ATS CLINICAL PRACTICE GUIDELINE: SUMMARY FOR CLINICIANS

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Pulmonary Hypertension in Sickle Cell Disease

Margaret M. Hayes¹, Amar Vedamurthy², Gautam George², Raed Dweik³, Elizabeth S. Klings⁴, Roberto F. Machado⁵, Mark T. Gladwin⁶, Kevin C. Wilson⁴, and Carey C. Thomson²; for the American Thoracic Society Implementation Task Force

¹Johns Hopkins University School of Medicine, Baltimore, Maryland; ²Mt. Auburn Hospital, Harvard Medical School, Boston, Massachusetts; ³Cleveland Clinic, Cleveland, Ohio; ⁴Boston University School of Medicine, Boston, Massachusetts; ⁵University of Illinois College of Medicine, Chicago, Illinois; and ⁶University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

Pulmonary hypertension (PH) is common in sickle cell disease and is known to be a risk factor for death. To improve the care of patients with sickle cell disease, the American Thoracic Society has developed a clinical practice guideline on the treatment of PH in sickle cell disease for pulmonologists, hematologists, cardiologists, pediatricians, and internists. The guideline was created by assembling a panel of experts, reviewing the literature, synthesizing the evidence, and then generating recommendations. This summary for practicing clinicians is prepared from the official guideline document (1).

Definitions

PH is defined as a resting mean pulmonary artery pressure (mPAP) ≥ 25 mm Hg. It occurs in 6 to 11% of patients with sickle cell disease and is classified in World Health Organization (WHO) PH group 5 because patients have variable hemodynamics (i.e., they may have precapillary, postcapillary, or both pre and postcapillary PH).

Precapillary PH is defined as a mPAP of ≥ 25 mm Hg with a mean pulmonary artery wedge pressure (PAWP) or left ventricular end diastolic pressure (LVEDP) of ≤ 15 mm Hg plus increased pulmonary vascular resistance (PVR). Patients with sickle cell disease may have a lower baseline PVR due to anemia; thus, increased PVR is defined as $\geq 160 \text{ dyn} \cdot \text{s} \cdot \text{cm}^{-5}$ or ≥ 2 Wood units.

Postcapillary PH is defined as a PAWP or LVEDP of ≥ 15 mm Hg (in the absence of mitral valve disease) without an increase in PVR.

Pre- and postcapillary PH is defined as a mPAP of ≥ 25 mm Hg, a PAWP of ≥ 15 mm Hg, and an increased PVR. These patients typically also have an elevated transpulmonary gradient (>12 mm Hg) (1).

Diagnosis

Hemodynamic measurements by right heart catheterization are the gold standard for diagnosing PH in sickle cell disease. Noninvasive tests, such as Doppler echocardiography, 6-minute walk tests, and serum N-terminal pro-brain natriuretic peptide (NT-pro-BNP), can aid in the diagnosis. The tricuspid regurgitant velocity (TRV) on Doppler echocardiography can be used to estimate the pulmonary artery systolic pressure. As an example, in a population with a prevalence of PH of 6%, a TRV of ≥ 2.5 m/s has a positive predictive value of 25% for PH, which increases to 62% when the TRV of ≥ 2.5 m/s is combined with an NT-pro-BNP of >164 pg/ml or a 6-minute walk distance of <333 m. Additionally, a TRV of ≥ 2.9 m/s alone has a positive predictive value of 64%. These noninvasive tests are not accurate enough to replace right heart catheterization but do identify patients who are at increased risk of having PH and at an increased risk of death (2).

Estimating Mortality Risk in Sickle Cell Disease

Mortality risk assessment is important in sickle cell disease because it estimates prognosis and guides therapy. However, right heart catheterization is too expensive and too invasive for screening; thus, noninvasive measurements, such as Doppler echocardiography and NT-pro-BNP, are used. The risk of premature death is increased if the TRV is ≥ 2.5 m/s, if the NT-pro-BNP is ≥ 160 pg/ml, or a right heart catheterization has confirmed PH (3, 4).

Doppler Echocardiography

Doppler echocardiography performed every 1 to 3 years to evaluate the TRV predicts mortality risk. The test should be conducted when the patient is clinically stable because vaso-occlusive crises and acute chest syndrome (ACS) can acutely raise the TRV. Screening echocardiograms should not be performed within 4 weeks of ACS or within 2 weeks of a vaso-occlusive crisis. Higher TRVs are associated with higher mortality risk. A TRV of ≥ 2.5 m/s indicates that the risk of death is increased about five times, whereas a TRV of ≥ 3.0 m/s indicates that the risk of death is increased about 10 times (1).

NT-pro-BNP

When Doppler echocardiography is unavailable or when there are difficulties with image acquisition, measurement of the serum NT-pro-BNP is an appropriate

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alternative. NT-pro-BNP is a marker of right and left ventricular strain. As in TRV, the higher the NT-pro-BNP level, the higher the risk of mortality. The mortality rates for a patient with a serum NT-pro-BNP of ≤ 30 , 31 to 159, and ≥ 160 pg/ml are 6, 7, and 26%, respectively. Serum NT-pro-BNP should not be used to screen patients with sickle cell disease who have renal insufficiency because renal dysfunction is associated with elevated NT-pro-BNP levels.

Treatment of Patients with SCD Who Have Increased Mortality Risk

Patients with sickle cell disease who are at an increased risk of death (defined as a TRV of ≥ 2.5 m/s, NT-pro-BNP ≥ 160 pg/ml, or PH confirmed by right heart catheterization) should be referred to a PH center and considered for treatments such as hydroxyurea, chronic transfusion therapy, chronic anticoagulation therapy, and targeted pulmonary arterial hypertension (PAH) treatments (1).

Hydroxyurea

Hydroxyurea is an antineoplastic agent that decreases sickle cell hemoglobin polymerization, vaso-occlusive events, and red blood cell hemolysis. We recommend hydroxyurea therapy for patients with sickle cell disease who have an increased risk for mortality (strong recommendation, moderate quality evidence). This is based on indirect evidence that hydroxyurea decreases 9-year mortality by $>10\%$, decreases hospitalization by about 20%, and decreases episodes of ACS and VOC by 15% among patients with the HbSS genotype who have ≥ 3 VOC or ≥ 1 ACS per year. The major side effect seen in most patients is bone marrow suppression, which usually resolves within 2 weeks of temporary cessation of the medication.

Chronic Transfusion Therapy

Chronic transfusions decrease the number of sickled red blood cells and decrease the

rate of hemolysis. We suggest chronic transfusion therapy for patients with sickle cell disease who have an increased risk of mortality and who are either not candidates for hydroxyurea or are unresponsive to hydroxyurea (weak recommendation, low quality evidence). This is based on indirect evidence that chronic transfusion therapy decreases the incidence of strokes, VOC, and ACS among children with sickle cell disease who are at increased risk for a stroke. There is an 11% incidence of alloimmunization with chronic transfusion therapy, and about 15% of patients will experience an adverse event, including febrile reactions, hemolytic reactions, and volume overload. Iron overload is a common problem with chronic transfusion therapy and is related to the volume of blood transfused.

Chronic Anticoagulant Therapy

Sickle cell disease is associated with an increased risk of large and small vessel pulmonary emboli and with an increased risk of intracerebral hemorrhage. Given these competing risks, venous thromboembolism (VTE) is challenging to treat in these patients. We suggest indefinite anticoagulant therapy rather than a limited duration of anticoagulant therapy for patients with sickle cell disease who have catheterization-confirmed PH, VTE, and no additional risk factors for bleeding (weak recommendation, low quality evidence). Indefinite anticoagulation in such patients is associated with a 13.8% decrease in recurrent VTE and with a possible decrease in mortality, in contrast to a 2.4% increased risk of bleeding.

Associated Conditions

Hypoxemic patients with sickle cell disease and PH should be treated with supplemental oxygen to keep the arterial

oxyhemoglobin saturation 90% or greater at all times. If sleep-disordered breathing is a concern, polysomnography should be performed, and diagnosed conditions should be treated. Proteinuria and microalbuminuria occur frequently in these patients and can be treated with an angiotensin-converting enzyme inhibitor. Diuretics are the treatment of choice for right ventricular volume overload, but in patients with sickle cell disease, diuresis should be managed cautiously because volume depletion promotes erythrocyte sickling.

Targeted Therapy for PAH

Prostacyclin agonists, endothelin receptor antagonists, soluble guanylate cyclase stimulators, and phosphodiesterase-5 inhibitors are targeted PAH therapies. We recommend against targeted PAH therapy for all patients with sickle cell disease who have an elevated TRV alone or an elevated NT-pro-BNP alone and for most patients who have catheterization-confirmed PH (strong recommendation, moderate quality evidence).

For select patients who have a catheterization-confirmed marked elevation of PVR (>2 Wood units), normal PAWP (<15 mm Hg), and related symptoms, we suggest a trial of either a prostacyclin agonist or an endothelin receptor antagonist (weak recommendation, low quality evidence). We recommend against phosphodiesterase-5 inhibitor therapy as first-line therapy (strong recommendation, moderate quality evidence). This therapy is considered off-label because patients with PH in sickle cell disease are classified as WHO group 5, not group 1. The soluble guanylate cyclase stimulators have not been studied in sickle cell disease (1). ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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