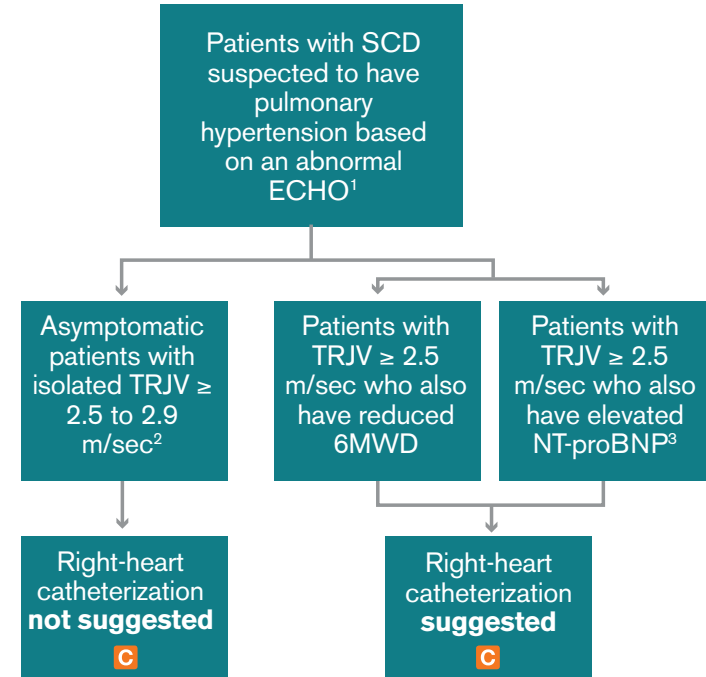
In asymptomatic children and adults with SCD, the ASH guideline panel **suggests against** performing routine echocardiogram (ECHO) to identify PH

Given the risk for cardiopulmonary disease in individuals with SCD, it is good practice to routinely take a targeted history for signs and symptoms that might indicate a need for further evaluation, including consideration for a diagnostic ECHO. The following signs or symptoms may warrant a consultation with a PH expert or a diagnostic ECHO in SCD patients who are not experiencing acute complications (such as painful episodes or acute chest syndrome):

- Dyspnea at rest or with exertion that is out of proportion to known condition, increased compared to baseline or unexplained
- Hypoxemia at rest or with exertion that is out of proportion to known condition, increased compared to baseline or unexplained
- Chest pain at rest or with exertion that is out of proportion to known condition, increased compared to baseline or unexplained
- Increase in exercise limitation compared to baseline that is unexplained by other factors
- History of recurrent hypoxemia at rest or with exertion
- Evidence for sleep-disordered breathing with or without hypoxemia (See “Sleep-Disordered Breathing: Screening” section of this guide)
- History of syncope or pre-syncope
- Evidence for loud pulmonary component of second heart sound or unexpected or new murmur on exam
- Signs of heart failure and/or fluid overload on exam
- History of pulmonary embolism

A diagnostic ECHO should be considered for patients with SCD who also have co-morbid conditions (e.g., connective tissue disease) or disease complications (e.g., leg ulcers, priapism) known to be associated with PH when signs or symptoms of PH are present.

Figure 1 – Right-Heart Catheterization vs. Non-Invasive Monitoring



¹ Decisions about the need for right-heart catheterization should be based on ECHOs obtained at steady state and not during illness such as hospitalization for pain or acute chest syndrome. ECHOs should be repeated in the setting of elevated TRJV prior to referral for right-heart catheterization under the guidance of a PH expert given the suboptimal reproducibility of TRJV measurements.

² For patients with an isolated TRJV ≥ 2.5 m/sec who are asymptomatic, other non-invasive evaluation (NT-proBNP or 6MWD) is suggested to increase the diagnostic accuracy for PH.

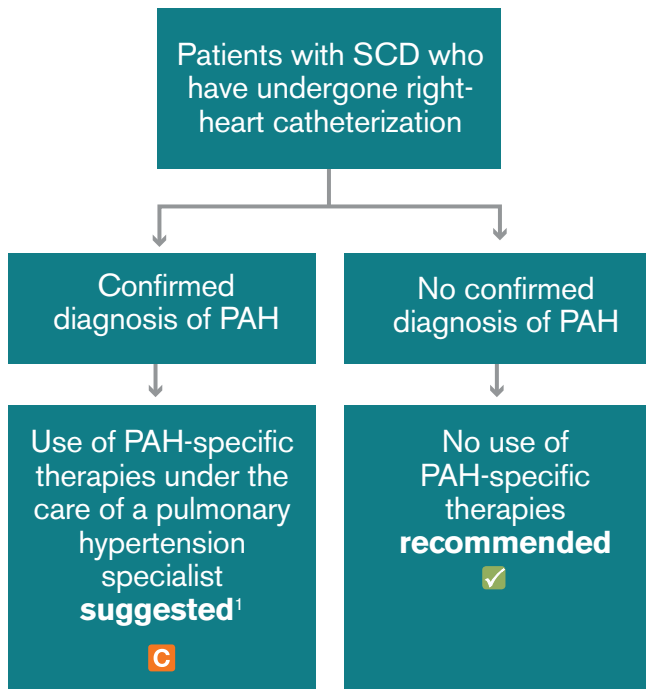
³ Abnormal cutoff values for NT-proBNP and 6MWD have not been firmly determined for patients with SCD. However, NT-proBNP values of ≥ 160 pg/mL and 6MWD < 333 meters represent reasonable thresholds for adults with SCD based on previously published studies in this population.

PULMONARY ARTERIAL HYPERTENSION (PAH): TREATMENT

Table 1 - Pulmonary Hypertension (PH) Classification by Etiology	
Group 1	Pulmonary Arterial Hypertension (PAH)
Group 2	PH due to left heart disease
Group 3	PH due to chronic lung disease and/or hypoxemia
Group 4	PH due to pulmonary artery obstructions (e.g., chronic thromboembolic pulmonary hypertension)
Group 5	PH due to unclear multifactorial mechanisms (e.g., SCD, beta-thalassemia, myeloproliferative disorders, sarcoidosis, and metabolic disorders)


Consult with a cardiologist, pulmonologist or an expert in PH when interpreting results of right-heart catheterization and considering therapeutic options based on type of PH and presumed pathophysiology. Pursue a multidisciplinary (i.e., hematology, PH specialist, pulmonary medicine or cardiology) approach when considering PAH-specific therapies.

Figure 2 – Pulmonary Arterial Hypertension (PAH) Therapies



¹ Given the lack of alternative treatment options and high morbidity and mortality associated with PAH.

PULMONARY FUNCTION SCREENING


For asymptomatic children and adults with SCD, the ASH guideline panel **suggests against** performing routine screening using pulmonary function testing (PFT) .

It is good practice for providers to understand the importance of educating patients, discussing patient and caregiver priorities and incorporating shared decision-making when considering carrying out PFT. The following signs, symptoms or diagnoses may warrant a diagnostic PFT for SCD patients who are not experiencing acute complications (such as painful episodes or acute chest syndrome) to evaluate for abnormal lung function:

- Wheezing or increased cough at rest or with exertion
- Wheezing or increased cough during episodes of acute upper respiratory infection
- Dyspnea at rest or with exertion that is increased compared to baseline or that is unexplained
- Chest pain at rest or with exertion that is out of proportion to known condition, increased compared to baseline or that is unexplained
- Increase in exercise limitation compared to baseline or that is unexplained (e.g., SCD pain or musculoskeletal disease)
- Abnormal 6-minute walk test defined by either reduced 6MWD or oxygen desaturation during test
- History of recurrent hypoxemia at rest or with exertion
- History of syncope or pre-syncope
- History of recurrent acute chest syndrome
- History of pulmonary embolism

Comprehensive PFT should include full spirometry as well as complete evaluation of diffusion capacity and lung volumes.

SLEEP-DISORDERED BREATHING: SCREENING


For asymptomatic children and adults with SCD, the ASH guideline panel **suggests against** screening with formal polysomnography (sleep study) for sleep-disordered breathing .

A comprehensive sleep history and review of systems are an essential part of the diagnostic strategy to identify patients with SCD for whom a low threshold should be considered for obtaining a formal sleep study. The following signs or symptoms may warrant a diagnostic sleep study in patients who are otherwise healthy:

- Snoring
- Witnessed or respiratory pauses
- Non-restorative sleep and/or excessive daytime sleepiness
- Obesity
- Early morning headaches
- Unexplained desaturation or hypoxemia during sleep, while awake or with exertion
- Carbon dioxide retention on arterial blood gas
- History of poorly controlled hypertension or congestive heart failure
- History of nocturnal enuresis in an older child (e.g., ≥10 years old)
- History of recurrent priapism or frequent daytime or nocturnal vaso-occlusive pain
- History of PH confirmed by right-heart catheterization
- History of ischemic stroke without evidence for vasculopathy
- History of memory loss, difficulty with concentration or unexplained episodes of mental confusion
- Symptoms of attention deficit-hyperactivity disorder, poor academic achievement and performance or behavior problems in children

Whenever appropriate, validated tools (e.g., Epworth Sleepiness Scale or Pittsburgh Sleep Quality Index) should be used to further identify which patients should be considered for formal sleep testing.




BLOOD PRESSURE MANAGEMENT

For adults with SCD, the ASH guideline panel **recommends** a blood pressure goal of ≤130/80 mm Hg over a goal of ≤140/90 mm Hg .

There is a lack of evidence to suggest that blood pressure goals should differ for individuals with and without SCD. The impact of hypertension on patient-important outcomes is significant for African Americans, who are often over-represented in the SCD population, and therefore requires adherence to guidelines developed for the general population independent of having SCD.

VENOUS THROMBOEMBOLISM (VTE) MANAGEMENT

Table 2 - Duration of Anticoagulation for Adults with SCD

First, unprovoked VTE	Indefinite anticoagulation ¹ 
First, provoked VTE ³	Defined period of anticoagulation (3 to 6 months) ² 
Recurrent, provoked VTE ³	Indefinite anticoagulation ¹ 

¹ The decision to remain on anticoagulation should be made through shared decision-making based on patient values/preferences and be subject to regular re-evaluation.

² Indefinite anticoagulation is not recommended for first provoked VTE such as secondary to a central venous line. However, anticoagulation should continue as long as any provoking risk factor, including central venous line, continues to be present.


³ The type, strength and duration of the provoking events are important to take into account when considering indefinite anticoagulation for patients with SCD and recurrent provoked VTE.

SCD is a chronic underlying risk factor for initial and recurrent VTE. Discussions of the benefits versus harms of anticoagulation, as well as duration of therapy, should consider bleeding risk, including from existing use of other medications that could further increase risk of bleeding (e.g., nonsteroidal anti-inflammatory drugs). Anticoagulant selection in patients with SCD should account for co-morbidities such as renal impairment that may affect drug clearance.

Chronic Kidney Disease Management

Advanced chronic kidney disease is frequently found in older adults living with SCD and is associated with increased morbidity and mortality in this older population.


HYDROXYUREA AND ERYTHROPOIESIS-STIMULATING AGENTS

In children and adults with SCD and worsening anemia associated with chronic kidney disease, the ASH guideline panel **suggests** combination therapy with hydroxyurea and erythropoiesis-stimulating agents .

In patients already on steady-state hydroxyurea, erythropoiesis-stimulating agents are appropriate in the setting of chronic kidney disease when there is a simultaneous drop in hemoglobin and absolute reticulocyte count.

A conservative hemoglobin threshold is advised for patients undergoing treatment with erythropoiesis-stimulating agents, above which treatment should be decreased or held to reduce the risk of vaso-occlusion-related complications, stroke and VTE. The ASH guideline panel advises not exceeding a hemoglobin threshold of 10 g/dL (hematocrit of 30%).


ALBUMINURIA MANAGEMENT

For children and adults with SCD and albuminuria, the ASH guideline panel **suggests** the use of angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARB) .

The initiation of ACEi and ARB for patients with SCD requires adequate follow-up and monitoring of side effects (e.g., hyperkalemia, cough, hypotension). As recommended by the Kidney Disease Improving Global Outcomes guidelines for the general population, the following attention to baseline and changes in renal function is appropriate when prescribing ACEi or ARB for patients with SCD:

- Start medication at a lower dose in individuals with a glomerular filtration rate (GFR) of <45 mL/min/1.73m²
- Assess GFR and measure serum potassium within 1 week of starting medication or following any dose escalation
- Temporarily suspend medication during interval illness, planned intravenous radiocontrast administration, or bowel preparation for colonoscopy or prior to major surgery



RENAL TRANSPLANT FOR END-STAGE RENAL DISEASE

For children and adults with SCD and advanced chronic kidney disease or end-stage renal disease, the ASH guideline panel **suggests** referral for renal transplant .

It is essential that providers adhere closely to general guidelines and recommendations for perioperative transfusion requirements for surgery in adults with SCD. Judicious use of corticosteroids as part of the posttransplant immunosuppression regimen is advised given the potential relationship between steroid exposure and vaso-occlusive pain in patients with SCD.

Strength of Recommendations and Quality of Evidence

The methodology for determining the strength of each recommendation and the quality of the evidence supporting the recommendations was adapted from GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. Guyatt GH, et al; GRADE Working Group. 2008;336(7650):924–926. More details on this specific adaptation of the GRADE process can be found in American Society of Hematology 2019 Guidelines for Sickle Cell Disease: Cardiopulmonary and Kidney Disease.¹

Strength of Recommendation	
	Strong recommendations - Most individuals should follow the recommended course of action. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.
	Conditional recommendations - Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their individual risks, values and preferences.

How to Use This Pocket Guide

ASH pocket guides are primarily intended to help clinicians make decisions about diagnostic and treatment alternatives. The information included in this guide is not intended to serve or be construed as a standard of care. Clinicians must make decisions on the basis of the unique clinical presentation of an individual patient, ideally through a shared process that considers the patient's values and preferences with respect to all options and their possible outcomes. Decisions may be constrained by realities of a specific clinical setting, including but not limited to institutional policies, time limitations, or unavailability of treatments. ASH pocket guides may not include all appropriate methods of care for the clinical scenarios described. As science advances and new evidence becomes available, these pocket guides may become obsolete. Following these guidelines cannot guarantee successful outcomes. ASH does not warrant or guarantee any products described in these guidelines.

The complete 2019 ASH Clinical Practice Guideline for Sickle Cell Disease: Cardiopulmonary and Kidney Disease¹ include additional remarks and contextual information that may affect clinical decision making. To learn more about these guidelines, visit hematology.org/SCDguidelines.

Conflict of interest information for Drs. Liem, Lanzkron, Osunkwo, and Verhovsek may be found at hematology.org/pocketguidesCOI.

¹ Liem RI, Lanzkron S, Coates T, et al. American Society of Hematology 2019 guidelines for sickle cell disease: cardiopulmonary and kidney disease. *Blood Adv*. 2019. In press.



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