6. PULMONARY HYPERTENSION AND CHRONIC PULMONARY DISEASE

Acute chest syndrome is covered in detail in Part II, section 2.

Principles

- To screen all individuals with SCD for pulmonary hypertension.
- To evaluate with echocardiogram, and determine which patients require further testing with right heart catheterization.
- To evaluate for possible underlying causes of pulmonary hypertension.
- To prevent new-onset or progression of pulmonary hypertension.
- To diagnose asthma, sickle cell chronic lung disease, and obstructive sleep apnea in affected patients.
- To appropriately manage chronic pulmonary disease following diagnosis.

Recommendations

A. Pulmonary Hypertension

- All SCD patients should have regular clinical evaluation for cardiorespiratory symptoms, including shortness of breath on exertion, exertional chest pain, syncope, palpitations, peripheral edema, hepatic congestion and ascites.
- Regular pulse oximetry monitoring of oxygen saturation (SpO_2) during medical visits is recommended to determine baseline status. Patients with deteriorating or low (≤95%) measurements should be referred to a respiratory specialist. (Note that transcutaneous monitoring can underestimate oxygen saturation, so appropriate follow-up is recommended to avoid misdiagnosis.)[14,15]
- All SCD patients should have a baseline screening echocardiogram starting at the age of 3 years, including measurement of tricuspid regurgitant jet velocity (TRV).
- Echocardiogram should be repeated at least every 5 years if normal and if the patient is asymptomatic.
- Adult patients should be considered for right-heart catheterization (RHC) as the gold standard for pulmonary hypertension (PHTN) diagnosis if:
  - TRV ≥2.8 m/sec, or
  - TRV ≥2.5 m/sec and symptoms of PHTN, high NT-proBNP testing (>164.5 pg/mL), and/or low six-minute walk distance (≤333 m)
- In patients with PHTN confirmed on RHC, thromboembolic disease, iron overload, systemic hypertension, obstructive sleep apnea, and chronic hypoxemia must be ruled out and treated.
- Hydroxyurea and/or transfusion (simple or exchange) may be considered in patients with PHTN confirmed on RHC. Selection of therapeutic strategy may depend upon the physician and patient preference, and the severity of PHTN.
- Targeted therapy may be considered in consultation with a PHTN specialist. When possible, patients should be considered for enrollment in an available clinical trial.
- Hydroxyurea therapy should be considered even if RHC shows normal pulmonary-artery pressure, as raised TRV on echocardiogram remains a poor prognostic marker, with increased mortality in adults with SCD.

B. Chronic Pulmonary Disease

- Patients should be screened for respiratory symptoms associated with asthma, chronic lung disease, and obstructive sleep apnea (OSA) on routine clinical visits.
- Routine screening pulmonary function testing (including lung-volume measurements and DL_{CO}) should be considered for both adult and pediatric patients to identify subclinical abnormalities.

Asthma

- Patients describing symptoms suggestive of asthma should have spirometry testing with bronchodilator challenge.
- Young children (e.g., those under 6 years of age) with respiratory signs and/or symptoms who are unable to perform pulmonary function testing may benefit from consultation with an asthma specialist, as a diagnosis of asthma can be difficult to establish.
- Medical management of asthma in patients with SCD should follow established clinical practice guidelines.
- Consultation or co-management with an asthma expert is recommended.

Obstructive Sleep Apnea

- Patients with symptoms of obstructive sleep apnea or sleep-disordered breathing should be referred for overnight polysomnography and/or consultation with a sleep specialist physician or ENT specialist.

Smoking

- Patients with SCD should be discouraged from smoking, as smoking has been independently associated with mortality in young adults with SCD.

Background

A. Pulmonary Hypertension

Chronic hemolysis in sickle cell disease (SCD) results in depletion of nitric oxide, and probable resultant increase in pressures in the pulmonary arterial circulation. Pulmonary embolization, fat emboli, or in situ thrombosis may also be involved in the pathophysiology.[1]

B. Other Chronic Pulmonary Disease

a) Asthma

Patients with SCD have been reported to have either similar or higher rates of asthma compared with peers. Asthma is associated with increased rates of sickle pain, acute chest syndrome, stroke, and premature death.[16-18] As per the Canadian Thoracic Society (CTS) guidelines, "a diagnosis of asthma should be considered in individuals of all age groups with recurrent symptoms (e.g., frequent episodes of breathlessness, chest tightness, wheezing or cough, that are often worse at night and in the early morning) and signs of variable airway obstruction".[19] These symptoms may present after exposure to certain triggers (e.g., allergens, cold air, exercise, viral upper respiratory tract infection). Physical findings may include diffuse, high-pitched expiratory wheezes on respiratory exam, but this exam finding has poor positive- and negative-predictive value. Diagnosis is based on the demonstration of airflow limitation on spirometry, and reversibility with bronchodilator. Methacholine challenge should only be performed in consultation with sickle cell disease (SCD) and asthma experts, due to the theoretical risk of bronchoconstriction triggering a vaso-occlusive episode.[20]

Patients with SCD and asthma should receive attentive management to improve symptoms and prevent complications.[20] Established clinical practice guidelines, such as those from the Canadian Thoracic Society, should be followed.[19] Consultation or co-management with an asthma expert is recommended.

b) Sickle Cell Chronic Lung Disease

In adult patients with sickle cell anemia (HbSS), 90% of the population has abnormalities upon pulmonary function testing, with the most common abnormalities being mild restrictive defects (74%) and isolated low diffusing capacity for carbon monoxide (DL_{CO}) (13%).[21] These changes may occur as a result of repeated episodes of acute chest syndrome, causing patchy areas of lung fibrosis. Recurrent chest wall vaso-occlusive episodes, spinal osteoporosis, and osteomalacia have also been postulated to play a role in the development of these changes. In children, restrictive patterns and progressive decline in lung volumes have also been observed.[22]

c) Obstructive Sleep Apnea

Children and adolescents with SCD have higher rates of obstructive sleep apnea (OSA) and sleep-disordered breathing (SDB) than their peers, with estimated prevalence of 10% to 20%.[23,24] Studies have demonstrated a link between nocturnal desaturations and cerebrovascular ischemia,[25] sickle painful episodes, left ventricular hypertrophy, and diastolic dysfunction.[26]

OSA in patients with SCD may be related to a relatively increased size of oropharyngeal lymphoid tissue and reduced airway dimensions.[24] Therapeutic options may include medical treatment, continuous positive airway pressure, or surgery. Adenotonsillectomy has been shown to decrease the severity of OSA in children with SCD, with fewer obstructive respiratory events and less severe nocturnal oxygen desaturation post-operatively.[27] Specialist hematologist, respirologist, and/or ear, nose and throat specialists should assess the patient, selecting optimal therapy based on individual patient factors.

d) Smoking

Patients with SCD should be discouraged from smoking, as smoking has been independently associated with mortality in young adults with SCD.[18]

Diagnosis

a) Clinical Evaluation

With current screening practices in SCD, many patients are asymptomatic at diagnosis. Symptoms of moderate or severe pulmonary hypertension may include shortness of breath on exertion, exertional chest pain, exertional syncope, peripheral edema, palpitations, hepatic congestion, and ascites.

b) Echocardiogram

Estimates of the prevalence of pulmonary hypertension (PHTN) in patients with SCD vary based on the testing method employed. Echocardiogram is a simple, noninvasive method to screen for PHTN. Estimated right-ventricular and pulmonary-artery systolic pressure are calculated from the measured tricuspid regurgitant jet velocity (TRV); TRV ≥2.5 m/sec corresponds to elevated pulmonary artery pressure.

Echocardiogram findings suggestive of PHTN are present in 11% to 32% of children and adolescents with SCD,[2,3] and approximately 30% of adults with SCD.[4-6] Furthermore, elevated TRV (≥2.5 m/sec) in adults is associated with an increased risk of death,[4,6] regardless of its etiology, and is thus a biomarker of severe SCD. Elevated TRV can be seen in children with SCD as early as the age of 3 years.[7,8] No association has been clearly established between elevated TRV and morbidity or mortality in children.[9,10]

c) Right-Heart Catheterization

Compared with right heart catheterization (RHC), which is the gold-standard method for diagnosis of PHTN, echocardiography had a false positive rate of 75% in one large adult SCD study – a positive predictive value of only 25%.[5] In this study, the prevalence of PHTN by RHC in the adult SCD population was approximately 6%. The authors found that when TRV was ≥2.5 m/sec, propeptide of brain natriuretic peptide (NT-proBNP) was high (>164.5 pg/mL), and the six-minute walk distance was low (≤333 m); the positive predictive value of echocardiography was 62% with a false negative rate of 7%. Using the above criteria may be beneficial in selecting patients for RHC after positive echocardiogram screening. There are limited data available on the role of RHC in diagnosis of PHTN in pediatric SCD patients.

A recent study found that survival estimates for subjects with PHTN diagnosed by RHC versus those subjects without PHTN by RHC were 63% versus 83% at 5 years from diagnosis.[11] Further study of the relative importance of echocardigraphic versus RHC findings is required, as is the development of more predictive non-invasive screening tools. The current body of available evidence indicates that echocardiogram alone is insufficient for the diagnosis of pulmonary hypertension in adult SCD patients. Of note, the role of RHC in diagnosing PHTN in pediatric patients with SCD has not been reported.

Prevention and Treatment

Since hemolysis is believed to play a central role in the pathophysiology, reducing the hemolytic rate is likely to be beneficial. Thromboembolic disease, iron overload, systemic hypertension, obstructive sleep apnea, and other causes of chronic hypoxemia must be ruled out and treated, if identified.[12]

Higher levels of fetal hemoglobin F (HbF) are associated with a reduced risk of PHTN.[13] HbF-inducing therapies such as hydroxyurea, therefore, may be beneficial in preventing PHTN onset or progression. Prospective studies are required to evaluate this hypothesis.

There is no current standard of care for pharmacologic treatment of symptomatic PHTN in SCD. Hydroxyurea and chronic exchange transfusion may be beneficial in preventing disease progression, although there have been no prospective trials studying PHTN as an outcome. Targeted therapeutic options for RHC-confirmed PHTN should be guided by a team of PHTN specialists and hematologists specializing in SCD care.

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