



Asthma in children with sickle cell disease

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Purpose of review

Asthma is common in children with sickle cell disease (SCD) and appears to be associated with increased morbidity. Providers caring for children with SCD have struggled with the question of whether asthma exists as a true comorbidity or whether certain aspects of the chronic inflammatory disease gives children with SCD an asthma-like phenotype.

Recent findings

Clinical signs and symptoms seen in children with asthma in the general population, such as wheezing, airway hyperresponsiveness, atopy, elevated leukotrienes, and abnormal lung function are seen in children with SCD both with and without a diagnosis of asthma.

Summary

Current evidence highlights that the presence of lung disease in children with SCD has significant implications irrespective of the underlying cause, including asthma. Further research should focus on well tolerated and effective interventions to prevent disease-related complications for children with pulmonary complications of SCD.

Keywords

anemia, asthma, children, lung disease, sickle cell disease

INTRODUCTION

Asthma has been defined as a chronic inflammatory disease of the airways and is one of the most common chronic diseases of childhood [1], affecting 8% of children aged 0–17 years in the United States in 2016 [2]. Asthma is more prevalent in African American children (15.7%) as compared with Caucasians (7.1%) [2] and is associated with an increased risk of hospitalization and death among this population [3].

Sickle cell disease (SCD) is also a chronic illness characterized by inflammation, anemia, hemolysis, and vascular injury. In North and South America, SCD primarily impacts individuals of African descent, but is also present in individuals from the Mediterranean, middle East and India. The prevalence of asthma in individuals with SCD has been reported between 17 and 28% [4–6]. Asthma in individuals with SCD is associated with increased incidence of vaso-occlusive pain episodes [4,5], acute chest syndrome (ACS) [4,5,7–10], and mortality [11]. Since the initial recognition of asthma as a comorbidity, providers have questioned the contribution of the asthma diagnosis as well as the various phenotypic features of asthma to the clinical course for individuals with SCD.

Given the protean nature of asthma in the general population, the challenges of making the diagnosis of asthma in children with SCD is more

difficult. With the observation that the underlying pathophysiology of SCD includes chronic inflammation, providers have postulated if asthma exists as a true comorbid condition, or whether SCD-related airway disease that mimics asthma is more representative of chronic pulmonary inflammation, vasculopathy, and hemolysis-associated pulmonary dysfunction [12–14]. Symptoms of an acute asthma exacerbation, such as cough, wheezing, shortness of breath, and chest pain are similar to symptoms associated with an episode of ACS seen in individuals with SCD [15,16]. Additionally, clinical signs and symptoms, such as wheezing [17], airway hyperresponsiveness [10,18–20], atopy [21], elevated leukotrienes [22–24], and abnormal lung function

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KEY POINTS

- Pulmonary disease and manifestations are an important cause of disease-related complications in children with SCD.
- A physician diagnosis of asthma, as well as various asthma-like features, are associated with increased risk for pain and acute chest syndrome episodes for children with SCD.
- Even in children without a diagnosis of asthma, providers should screen children for pulmonary symptoms and asthma risk factors and consider referral for comprehensive care for children with SCD.
- Additional studies should focus on therapies targeting lung disease for children with SCD.

measurements [25] may be seen in individuals with SCD either with or without asthma. Whether these are separate entities or if there is considerable overlap is not completely clear (Fig. 1).

The following review will examine how a diagnosis of asthma as well as the various asthma-like

features contributes to the morbidity and mortality of SCD. This discussion can be challenging, given the multiple different definitions of asthma used across various studies. The most commonly used definitions include a physician diagnosis of asthma, parental report, and use of an asthma-controller medication [4,5,7,26,19,27]. We will also examine how asthma risk factors have been associated with disease-related complications in individuals with SCD. Given this association, we will delineate when primary providers (general pediatricians or hematologists) should consider subspecialty referral for children with pulmonary complications of SCD.

DIAGNOSIS OF ASTHMA IS ASSOCIATED WITH INCREASED DISEASE-RELATED MORBIDITY IN CHILDREN WITH SICKLE CELL DISEASE

The Cooperative Study of Sickle Cell Disease (CSSCD) examined 291 children with hemoglobin SS enrolled from 1978 to 1988 with a mean follow-up of 11 years and 3206 patient years of follow-up. In this cohort, 16.8% of children were diagnosed with asthma, as defined as a clinical diagnosis in the

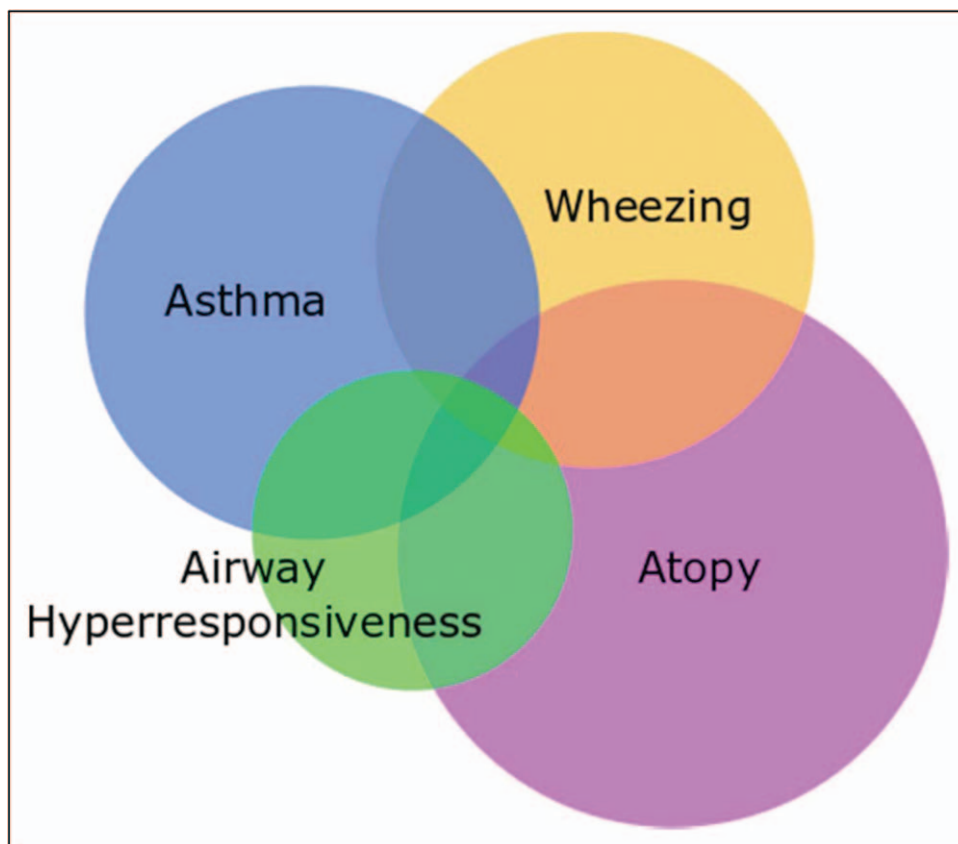


FIGURE 1. Venn diagram to illustrate the overlap of asthma with the additional asthma-like features contributing to disease-related complications for children with sickle cell disease. The size of the circles represents the relative incidence of each feature in children with sickle cell disease; however, the incidence of overlap is uncertain in this population.

medical record during any study visit or any documented use of an asthma medication, such as bronchodilators or inhaled corticosteroids, in children older than 5 years of age [4]. Participants with a diagnosis of asthma were noted to have an increased incidence of painful episodes compared with those without asthma, 1.39 vs. 0.47 events per patient-year ($P < 0.001$). Asthma was also associated with more frequent ACS episodes, 0.39 vs. 0.20 events per patient year ($P < 0.001$) [4].

A more contemporary cohort of 1016 children from the Silent Cerebral Infarct Transfusion (SIT) trial were enrolled from 2004 to 2010 and clinical data was collected retrospectively with a total of 3048 years of follow-up. A similar diagnosis of asthma was used, including a physician diagnosis documented in the medical record or use of an asthma medication with support by parental report. Children with a diagnosis of asthma had increased incidence rates of vaso-occlusive pain as compared with those without asthma (67 vs. 51 episodes per 100 patient years; $P = 0.046$). Similarly, participants with a diagnosis of asthma had increased incidence rates of ACS episodes as compared with those without asthma (19 vs. 12 episodes per 100 patient years; $P = 0.02$) [5].

A third study, the Sleep and Asthma Cohort (SAC), enrolled 252 children with SCD and followed them prospectively for a median of 4.61 years for a total of 857 patient years of follow-up for examination of pain and ACS episodes. Asthma classification was determined similarly to the two prior studies [4,5]. A total of 187 participants had complete data for asthma classification and evaluated covariates. There was no association between asthma diagnosis and pain occurring after entry [incidence rate ratio (IRR) = 1.28; 95% confidence interval (CI) 0.78–2.10]. However, a diagnosis of asthma was associated with an increased incidence of ACS episodes after entry into the study (IRR = 2.21; 95% CI 1.31–3.76) [9].

We conducted a pooled analysis by combining the CSSCD, SIT, and SAC cohorts, resulting in a dataset with 1685 participants with a mean follow-up of 6.1 years and a total of 10216 patient years, with 390 patients (23.1%) having an asthma diagnosis. Using negative binomial regression, we estimated the association between asthma and pain and ACS, respectively, with covariates of sex, age, hemoglobin, and white blood cell count. There was a positive association of asthma diagnosis with pain (IRR = 1.34, 95% CI 1.16–1.55, $P < 0.001$), and a positive association with ACS episodes (IRR = 1.89, 95% CI 1.61–2.22, $P < 0.001$; Fig. 2).

Given the challenge in making a diagnosis of asthma in children with SCD, investigators have sought to identify the clinical factors, which may

differentiate those with and without a physician's diagnosis of asthma. Authors from the SAC study concluded that having a parent with asthma and presence of wheezing symptoms are the best features to aid in identifying children with SCD and asthma [9]. In the SIT trial, 261 of 521 participants had total IgE levels greater than the 90th percentile when compared with the general population. This study also showed that children with higher IgE levels had higher odds of having a physician diagnosis of asthma [5]. Clinically many children with SCD may present with elevated IgE levels or wheezing symptoms who are not given a physician diagnosis of asthma. Additional studies have examined certain features associated with asthma to attempt to understand if there are certain components of the asthma-like phenotype in individuals with SCD, which may be related to the increased incidence of pain or ACS episodes.

WHEEZING WITHOUT A DIAGNOSIS OF ASTHMA IS ASSOCIATED WITH INCREASED INCIDENCE OF PAIN AND ACUTE CHEST SYNDROME EPISODES IN INDIVIDUALS WITH SICKLE CELL DISEASE

Recurrent wheezing causing shortness of breath has been demonstrated to be an independent predictor of increased risk for vaso-occlusive pain and ACS in adults with SCD, independent of asthma diagnosis [28]. In a prospective cohort of 262 adults and children with SCD (aged 6–68 years), documentation of wheezing on physical exam on presentation to the emergency department, irrespective of asthma, was associated with more than two times the incidence of vaso-occlusive pain and ACS episodes during a 4 year follow-up period [17]. Additionally, among 159 children with SCD in the SAC study, parental report of an episode of wheezing causing shortness of breath was associated with an increased risk of episodes of ACS during a 5-year follow-up period (IRR 1.4, $P = 0.04$) [29].

AIRWAY HYPERRESPONSIVENESS IS COMMON IN SICKLE CELL DISEASE BUT NOT ASSOCIATED WITH INCREASED RISK FOR PAIN OR ACUTE CHEST SYNDROME EPISODES

Airway hyperresponsiveness is a measure of airway lability that is thought to reflect bronchial inflammation. Airway hyperresponsiveness has been experimentally determined by methacholine, cold air, or exercise challenge testing. The prevalence of airway hyperresponsiveness in individuals with SCD appears to be high and has been seen in children without a

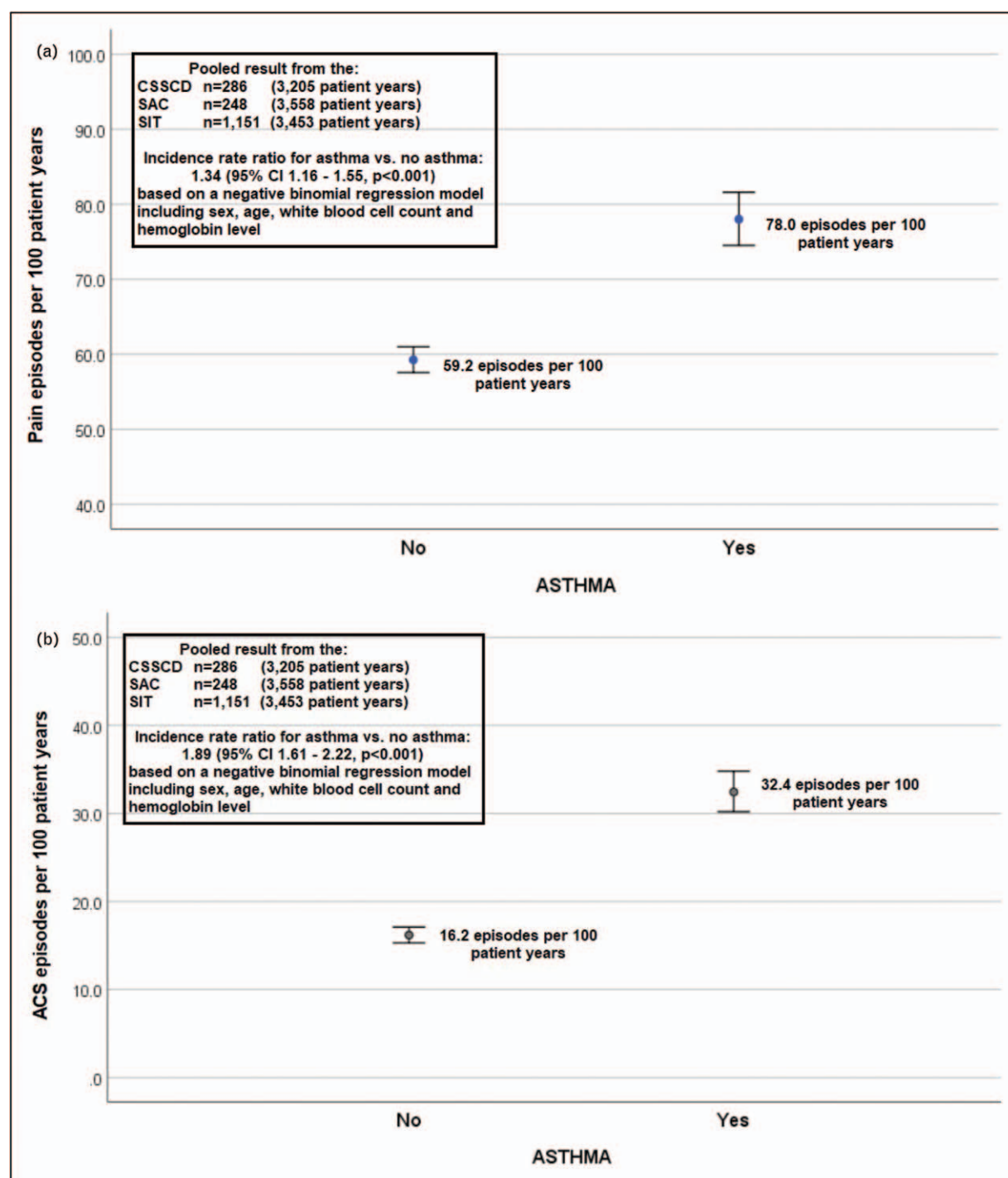


FIGURE 2. Pooled analysis showing the relationship between asthma and pain and acute chest syndrome in children with sickle cell disease. (a) Relationship between pain and asthma from CSSCD, SIT, and SAC studies. (b) Relationship between acute chest syndrome and asthma from CSSCD, SIT, and SAC studies. CSSCD, Cooperative Study of Sickle Cell Disease; SAC, sleep and asthma cohort; SIT, Silent Cerebral Infarct Transfusion.

diagnosis of asthma [18,30]. Previous studies have shown mixed results when examining the relationship between ACS and airway hyperresponsiveness. Ozbek *et al.* [19] demonstrated a relationship between a history of ACS episodes and increased

airway hyperresponsiveness, whereas Sylvester *et al.* [20] showed no difference in the prevalence of airway hyperresponsiveness among children with a history of ACS compared with those without a history of ACS, and Knight-Madden *et al.* [10] did not

find an association between airway lability and recurrent ACS. In a cohort of 70 children with SCD, airway hyperresponsiveness, as measured by methacholine challenge, was not found to be predictive of future risk for pain or ACS episodes [31]. A study of 99 children with SCD showed that lactate dehydrogenase (LDH) was associated with methacholine responsiveness [18]. LDH is a marker of hemolysis, which has been associated with nitric oxide resistance as well as other disease-related complications in SCD [32]. The association with LDH may suggest a connection between chronic hemolysis and pulmonary inflammation in children with SCD, independent of asthma.

ATOPY IS NOT MORE COMMON IN CHILDREN WITH SICKLE CELL DISEASE BUT IS ASSOCIATED WITH INCREASED RISK FOR ACUTE CHEST SYNDROME

Atopy has been identified as the most significant risk factor for the development of asthma in the general population, with an increased risk of 10–20-fold [33]. According to the American Academy of Allergy Asthma and Immunology, atopy is a genetic tendency to develop allergic diseases, such as allergic rhinitis, asthma, and atopic dermatitis. This is typically associated with a heightened immune response to common allergens, such as inhaled aeroallergens or certain foods, which can be identified by allergy skin test reactivity or serum antigen-specific IgE testing. Given that IgE blood testing for allergic sensitization is not as sensitive as allergy skin test reactivity [34,35], for research purposes, many studies have used the definition of a positive skin test to indicate atopy. In a study of 165 children with SCD in the United States, 67 participants (40.6%) were found to have at least one positive skin test [21^{*}]. Data from adults and children in the general population has shown that 54.3% of individuals in the United States has had positive skin test responses to one or more allergens [36].

A case control study of 80 children with SCD aged 5–10 years found a similar incidence of having at least one positive skin test among those with SCD (36%) and those without (34%), $P = 0.75$. This study also demonstrated that children with a history of atopy (one or more positive skin test), and atopic asthma (positive skin test as well as a physician diagnosis of asthma), were more likely to have a history of recurrent ACS episodes [10]. Prospective data from SAC has shown additive effects of having positive skin tests on future rates of ACS (IRR for each positive test 1.23, 95% CI 1.11–1.36, $P < 0.001$), independent of asthma diagnosis. No association was found between atopy and future

vaso-occlusive pain episodes. Furthermore, these data have shown that a positive allergy skin test may be the most important feature of atopy contributing to future ACS episodes [21^{*}].

LEUKOTRIENES ARE ELEVATED IN INDIVIDUALS WITH SICKLE CELL DISEASE, BOTH WITH AND WITHOUT ASTHMA, AND INCREASE WITH AN ACUTE PAIN OR ACUTE CHEST SYNDROME EPISODE

Leukotrienes are mediators of inflammation derived from arachidonic acid. Cysteinyl leukotrienes have been well studied in asthma pathogenesis and increased levels correlate with increased asthma severity [37] and asthma exacerbations [38]. Leukotriene B₄ has been shown to trigger neutrophil migration through induction by free heme [39]. Baseline levels of both cysteinyl leukotrienes and leukotriene B₄ have been identified in individuals with SCD at steady state when compared with controls [23,40,41]. Levels of these leukotrienes are also noted to increase during an acute pain [23,41] or ACS episode [40]. Cysteinyl leukotriene levels seemed to be most elevated among children with SCD and a physician diagnosis of asthma, however, levels are increased in individuals with SCD without asthma when compared with the general population [41]. These data have provided preliminary evidence that leukotrienes contribute to the pathogenesis of vaso-occlusive disease and suggest that leukotriene receptor antagonists may be beneficial for individuals with SCD, as they have been used in the treatment of allergic disease and asthma.

RESULTS OF PULMONARY FUNCTION TESTING DOES NOT PREDICT PAIN OR ACUTE CHEST SYNDROME BUT MAY BE ASSOCIATED WITH MORTALITY

Asthma is a clinical diagnosis. However, after the diagnosis has been made, National Heart, Lung and Blood Institute (NHLBI) recommends routine use of spirometry to demonstrate airway obstruction is reversible, classify severity, and manage the disease [1]. However, many children with asthma, even severe asthma, may have normal spirometry measurements [42]. Similarly, in SCD, spirometry findings have yielded variable results. Most children with SCD have lung function that is within normal limits [25,43]; however, lung growth appears to be significantly reduced compared with age, race-matched controls [44]. In adults with SCD, restrictive defects are commonly reported [45,46]. Current SCD management guidelines do not recommend routine use of pulmonary function testing [47]. In a study of 149 children

from SAC, neither retrospective rates of pain nor ACS was associated with obstructive lung function patterns. Additionally, baseline obstructive lung function patterns were not predictive of future pain or ACS episodes [25]. However, spirometry findings can provide important prognostic information. Longitudinal data from the CSSCD has shown that young adults with SCD and a decreased forced expiratory volume in 1 s (FEV1) had an increased risk for death over the course of 5 years [48]. What factors contribute to a decline in FEV1% predicted over time is not clear. In a prospective study of 197 children with SCD, only a very small decline in FEV1% predicted was noted over time (0.3% per year) and none of the examined clinical covariates (sex, baseline hemoglobin, white blood cell count, reticulocyte count, incidence rate of pain or ACS, asthma diagnosis, or treatment with hydroxyurea) were associated with this decline [49].

COMORBIDITIES OF ASTHMA MAY EXACERBATE SYMPTOMS IN CHILDREN WITH SICKLE CELL DISEASE

Children with severe asthma, without SCD, are more likely to have additional comorbidities that may exacerbate their symptoms, such as obesity or obstructive sleep apnea syndrome (OSAS) [50]. These additional factors should be considered in children with difficulty to control asthma and SCD. Obesity is uncommon in children with SCD, as these children are more likely to suffer from growth failure and malnutrition because of an increase in metabolic demand and reduced protein-calorie intake [51,52]. However, both obesity and malnutrition are associated with increased systemic inflammation. Lung function [53], cognitive function [54], and hospitalizations [55] have all been associated with poor nutrition in children with SCD. Micronutrient deficiencies, such as vitamin D, has been related to complications in both asthma [56] and SCD [57–59].

OSAS is thought to be an independent risk factor for asthma exacerbations and is an important consideration for clinicians when seeing patients with poorly controlled asthma [60]. Cross-sectional baseline data from 243 children in SAC has demonstrated a higher prevalence of OSAS in children with SCD than in the general pediatric population [6]. However, the prospective cohort study did not demonstrate an increased incidence rates of acute severe pain episodes or episodes of ACS in children with sleep disordered breathing. This study did not specifically examine children with OSAS and asthma [61]. Although OSAS may be more common in children with SCD with proposed increased risks

for asthma exacerbations, the connection between this comorbidity and disease-related complications in SCD is not as clear.

TREATMENT OPTIONS FOR CHILDREN WITH ASTHMA AND SICKLE CELL DISEASE IS LIMITED BY LACK OF LARGE MULTICENTER-CONTROLLED TRIALS

Asthma is a very heterogeneous condition in children with a spectrum of severity of inflammation. An underlying assumption exists that there is concordance between the inflammation and symptoms and that the inflammation is responsive to corticosteroid treatment [62]. There is currently very little evidence for the effects of asthma therapies in children with SCD, as large multicenter controlled trials have not been completed to date. Current treatment guidelines for asthma in children with SCD is based on the NHLBI guidelines for asthma treatment in children without SCD [63].

Given the high prevalence of asthma in in SCD and its association with increased morbidity, SCD-specific asthma guidelines are needed. Specifically, the role of steroids for treatment of acute asthma exacerbations, has to be carefully considered in children with SCD. Oral corticosteroids, the standard therapy for acute asthma exacerbations, are associated with an increased risk for acute vaso-occlusive pain and hospital readmission temporally associated with the steroids [64,65]. A similar risk has not been observed with inhaled corticosteroids. A feasibility study had been completed examining the use of inhaled corticosteroids for preschoolers following a first episode of ACS to prevent subsequent vaso-occlusive events [66]. The study demonstrated feasibility, but a larger efficacy study needs to be completed in children. In a single-center trial in nonasthmatic adult participants with SCD receiving daily inhaled mometasone furoate for 16 weeks, a significant decrease in daily pain scores was demonstrated over time [67]. In an observational cohort study of 120 children with SCD admitted for ACS, the use of inhaled corticosteroids did not demonstrate a significant reduction in ACS morbidity, such as PICU transfer, intubation, oxygen requirement, length of stay, and hospital readmission [68]. Additional studies are needed to better understand the pathophysiology and ideal interventions for asthma and asthma-related complications in children with SCD.

CONCLUSION

Evidence supports the notion that the presence of lung disease in children with SCD significantly increases morbidity. Whether a patient with SCD

Table 1. Considerations for management of children with pulmonary complications of sickle cell disease

Indications for subspecialist referral (pulmonary or allergy)

- Two or more episodes of acute chest syndrome
- First episode of acute chest syndrome occurring in child less than 4 years old
- Episode of acute chest syndrome in a child with a significant family history of asthma (parent or sibling)
- Life-threatening episode of acute chest syndrome requiring red blood cell exchange transfusion
- History of atopy (eczema, food and/or aeroallergy sensitization) wheezing, exercise intolerance, or chronic cough
- Concerns for sleep disordered breathing

Considerations for additional testing/management by pulmonary or allergy subspecialist

- Spirometry
- Allergy skin testing
- Plasma total IgE
- Treatment of asthma based on NHLBI guidelines with the exception of systemic corticosteroids for acute exacerbations (consideration of a single dose of oral corticosteroids with close monitoring for rebound acute vaso-occlusive pain)

NHLBI, National Heart, Lung, and Blood Institute.

has lung disease owing to classical asthma or an asthma-like phenotype is less important than the presence of pulmonary disease. With the growing body of literature supporting the idea that lung disease is a poor prognostic indicator in adults and children with SCD, two pressing questions are raised: how do we treat these patients? And who is going to manage lung disease in patients with SCD? (Table 1) An assumption has been made to treat individuals based on the current, extensively studied asthma guidelines. However, our patient population needs large multicenter trials to truly understand the implications and potential benefits of both acute and chronic therapies for children with SCD. The management of lung disease in children with SCD merits multidisciplinary care. Engaging Pediatric Pulmonologist or Allergists in the management of children with SCD and lung disease seems both indicated and prudent. Clearly, research will be ongoing on how to identify the optimal therapeutic strategies and to elucidate the underlying mechanism between the increased morbidity of asthma in children with SCD.

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Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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