Cardiopulmonary and Kidney Disease

An Educational Slide Set

American Society of Hematology 2019 Guidelines for Sickle Cell Disease

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Clinical Guidelines

American Society of Hematology 2019 guidelines for sickle cell disease: cardiopulmonary and kidney disease

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CLINICAL GUIDELINES

blood advances

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American Society of Hematology 2019 guidelines for sickle cell disease: cardiopulmonary and kidney disease

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Background: Prevention and management of end-organ disease represent major challenges facing providers of children and adults with sickle cell disease (SCD). Uncertainty and variability in the screening, diagnosis, and management of cardiopulmonary and renal complications in SCD lead to varying outcomes for affected individuals.

Objective: These evidence-based guidelines of the American Society of Hematology (ASH) are intended to support patients, clinicians, and other health care professionals in their decisions about screening, diagnosis, and management of cardiopulmonary and renal complications of SCD.

Methods: ASH formed a multidisciplinary guideline panel that included 2 patient representatives and was balanced to minimize potential bias from conflicts of interest. The Mayo Evidence-Based Practice Research Program supported the guideline development process, including performing systematic evidence reviews up to September 2017. The panel prioritized clinical questions and outcomes according to their importance for clinicians and patients. The panel used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, including GRADE evidence-to-decision frameworks, to assess evidence and make recommendations, which were subject to public comment.

Results: The panel agreed on 10 recommendations for screening, diagnosis, and management of cardiopulmonary and renal complications of SCD. Recommendations related to anticoagulation duration for adults with SCD and venous thromboembolism were also developed.

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

Summary of recommendations

The management of end-organ damage represents a major challenge facing individuals living with sickle cell disease (SCD), the majority of whom now survive into adulthood.[1] The prevention and treatment of SCD-related complications linked to cardiopulmonary and kidney disease are especially challenging for providers and thus are the focus of these guidelines. The American Society of Hematology (ASH) guideline panel addressed specific questions related to screening, diagnosis, and management of these complications, with special emphasis on the following areas: screening, monitoring, and management of pulmonary hypertension (PH) and pulmonary arterial hypertension (PAH); screening for chronic lung disease;

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The full-text version of this article contains a data supplement.

ASH Clinical Practice Guidelines on SCD

1. **Cardiopulmonary and Kidney Disease**
2. Transfusion Support
3. Cerebrovascular Disease
4. Acute and Chronic Pain
5. Stem Cell Transplantation

How were these ASH guidelines developed?

PANEL FORMATION

Each guideline panel was formed following these key criteria:

- Balance of expertise (including disciplines beyond hematology, and patients)
- Close attention to minimization and management of conflicts of interest

CLINICAL QUESTIONS

10 **clinically-relevant questions** generated in **PICO format** (population, intervention, comparison, outcome)

Example: PICO question

"Should automated red cell exchange vs simple transfusion or manual red cell exchange be used for patients with SCD receiving chronic transfusions?"

EVIDENCE SYNTHESIS

Evidence summary generated for each PICO question via systematic review of health effects plus:

- Resource use
- Feasibility
- Acceptability
- Equity
- Patient values and preferences

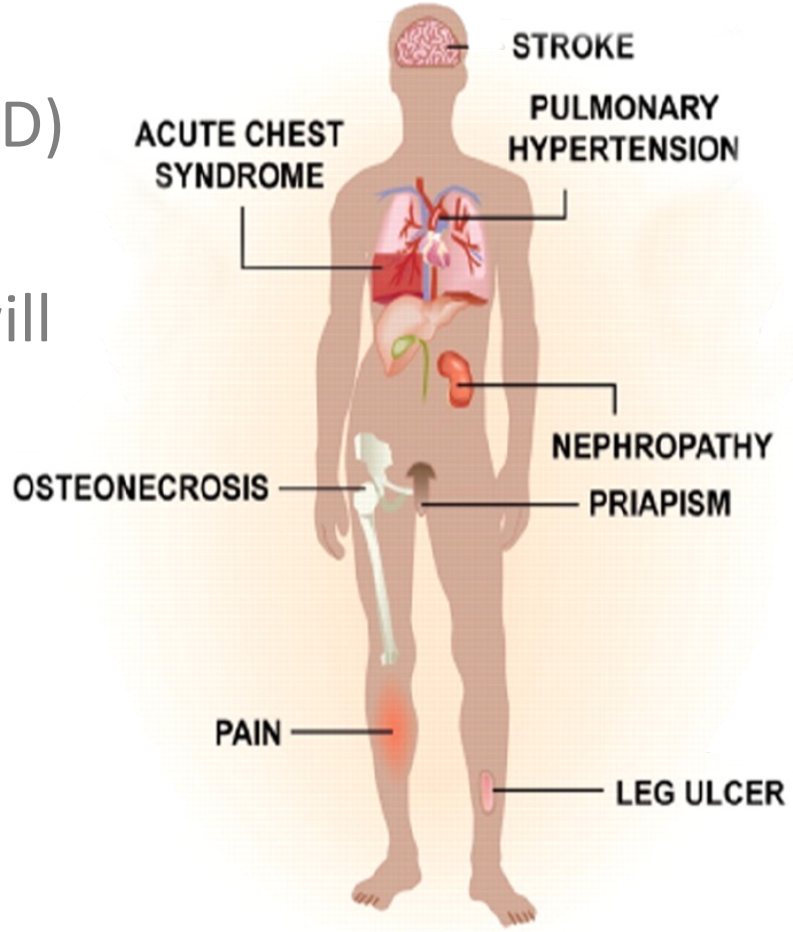
MAKING RECOMMENDATIONS

Recommendations made by guideline panel members based on evidence for all factors.

ASH guidelines are reviewed annually by expert work groups convened by ASH. Resources, such as this slide set, derived from guidelines that require updating are removed from the ASH website.

Background

- About 100,000 Americans have sickle cell disease (SCD)
  - An autosomal recessive hemolytic anemia
- Over 98% of children with SCD in the United States will live to 18 years of age
  - Newborn screening and infection prophylaxis
  - Stroke screening and primary stroke prevention
- End-organ damage is common and progressive
  - Management is challenging



Idowu Akinsheye et al.
Blood 2011;118:19-27

Common End-organ Complications

- Stroke
- Pain
- Chronic lung disease
- Sleep disordered breathing
- Hypertension
- Proteinuria
- Renal insufficiency
- Venous thromboembolism (VTE)

Challenges in Managing Cardiopulmonary Disease in SCD

- Role of screening for pulmonary hypertension (PH), chronic lung disease and sleep-disordered breathing in asymptomatic individuals with SCD has been controversial
- Thresholds for right-heart catheterization to confirm pulmonary arterial hypertension (PAH) need to be better delineated
- Treatment recommendations for confirmed PAH in SCD are also uncertain

Overview of Cardiopulmonary and Kidney Disease Guidelines

Multidisciplinary group of experts reviewed the evidence-based literature to address questions related to

- Screening, monitoring and management of PH and PAH
- Screening for chronic lung disease
- Screening for sleep-disordered breathing
- Management of hypertension
- Management of proteinuria and chronic kidney disease
- Anticoagulation after venous thromboembolism

Objectives

By the end of this session, you should be able to

1. Describe recommendations for routine screening echocardiogram (ECHO) to identify PH
2. Describe recommendations for right-heart catheterization (RHC) in individuals with abnormal ECHO
3. Describe the treatment of PAH identified by RHC
4. Describe recommendations for routine screening pulmonary function testing (PFT)
5. Describe the recommendations for routine sleep study screening

Case

A 21-year-old with hemoglobin SS disease presents as a new patient to your clinic. He feels well and on review of systems, denies shortness of breath, wheezing, chest pain, snoring, headaches, challenges staying awake or exercise intolerance. He reports that he is on hydroxyurea and needs a refill.

On physical exam, he is well appearing. He is afebrile with a respiratory rate of 16, blood pressure of 125/80 and oxygen saturation of 99% on room air. His exam is unremarkable. His CBC revealed a WBC of 10 $x10^3$/uL, Hgb 9 g/dL, MCV 101 fL and platelet count of 280,000.

Case

What health maintenance screenings are indicated?

- PFT
- ECHO
- Urinalysis to screen for proteinuria
- Sleep study
- None at this time

Criteria for Screening Tests

- The condition being screened for should be an important health problem
- The condition being screened for should have a natural history that is understood and a recognized latent or early symptomatic stage
- The screening test should be acceptable to patients
- The screening test should be sensitive and specific
- There should be acceptable treatment for patients with the condition that is more effective if it is started early
- The cost of screening and subsequent treatment should be cost-effective

*adapted from Wilson and WHO criteria and based on GRADE for diagnosis principles

Diagnostic Test Accuracy Synthesis

Diagnostic Test Accuracy Quality of evidence

Assess linked evidence

Final Quality of evidence for each outcome based on DTA and linked evidence and development of recommendations

STUDIES

Sensitivity

Specificity

(+) **TP**
FP

- Those with +ve test/screen +ve will get a different management
- The treatment/management improves outcome

(-) **TN**
FN

- Mortality
- Morbidity
- QoL
- Harms
- Resources
- Other

Recommendation: Screening ECHO

In asymptomatic children and adults with SCD, the ASH guideline panel suggests **against performing a routine screening ECHO to identify PH** *(conditional recommendation, very low certainty in the evidence about effects)*

Evidence: Accuracy of ECHO to Screen for PH

A total of 4 studies (n=1,082) were analyzed for diagnostic accuracy:

- Total of 231 with elevated peak tricuspid regurgitant jet velocity (TRJV) proceeded to RHC
- Of those screened, PH confirmed in 96/1082 (8.9%) and PAH in 48/1082 (4.4%)
- Of those with elevated peak TRJV, PH confirmed in 96/231 (41.6%) and PAH in 48/321 (20.8%)
- Rest did not undergo further evaluation to confirm or exclude PH or PAH

Certainty of Evidence: Screening ECHO

Certainty of evidence to support **screening ECHO** is low because of the following reasons:

- Absence of direct head-to-head comparisons of screening vs. no screening
- High false positive rate using peak TRJV to screen for PH or PAH
- Not clear if screening ECHO results in changes in management (e.g. RHC)
- Unclear which therapies represent appropriate management of elevated peak TRJV and/or PH in SCD
- Not clear if changes in management based on results affect outcomes
- Most patients undergoing screening ECHO who have elevated peak TRJV die from causes other than PH

When is it appropriate to get an ECHO?

Signs, symptoms or diagnoses that may warrant a diagnostic ECHO:

- Dyspnea at rest or with exertion
- Hypoxemia at rest or with exertion
- 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
- History of recurrent hypoxemia at rest or exertion
- Evidence of sleep-disordered breathing with or without hypoxemia
- History of syncope or pre-syncope
- Evidence of loud P2 of second heart sound
- Signs of right heart failure
- History of a pulmonary embolism

Recommendation: Screening PFT

For asymptomatic children and adults with SCD, the ASH guideline panel suggests **against performing routine screening PFT** *(conditional recommendation, very low certainty in the evidence about effects)*

Evidence: Relationship between PFT and outcomes

Outcome	No. of studies (n patients)	Summary of Findings
Sickle cell pain	2 (n=1,442)	Pain not significantly different among those who received vs did not receive PFT
Acute chest syndrome	3 (n=1,564)	No relationship between ACS and either PFT screening or PFT findings
Decline in lung function	8 (n=758)	Observable decline over time in various parameters on PFT between baseline and follow-up measurements
Mortality	2 (n=1,484)	Lower % predicted forced expiratory volume in 1 second associated with higher mortality but mortality rates not different among those who received vs did not receive PFT

Certainty of Evidence: Screening PFT

Certainty of evidence to support **screening PFT** is low because of the following reasons:

- Absence of direct head to head comparisons of screening vs. no screening
- Inconsistent data on relationship between abnormal lung function and outcomes
- Not clear if screening PFT results in changes in management
- Unclear which therapies represent appropriate management of abnormal lung function in SCD
- Not clear if changes in management changes based on results affect outcomes

When is it appropriate to get PFT?

Signs, symptoms or diagnoses that may warrant a diagnostic PFT:

- Wheezing or increased cough during URI
- Dyspnea at rest or with exertion that is new or unexplained
- Chest pain at rest or with exertion that is increased or unexplained
- Increase in exercise limitation
- Abnormal 6-minute walk test defined by either reduced 6MWD or oxygen desaturation
- Recurrent hypoxemia at rest or with exertion
- Syncope or pre-syncope
- Recurrent acute chest syndrome
- Pulmonary embolism

Case

- Your patient returns only every 4 to 6 months even though you provided refills for 3 months at a time. You have reinforced the need to take hydroxyurea daily and tried to help him improve his adherence. Two years after his first visit, the patient returns for a hydroxyurea refill and complains of having a *hard time catching his breath* as he walks across his college campus. This is a *new complaint*.
- On exam, his oxygen saturation is now 93% on room air and his blood pressure is 125/80 mm Hg. His Hgb is 7 g/dL with an MCV of 88 fL on hydroxyurea. A chest X-ray shows clear lungs but mild cardiomegaly.

Case

- Since your patient is now symptomatic, you obtain a diagnostic PFT and an ECHO. His PFT was not diagnostic or conclusive for a cause of his symptoms. His ECHO demonstrates a peak TRJV of 2.8 m/sec.
- You repeat his ECHO in 6 months, which shows a peak TRJV of 2.9 m/sec. At that time, you have him undergo a 6 minute walk test. He is able to walk 250 meters, and his oxygen saturation ranges from 88 to 92% throughout the test.

Case

What laboratory test would be most informative for your next step?

- Repeat CBC with diff and retic
- N-terminal brain natriuretic peptide (NT-BNP)
- D-Dimer
- Hemoglobin electrophoresis

Case

A week later, you see the patient back in clinic. His oxygen saturation is 91% on room air and he only feels short of breath under exertion. He has avoided running and walking long distances. You review the NT-BNP results with him, which was 170 pg/ml.

Case

What are your next steps in managing this patient?

- Repeat ECHO every 6 months
- Referral to a pulmonary hypertension expert
- Referral to cardiology for a right-heart catheterization
- Prescribe selexipag
- Exchange transfusion
- CT of his chest

Recommendations: Management of Abnormal ECHO

- For asymptomatic children and adults with SCD and an isolated peak TRJV of ≥ 2.5 to 2.9 m/s, the ASH guideline panel suggests **against right-heart catheterization** *(conditional recommendation, very low certainty in the evidence about effects).*
- For children and adults with SCD and a peak TRJV of ≥ 2.5 m/s who also have a reduced 6MWD and/or elevated NT-BNP, the ASH guideline panel suggests **right-heart catheterization** *(conditional recommendation, very low certainty in the evidence about effects).*

Evidence: Mortality and adverse events associated with right-heart catheterization

- A total of 3 studies (n=206) examined mortality among selected patients with peak TRJV ≥ 2.5 m/sec who underwent RHC for suspected PH:
  - Among patients who underwent RHC, 29/206 (14.1%) patients died, compared with 54/795 (6.8%) patients who died among those not undergoing RHC
- In the only study that reported adverse events after RHC, pain occurred in 3/96 (3%) of SCD patients after RHC

Certainty of Evidence: Proceeding with RHC versus monitoring TRJV

Certainty of evidence to support proceeding with RHC in asymptomatic patient with peak TRJV of ≥ 2.5 to 2.9 m/sec is low because of the following:

- Absence of direct head to head comparisons of RHC vs. serial monitoring of peak TRJV
- Variability in how existing studies determined which patients with elevated peak TRJV underwent RHC
- Diagnostic limitations of peak TRJV as a screening test for pulmonary hypertension
- Unclear if proceeding with RHC or the results of RHC leads to changes in management that impact outcomes

Other considerations

- Decisions about the need for RHC should be based on ECHOs obtained at steady state and not during acute illness
- Repeating ECHOs demonstrating elevated peak TRJV is important prior to referral for RHC, since reproducibility of TRJV measurements may vary due to technical factors, severity of anemia or increased cardiac output.
- For patients with TRJV of ≥2.5 m/sec who are asymptomatic, the addition of NT-BNP and 6MWD may help to improve the diagnostic accuracy for PH.

Case

- Your patient undergoes a RHC. The results were significant for a mean pulmonary artery pressure of 21 mmHg, pulmonary artery wedge pressure of 13 mm Hg and pulmonary vascular resistance of 5.2 Wood units. These results are consistent with a diagnosis with PAH.
- You discuss with him the need to evaluate him for causes of PAH other than from SCD, including a formal sleep study. You explain that a sleep study had not been necessary before because he did not have signs or symptoms suggesting he needed one.

Recommendation: Screening Sleep Study

For asymptomatic children and adults with SCD, the ASH guideline panel suggests **against screening with formal polysomnography (sleep study) for sleep-disordered breathing** *(conditional recommendation, very low certainty in the evidence about effects).*

Evidence

- A total of 7 studies reported the prevalence of sleep-disordered breathing in children and adults with SCD (n = 489), which ranged from 42% in children to 46% in adults
- In 2 studies that reported cardiovascular outcomes (n = 115), sleep-disordered breathing was associated with a higher mean systolic blood pressure and evidence for impaired left-ventricular diastolic dysfunction, and lower nocturnal oxygen saturation was associated with a shorter time to first cerebrovascular event.
- Sleep-disordered breathing was associated with nocturnal enuresis in 2 studies (n = 311)

Certainty of Evidence

- The overall certainty in the evidence of effects was very low, given that there are no direct head-to-head comparisons of the intervention on patient-important outcomes.
  - There was inadequate study design resulting in biased prevalence estimates
    - One study was prospective with a large, unselected sample
    - Limited sample sizes
    - Retrospective design for others
  - There was inability to determine whether changes or no changes in management based on screening itself affect outcomes in asymptomatic patients.

When is it appropriate to get a sleep study?

Signs, symptoms or diagnoses that may warrant a diagnostic formal sleep study:

- PH confirmed by RHC
- Snoring
- Poor sleep and/or daytime sleepiness
- Early morning headaches
- Poorly controlled hypertension or CHF
- Unexplained desaturation
- Witnessed respiratory pauses
- Obesity
- Early morning headaches
- CO_2 retention on arterial blood gas
- Recurrent priapism or frequent vaso-occlusive pain
- History of ischemic stroke without evidence of vasculopathy
- History of memory loss, difficulties with concentration or confusion
- Children: ADHD, poor academics, behavioral problems

Case

Your evaluation for other causes of PAH in your patient was unremarkable. What are the treatment options for your patient with PAH?

- Increase dose of his hydroxyurea to maximum tolerated dose
- Consider regular exchange transfusions to reduce his hemoglobin S percent to < 30%
- Referral to PH specialist for co-management of PAH
- Consider PAH-specific therapy in conjunction with PH specialist
- All of the above

Recommendations: Treatment of PAH

- For children and adults with SCD who do not have PAH confirmed by right-heart catheterization, the ASH guideline panel recommends **against the use of PAH-specific therapies** *(strong recommendation, low certainty in the evidence about effects).*
- For children and adults with SCD and a diagnosis of PAH confirmed by right-heart catheterization, the ASH guideline panel suggests **the use of PAH-specific therapies under the care of a PH specialist given the lack of alternative treatment options and associated high morbidity and mortality** *(conditional recommendation, low certainty in the evidence about effects).*

Evidence: Treatment of PH in SCD

- There was only one RCT that examined the effects of PAH-specific therapy on exercise tolerance of adults with SCD and PH
  - The efficacy of bosentan vs. placebo could not be determined due to early termination of the trial secondary to low accrual
- Effect of PAH-specific therapy on 6MWD, mortality and other outcomes was variable
  - Studies were limited by small sample size
  - Not all cases of PH were confirmed by RHC

Other Considerations

- *Indirect evidence* related to various classes of PAH-specific therapies was used to guide decision-making given the **high mortality associated with untreated PAH** and the lack of alternative therapies.
- Some PAH-specific therapies were associated with side effects such as pain, but the studies were limited in size and the magnitude of side effects did not seem large.
- PAH-specific therapy in SCD applies to patients with SCD who have no other clear reason for their PAH confirmed by right-heart catheterization.
  - Obstructive sleep apnea
  - Significant lung disease
  - Left-sided heart failure

Other Considerations

- Consider initiation and/or optimization of disease-modifying therapy such as hydroxyurea or chronic transfusions for patients with PAH confirmed by right-heart catheterization.
- Treatment options may differ based on the subtype of PH as classified by findings on RHC and clinical evaluation by a PH specialist.
- Multidisciplinary care that includes a PH specialist is recommended given the increased side effects with PAH-specific therapy.

Other topics not covered in this slide set but are included in these guidelines

- Management of albuminuria
- Renal transplant for end-stage renal disease
- Use of hydroxyurea and erythropoiesis-stimulating agents for chronic kidney disease
- Management of blood pressure
- Management of venous thromboembolism

Summary of Recommendations

Topic	Panel Recommendation	Strength of Recommendation	Notes
Screening ECHO	**Suggests *against*** screening ECHO in asymptomatic patients to identify PH	Conditional	Comprehensive review of systems may identify indications for diagnostic study
Screening PFT	**Suggests *against*** screening PFT in asymptomatic patients	Conditional	Comprehensive review of systems may identify indications for diagnostic study
Screening Sleep Study	**Suggests *against*** screening sleep study in asymptomatic patients	Conditional	Comprehensive review of systems may identify indications for diagnostic study

Summary of Recommendations

Topic	Panel Recommendation	Strength of Recommendation	Notes
Managing abnormal ECHO	**Suggests *against*** RHC for patients with isolated peak TRJV of ≥ 2.5 to 2.9 m/s	Conditional	• Need for RHC should be based on ECHOs done at steady state • ECHOs showing elevated peak TRJV should be repeated • NT-BNP and 6MWD may improve diagnostic accuracy of elevated peak TRJV for PH
	Suggests RHC for patients with peak TRJV ≥ 2.5 m/s and also reduced 6MWD and/or elevated NT-BNP	Conditional	
Treatment of PAH	**Recommends *against*** PAH-specific therapies for patients without PAH confirmed by RHC	Strong	• Disease-modifying therapies should be initiated or optimized • Patients receiving PAH-specific therapies should also be under care of PH specialist
	Suggests PAH-specific therapies for patients with PAH confirmed by RHC	Conditional	

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See more about the ASH SCD guidelines: https://hematology.org/scdguidelines