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Asthma morbidity and treatment in children with sickle cell disease

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Abstract

Children with sickle cell disease (SCD) and a comorbid condition of asthma have increased numbers of vaso-occlusive pain and acute chest syndrome episodes, and all-cause mortality. When assessed systematically, asthma prevalence is probably similar among children with SCD when compared with the general African–American population. With increasing recognition of the importance of asthma in the management of SCD, hematologists must become familiar with asthma and develop a multidisciplinary approach, including early recognition, appropriate management and referral to asthma specialists.

Keywords

acute chest syndrome; asthma; bronchial hyper-reactivity; bronchodilator response; pulmonary function tests; sickle cell disease; sickle cell pain

Sickle cell disease (SCD) is one of the common hemoglobinopathies worldwide and is inherited as an autosomal recessive disorder by mendalian genetics [1,2]. Hemoglobin SS (SCD-SS) and sickle cell-β^0 thalassemia (SCD-S β^0thal) are the most severe phenotypes, occurring in approximately 60% of individuals with SCD in North America. Other compound heterozygote phenotypes, including hemoglobin SC (SCD-SC) and sickle cell-β+ thalassemia (SCD-Sβ+ thal) occur in approximately 9–12% and 1%, respectively, based on data from newborn cohort studies [3–5]. The underlying defect in SCD-SS is a single nucleotide substitution, which results in a hemoglobin molecule that has substitution of glutamic acid with valine at position 6 of the β-globin molecule [6]. SCD-SC occurs from single nucleotide exchange resulting in the substitution of glutamic acid with lysine also at position 6 of the hemoglobin molecule. These amino acid switches change the net electrical charge of the hemoglobin molecule making it easily susceptible to polymerization under

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states of low oxygen tension and stress [7]. SCD-Sβ+ thal and SCD-Sβ^{0}thal phenotypes are due to impaired production of β-hemoglobin chains resulting from gene deletions or mutations in the presence of the sickle cell mutation in the other β-globin allele. SCD-Sβ+ thal is characterized by decreased production, and SCD-Sβ^{0}thal by complete absence, of the β-chain. Atopic asthma, a chronic disorder of the airways, is characterized by recurrent episodes of airway narrowing from inflammation, mucus plugging and bronchoconstriction culminating in airway remodeling [8,9]. Similar to SCD, asthma exhibits significant heterogeneity in clinical presentation in children. Diagnosis of asthma is primarily based on symptoms and clinical findings, and can be supported by pulmonary function tests, such as the presence of airway obstruction and bronchodilator response on spirometry, which may also be useful in monitoring effectiveness of treatment. Supporting laboratory tests include elevation of total serum IgE levels, peripheral blood eosinophilia and specific allergen sensitivity. Despite being supportive for the diagnosis of asthma, the use of laboratory or pulmonary function studies alone are not indicative of an asthma diagnosis. In our clinical experience, in the setting of acute asthma exacerbation, many patients with SCD will not have decreased oxygen saturation [10] and will not have any audible wheezing; however, when spirometry is performed there is evidence of airway reversibility that correlates with the current symptoms.

Epidemiology of asthma & SCD

Newborn screening data between 1990 and 1999 reported an incidence of SCD of one in 2474 of live births [11]. All 50 states and the District of Colombia currently have active screening programmes for hemoglobinopathies [12]. In the USA, SCD population estimates ranged from 104,000 to 138,900 based on birth cohort disease prevalence, but from 72,000 to 98,000 when corrected for early mortality [13].

The past 20 years have seen a doubling in the incidence of asthma, with about 34 million people affected [14]. Between 2006 and 2008, asthma prevalence was 9.3% amongst children under the age of 17 years, with prevalence in African–Americans at 14.6% and multiracial children, 13.6%, when compared with Caucasians, 8.2% [15]. Unlike children, the prevalence of asthma in African–Americans adults is 7.8%, similar to the general population prevalence of 7.3% [15]. These prevalence estimates for asthma were based on eliciting a positive response by an adult member of a family to the question ‘have you ever been told by a doctor or other health care professional that you have asthma?’ and ‘do you still have asthma?’ [15]. When the prevalence of asthma in SCD is compared with the general African–American population, there appears to be a similar or slightly higher prevalence of asthma, only one study was designed to address prevalence in the same geographic area (Table 1) [16]. Variation in asthma prevalence in SCD (Table 1) is as a result of different definitions used in the diagnosis of asthma. Less stringent definitions of asthma as well as a selection bias towards individuals with underlying lung disease results in a higher prevalence of asthma. However, in Saint Louis (MO, USA) where children with SCD have been assessed for asthma using standardized clinical and pulmonary function criteria, the prevalence of asthma in SCD is similar to that seen in the Saint Louis city elementary schools where the racial mixture is similar to that in the SCD clinic [17].

Rationale for article

Asthma is a distinct, common comorbid condition in SCD; associated with an increase in SCD-related morbidity and premature mortality. Despite the well recognized clinical entity of asthma, particularly in children, nuances of asthma diagnosis in children with SCD are challenging with common symptoms of asthma such as cough, wheeze, chest pain and exercise intolerance attributed to infection or SCD instead of asthma. Further compounding

the diagnosis is the fact that while positive test results for airway lability, such as methacholine challenge test and bronchodilator response, are strong predictors for asthma in the general population, their association with asthma in SCD is far less clear. In children with SCD, a physician diagnosis of asthma remains the primary basis of children at risk for pain and acute chest syndrome [18,19]. Among all children with SCD, evaluation for asthma risk factors should be carried out routinely and repeatedly, but the results of these tests should not supersede the physician diagnosis of asthma. Understanding the nuances of diagnosis of asthma, particularly in children with SCD, is critical because a physician diagnosis of asthma is one of the few established risk factors associated with SCD-related morbidity.

Optimal management of asthma in children with SCD has not been established, but practical approaches to care can be gleaned from asthma management in the general population. Until more asthma specific studies on therapy in SCD are available, asthma in children and adults with SCD should be recognized early and managed according to National Heart, Lung and Blood Institute (NHLBI) guidelines for asthma therapy in the general population [20]. This article will highlight challenges in diagnosis and management of asthma among individuals with SCD.

Asthma & sickle cell pain

Vaso-occlusive pain is the leading cause of admissions to hospital, and even in a state of relative good health, a significant number of children have some amount of pain. In the multi-institutional study, Cooperative Study of Sickle Cell Disease (CSSCD), a prospective cohort of 291 infants was followed for a mean length of 11 years and 4062-patient-years. Of these children, 16.8% had a diagnosis of asthma. An increased incidence of painful episodes (1.39 vs 0.47 events per patient-year; $p < 0.001$) was noted in children with asthma compared with those without asthma [18]. In a second cohort study of 1016 children from the Silent Cerebral Infarct Multi-Center Clinical (SIT) trial, a diagnosis of asthma occurred in 22% of the cohort and was associated with an increased rate of vaso-occlusive pain episodes that resulted in hospitalization and acute chest syndrome (ACS) episodes [19]. After final adjustment for age, hemoglobin F and baseline hemoglobin levels, vaso-occlusive pain rates were 73 and 57 episodes per 100 patient-years among children with and without an asthma diagnosis respectively ($p = 0.0176$) [19]. However, a single institution retrospective cohort study from France did not find an impact of asthma on pain episodes. A total of 297 children with sickle cell anemia were enrolled, 25 with a history of asthma and 272 without a history of asthma, with follow-up at 7 and 6 years, respectively, for a total of 1805 patient-years. No association existed between asthma and the rate of vaso-occlusive pain episodes (72 and 60 pain episodes per 100 patient-years; $p = 0.53$). This lack of association between asthma and SCD-related pain might be attributed to: the sample size, as the absolute rate of pain for patients with and without asthma were similar to that obtained in the CSSCD; differences in management of pain within France [21]; or the inherent limitations of a single-center study when compared with a multicentered study that did find a significant relationship between vaso-occlusive pain and asthma.

Lower airway obstruction (LAO) is a common risk indicator of asthma. Using spirometry in a single institutional study with LAO defined as forced expiratory volume in 1 s (FEV_1)/ forced vital capacity ratio (FVC) < 95% CI and adjusted for age and gender [22], children with LAO had more than twofold the admission rates for either pain or ACS compared with children with normal lung function when assessed prospectively from time of pulmonary function test (PFT) [23]. In this review of PFT records of 102 children with SCD, children with LAO had twice the rate of morbidity when compared with children with normal lung function (2.5 vs 1.2 hospitalizations for pain or ACS per patient-year; $p = 0.003$; risk ratio: 2.0; 95% CI: 1.3–3.3). Children with restriction did not have different rates of future

morbidity compared with children with normal lung function (1.4 vs 1.2 hospitalizations for pain or ACS per patient-year; p = 0.68; rate ratio: 1.1; 95% CI: 0.6–2.1). LAO was also associated with increased risk of morbidity, even in those children without a diagnosis of asthma. Several limitations exist in this study, including but not limited to referral bias of a hospital based cohort that had to receive spirometry evaluation for inclusion and a small sample size that is sensitive to outliers. As a single institution study with several limitations, the study results require repeating before significant confidence can be placed in the association between LAO- and SCD-related morbidity.

Asthma & acute chest syndrome

Acute chest syndrome is the leading cause of death and admissions to the pediatric intensive care unit in children and adolescents, and the second most common cause of admission after vaso-occlusive pain episodes in children [24]. Multiple ACS definitions have been proposed; although significant differences exist in terms of clinical symptoms needed, it is accepted that an infiltrate or new radiodensity on imaging is an important criterion that needs to be fulfilled. Other clinical features include hypoxemia, respiratory distress, fever, need for blood transfusion and rapid deterioration in clinical status [25,26]. Differentiating between an acute asthma exacerbation and ACS is a challenge clinically as they can present with similar symptoms. Wheezing and cough, a common clinical presentation of asthma, are also common findings of ACS, and a new radiodensity on chest x-ray may represent either atelectasis or infiltrate. One usually needs to treat for both asthma and ACS in the setting of a previous doctor diagnosis of asthma. In the CSSCD infant cohort, asthma was associated with more frequent ACS episodes, 0.39 versus 0.20 events per patient-year ($p < 0.001$) [18], and a similar twofold rate of ACS per patient-year (0.31 vs 0.16 events/patient; $p = 0.03$) was found in the French study [21]. Recurrent ACS episodes are associated with abnormal lung function among children with SCD [27]. Also, the proportion of children with a physician diagnosis of asthma increases linearly as the number of ACS episodes increase [28].

Given, the intrinsic limitations of the study design of most SCD studies, where careful delineation of asthma was not part of the original purpose of the study, we are unable to determine whether ACS predisposes to asthma or vice versa. However, children with ACS are diagnosed with asthma at a younger age compared with those without ACS [29], suggesting that asthma is a predictor of the occurrence of ACS. In the SIT trial, involving 1016 children with SCD, An *et al.* also confirmed that a doctor diagnosis of asthma was associated with increased incidence rates of ACS [19]. In this large study, after final adjustment for age, hemoglobin F and baseline hemoglobin levels, ACS incidence rates were 22 and 12 episodes per 100 patient-years among children with and without an asthma diagnosis, respectively ($p < 0.0001$) [19]. Severe recurrent wheezing is associated with increased rates of hospitalization for ACS, risk ratio = 2 (95% CI: 1.2–3.4; $p = 0.005$) [30]. In a retrospective study, by Knight-Madden *et al.* children with recurrent episodes of ACS were more likely to have atopic asthma and bronchial hyper-reactivity compared with those with only a single ACS event, 53 versus 8% (Odds ratio [OR]: 8.1; 95% CI: 2.3–28.6; $p < 0.001$) [16]. While the results of these studies do not demonstrate causality, they show a close association between ACS and asthma, suggesting that a diagnosis of asthma predisposes to future ACS episodes.

The diagnosis of asthma at different ages is a challenge particularly in younger children; our group follows the premise that asthma is a lifelong condition, as demonstrated by progressive decline in lung function over 15 years in persons who gave a self report of asthma [31] and at 28 years in children with frequent wheezing [32]. Probably the most compelling support that a diagnosis of asthma precedes ACS is based on the observation that in the CSSCD, children with a diagnosis of asthma presented with ACS at 2.4 years

compared with 4.6 years in children without asthma (hazard ratio: 1.64; 95% CI: 1.13–2.39; p = 0.01) [18]. Additionally, results from two retrospective studies, suggest, but do not confirm, that a previous diagnosis of asthma is associated with future ACS episodes. In the first study a history of asthma and home use of inhaled β adrenergic agonists were associated with increased readmission within 14 days of discharge for an ACS episode, OR = 3.8 (95% CI: 0.9–15; p = 0.06) and OR = 6 (95% CI: 1.2–3; p < 0.05), respectively [33]. In the second study, Boyd *et al.* reviewed medical records of children admitted for pain of children with asthma (cases), 35% developed ACS in hospital compared with 12% in children without asthma (controls) [34]. Children with a physician diagnosis of asthma were about four-times more likely to develop ACS and also had longer hospitalizations for ACS, 5.6 compared with 2.6 days (p = 0.01) [34]. The association between asthma and SCD is not limited to patients with hemoglobin SS. In a retrospective study, a greater proportion of children with SCD-SC had a prior history of asthma or wheezing than those with SCD-SS, 50.7 versus 33.8% (p = 0.04) [35].

Asthma & mortality

Life expectancy in SCD has improved over the past 20–30 years and is partially dependent on SCD phenotype. In a prospective study that followed 3764 individuals from birth to 66 years of age, the median age at death for males and females were 42 and 48 years of age for SCD-SS and SCD-Sβ^0thal, but 60 and 68 years of age for SCD-SC, respectively (p < 0.001) [36], much lower than the general population. Pulmonary findings on autopsy may include findings consistent with acute asthma exacerbation and or pulmonary hypertension [37–39].

A risk for premature death among those with SCD-SS and asthma was demonstrated in the CSSCD prospective cohort of 138 individuals with asthma and 1825 individuals without asthma [40]. Individuals were identified at a mean age of 9.7 and 14.2 years (p < 0.001), respectively, and followed for a total of 18,495 patient-years. Hazard ratio for the comorbid condition of asthma was 2.36 (95% CI: 1.21–4.62; p = 0.01) [40]. Although result of this study does not establish a cause and effect relationship between asthma and premature mortality, it provides compelling support of at least a strong association.

A causal link between the presence of asthma and premature death is suggested by the report of Field *et al.* of two adolescents with histories of severe persistent asthma in addition to SCD [37]. Both individuals were prescribed appropriate treatment for their asthma and had recently received medical care from a pediatric asthma specialist; however, both adolescents died suddenly in the midst of increased respiratory symptoms consistent with asthma exacerbation, where post mortem findings were consistent with asthma [37]. Taken together, these data underscore the importance of not only diagnosing asthma in children and adults with SCD, but also understanding the optimal management for this vulnerable population.

SCD is associated with airway hyper-responsiveness & bronchodilator reactivity

Airway hyper-responsiveness (AHR) and increased bronchodilator reactivity (BDR) are measures of airway lability. Tests for AHR and BDR are often used as evidence to support a diagnosis of asthma in children without SCD; however, asthma is ultimately a clinical diagnosis and individuals with asthma may not have either a positive AHR or increased BDR.

Measurement of AHR can be done either with methacholine, cold air or exercise challenge tests, and BDR is measured with administration of inhaled short-acting β-adrenergic agonist. Reported prevalence of airway lability in children with SCD is variable with rates between 14 and 75% [41–44]. In part, the large range of airway lability is related to the different

definitions of a positive result as well as the methodology used. Several studies have documented that both AHR and increased BDR in SCD are higher than the prevalence of asthma in the cohort, indicating that a high false positive rate is likely to arise if these tests are used as a diagnostic criterion (Tables 2 & 3).

American Thoracic Society criterion for positive BDR response requires an increase in $FEV_1 \geq 12\%$ predicted after bronchodilator administration, and among adults an increase in FEV_1 of at least 200 ml [45]. Leong *et al.* compared 40 children with SCD, aged 6–19 years with 14 healthy controls made up of siblings of patients with SCD, but no family history of asthma. Reactive airway disease (RAD) was defined in this cohort as a recurrent wheezing responsive to bronchodilator [44]. Airway lability was defined as either a positive cold air challenge or an increase in FEV_1 of at least 12% if the initial FEV_1 was too low to allow the cold air challenge. Prevalence of airway lability was 64% in the whole SCD population and 73% in the children with RAD, which was not statistically different from those without RAD ($p = 0.2$) [44]. One postulate is that ACS increases airway sensitivity, and as such, children with a history of ACS are more likely to have airway lability. This temporal relationship of ACS and increased airway lability has not been established and the opposite could as easily be true, namely that airway lability is associated with an increase rate of ACS episodes. Sylvester *et al.* did not see any difference in the prevalence of AHR defined using cold air and exercise challenge tests among children with a history of ACS compared with those without a history of ACS [41]. Further, Knight-Madden *et al.* did not find a significant association between airway lability and recurrent ACS. In this retrospective study, the investigators compared 80 children with SCD to an equal number of appropriately matched controls without SCD [16]. Prevalence of airway lability, defined as hyper-responsiveness with a decrease in FEV_1 of at least 10% with exercise test or BDR of ≥12%, was 14 versus 6% in children with SCD and healthy controls, respectively ($p = 0.12$). In the group with recurrent ACS compared with a single ACS episode, the proportion of children with airway lability, 71 versus 39%, was also not statistically significant ($p = 0.133$) [16]. Further prospective and more complete lung studies are needed to determine the relationship between airway lability and the incidence of ACS. If such a relationship is established, then perhaps targeted therapeutic interventions can be introduced in a clinical trial.

As part of a prospective NIH-funded study, Field *et al.* explored the relationship between methacholine responsiveness, asthma diagnosis, determinants of atopy, and a measure of hemolysis in a multicenter prospective study involving 99 children aged between 5.6 and 19.9 years, all with SCD-SS [43]. Using the outcome of the methacholine challenge of provocative concentration that causes a decrease in FEV_1 by 20% from baseline (PC_{20}), 2 mg of methacholine/ml was needed in 42% (41 out of 98) of the cohort for a positive methacholine challenge test. Despite the well established relationship between methcholine and asthma in the general population, no such association exists in children with SCD ($p = 0.986$). However, methacholine responsiveness was associated with elevated IgE levels ($p < 0.009$), younger age ($p < 0.001$) and elevated lactate dehydrogenase (LDH) levels ($p = 0.005$). The observation that an elevated LDH level, a marker of increased hemolysis, was associated with PC_{20} levels suggest that chronic hemolysis in children with SCD may play a role in the pathogenesis of AHR [43]. AHR testing appears to be safe in children without SCD; however, in children with SCD, no additional data appears to be obtained that will change the clinical management of the patient and there is a possibility that adverse side affects due to the administration of methacholine may occur [46]. Similarly, the utility of the cold air challenge is also in question because cold air used in the cold air challenge test can trigger sickle cell pain and wheezing among children with SCD [44].

Role of IgE levels as a predictor of asthma

Elevated total or specific IgE levels are involved in the pathogenesis of atopy and asthma. In the general population these tests can be used as a predictor of asthma. Burrows *et al.* examined the relationship between IgE levels and the self report of asthma among the general population [47]. Diagnosis of asthma was closely associated with IgE levels standardized for age and gender ($p < 0.0001$). Of the 177 individuals with the lowest levels of IgE, there were no reports of asthma, in contrast to a prevalence of approximately 40% in those with high IgE levels [47]. A similar association between elevated IgE levels and physician diagnosis of asthma in SCD exists [19]. In the SIT trial cohort, approximately, 50% (261 of 521) of the population had a total IgE level greater than the 90th percentile when compared with the general population; whereas, only 10% would have been expected to exceed the 90th percentile. Furthermore, 25% of children with SCD had an IgE level above the 98th percentile. In this cohort, children with higher IgE levels had a higher odds of a diagnosis of asthma [19]. Higher IgE levels were documented in a second study, involving children with SCD in which a relationship between IgE levels and asthma was found [48]. In 297 children evaluated for asthma, the mean total IgE level, adjusted for age was higher in children with SCD compared with the general population 234.8 versus 62 IU/ml, respectively [48]. Comparison of total IgE levels in children with SCD with and without a physician diagnosis of asthma also showed a statistical difference of 623 versus 207 IU/ml, respectively ($p = 0.005$). In this same study, children with a physician diagnosis of asthma were more likely to be sensitized to aeroallergens using a skin test (79 vs 43%; $p = 0.03$). Thus different reference ranges, which have not yet been established, are required when considering use of IgE levels in predicting asthma in children with SCD.

In addition to total IgE levels being associated with asthma in SCD, total IgE levels are associated with ACS rates. In the SIT trial wherein, 1003 patients with over 3000 patient-years An *et al.* again demonstrated that IgE levels were associated with ACS ($p = 0.048$) but not pain episodes ($p = 0.28$) [19]. The biological basis for this association is unclear, but most likely is related to the strong relationship between IgE levels and asthma in SCD and IgE levels and the relationship between asthma as well as ACS in SCD [19].

Lung function abnormality & SCD

Restrictive lung function is the predominant lung function abnormality in adults, with a reported prevalence of 74% [49]. By contrast, lower airway obstruction is the predominant lung function abnormality in children [50]. Onset of abnormal lung function is prior to the development of overt SCD-related morbidity and most prevalent in children with severe phenotypes such as SCD-SS [50,51]. Valid lung function assessment by either spirometry or lung volumes are dependent on the effort of subjects. As such, pulmonary function tests should only be conducted when children with SCD are in their steady state or at least 2 weeks after discharge from hospital for a vaso-occlusive pain episode, ACS or other complications of SCD and conducted by technicians skilled in obtaining repeatable efforts from children. Appropriate reference ranges should be used in the interpretation of results and appropriately adjusted for age, ethnicity, gender and height, as these factors influence lung function. Optimal interval for PFT has not been determined, but should be at least annually and even more frequently in the setting of clinical symptoms of lung disease, or previous findings of LAO or restriction.

Asthma management in SCD

Early recognition and prevention of acute asthma exacerbation, SCD-related pain and ACS will decrease the effects of both asthma and SCD on the lungs, ultimately improving quality of life and survival. One of the barriers to effective management of children with respiratory

symptoms is failure to appropriately recognize asthma in these children [52]. In children with SCD, cough is likely to be interpreted as the presence of infection, while chest pain or tightness are likely to be interpreted as sickle cell pain requiring analgesics rather than as a sign of asthma. The misclassification of these symptoms may result in worsening asthma. In addition, significant heterogeneity exists in how physicians diagnose asthma in children with SCD. In a survey of clinicians on the important factors required in establishing an initial diagnosis of asthma, only 60% of physicians surveyed correctly identified wheeze, symptomatic improvement with bronchodilator, recurrent cough, exclusion of other diagnosis and peak flow measurements [53]. A significant number of physicians are reluctant to use systemic corticosteroids in these children because of side effects (see next section). In the absence of specific guidelines for this cohort, it is important that physicians familiarize themselves with the NHLBI recommendations for both prevention of asthma and treatment of acute asthma exacerbation (Box 1) [20].

Box 1

National Heart, Lung and Blood Institute recommendations for treatment of acute asthma

- Early recognition of worsening asthma symptoms by patient and physicians are important in the management that takes place in the acute care setting such as the emergency department, physician's office or urgent care.
- Oxygen to relieve hypoxemia in moderate or severe exacerbations.
- SABA to relieve airflow obstruction.
- Addition of inhaled ipratropium bromide in severe exacerbations.
- Systemic corticosteroids to decrease airway inflammation in moderate or severe exacerbations for patients who fail to respond promptly and completely to a SABA.
- Consideration of adjunct treatments, such as intravenous magnesium sulfate or heliox, in severe exacerbations that are unresponsive to the initial treatments listed above.
- Monitoring response to therapy with serial measurements of lung function.
- Preventing relapse of the exacerbation, or recurrence of another exacerbation by providing: referral to follow-up asthma care within 1–4 weeks; an ED asthma discharge plan with instructions for medications prescribed at discharge, increased medications or advice to seek medical care if asthma worsens; review of inhaler techniques whenever possible; and consideration of initiating inhaled corticosteroids.

ED: Emergency department; SABA: Short-acting β-agonsit.

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Typical chest x-ray findings of asthma include hyperinflation of the lungs with flattening of the diaphragm, increased bronchial markings and atelectasis from mucus plugging [54]. These findings can easily be mistaken for and managed as an infiltrate associated with ACS, instead of an acute asthma exacerbation.

Treatment to reduce asthma-related morbidity requires that asthma severity be classified based on frequency of symptoms and history of exacerbation. Additionally, attempts should be made to recognize exercise-induced symptoms because the majority of these children

may not be very active in sports and might have difficulty with activities of daily living, such as coughing or wheezing while walking or climbing up stairs.

Bronchodilators are one of the most commonly prescribed medications for the management of asthma particularly in the setting of an acute exacerbation. These may be in the form of albuterol or other β adrenergic agonists. To date, no randomized controlled studies have been done examining the specific effects of inhaled bronchodilators in children with SCD [55]. In the setting of ACS, however, bronchodilator use improves oxygenation, clinical outcome and is associated with a mean improvement in FEV_1 of about 27% [56,57]. As such, in children with ACS where symptoms overlap with asthma, bronchodilator use may improve both asthma and ACS.

Leukotrienes are metabolites of arachidonic acid which, are released during inflammation. These metabolites have effects on both the vasculature as well as airways leading to vaso- and broncho-constriction, and may be important mediators in both SCD and asthma. Individuals with SCD have higher levels of urinary cysteinyl leukotrienes E4 at baseline and significantly increased levels during periods of sickle cell pain and ACS [58–60], making it particularly attractive as a future targeted treatment. No studies however have been done looking at the role of leukotriene modifiers in the treatment of asthma in this cohort.

Inhaled or systemic corticosteroids are the cornerstone of maintenance and acute management in children with asthma. However, guidelines for use of this class of medication for children with SCD are unclear. Inhaled corticosteroids were found to be superior to leukotriene modifiers in persistent asthma with the end points of decreased use of albuterol as rescue medication, lower asthma symptoms score, decreased night time cough and awakenings, as well as increased percentage of asthma symptom-free days [61]. Systemic corticosteroids can be used in the treatment of children with SCD to hasten recovery. Beneficial effect of systemic dexamethasone was demonstrated in a randomized controlled trial of 43 children with SCD and ACS, with a median age of 6.7 years. Duration of hospitalization was lower in children who received dexamethasone, at time intervals of 47 versus 80 h ($p = 0.005$) [62]. Other variables such as need for blood transfusions, mean duration of oxygen, analgesic therapy and duration of fever were also lower in the dexamethasone group. However, readmission rate within 72 h after discharge was increased in those who received dexamethasone, although not statistically significant between the two groups (27 vs 4.7%; $p = 0.095$). A significant weakness in the trial was the observation that participants were not evaluated for the presence of pre-existing asthma, as children with asthma have a higher rate of ACS [62]. Perhaps the beneficial effect of the corticosteroid treatment group when compared with the nontreatment group was related to being treated for an unrecognized asthma exacerbation.

The high readmission rate associated with steroid administration in SCD was supported in a large multi-institutional retrospective study consisting of 3090 individuals with 5247 hospital admissions for ACS, of which 874 (17%) were associated with corticosteroid use [63]. Using propensity score analysis to adjust for confounding factors, systemic corticosteroid use was associated with a comorbid asthma diagnosis (OR: 3.9; 95% CI: 3.2–4.8), increased length of stay (OR: 25; 95% CI: 14–38%) and readmission rates within 72 h of discharge (OR: 2.3; 95% CI: 1.6–3.4).

In addition to hospital readmission, systemic corticosteroid use in individuals with SCD is associated with cerebral hemorrhage and fat emboli. Strousse *et al.* identified systemic corticosteroid administration as a possible cause of life threatening problems [64]. In this retrospective case–control study looking for risk factors for hemorrhagic strokes in SCD, hemorrhagic stroke was associated with use of systemic corticosteroids within 14 days prior

to event (OR: 20; 95% CI: 2.9–217; $p < 0.0005$) [64]. While the exact mechanism for this association is not fully understood, the use of corticosteroid is associated with hypertension which is a well-established factor for stroke in patients without SCD [65]. Johnson *et al.* also reported a fatal case of methylprednisone used in the management of acute asthma exacerbation in a 25 year old male with history of SCD-Sβ+ thal [66]. Although asthma responded to treatment with corticosteroid the patient deteriorated 18 h after discontinuation of the corticosteroid with severe pain similar to his known vaso-occlusive pain. Autopsy findings were consistent with fat embolism in the lungs, multiple scattered foci of necrosis in the bone marrow as well as a decrease in the amount of fat in the bone marrow for his age [66].

Not all studies demonstrate adverse effects of corticosteroid in patients with SCD. In a retrospective chart review of 63 children aged 17 months to 20 years admitted for ACS who received prednisone as part of their treatment regimen, Kumar *et al.* did not find an increased rate of hospital readmission [67]. Although this difference is unclear, the most likely explanation is the exceeding small size of the study when compared with aforementioned hospital study, the lack of a prospective data collection with careful entry criteria, as was the case for the randomized trial and the possible difference between dexamethasone and prednisone, with the former having a longer half-life.

In summary, given the importance of corticosteroids in the management of an asthma exacerbation, corticosteroids should be used with caution, but not withheld when patients with SCD have asthma exacerbations. The optimal dosing schedule for systemic corticosteroids has not been established for individuals with SCD and asthma, but minimizing the exposure to corticosteroids in SCD while not eliminating its benefits is a solid strategy to undertake, until evidence-based guidelines are developed.

Expert commentary

Asthma is a distinct comorbid condition in SCD with inflammation being an integral part of both conditions [68–70]. Despite of advances in pulmonary medicine, asthma still remains a clinical diagnosis. In children with multiple admissions for vaso-occlusive pain and ACS episodes, as well as those with early presentation of ACS, asthma should be strongly considered as a potentially modifiable risk factor. In such cases, evaluation needs to include a thorough family history of asthma, clinical history with attention to asthma risk factors, such as environmental tobacco smoke exposure either *in utero* or in the first years of life, history of allergic rhinitis, eczema and history of food allergies. While there exists a relationship between other risk factors of atopy such as elevated IgE levels, peripheral blood eosinophilia and tests for airway lability, interpretation of positive results should be done with caution and only used to support a clinical diagnosis, rather than used as the sole diagnostic criterion. Exacerbation of asthma in children with SCD would be defined same as in children without underlying SCD, as wheeze that is not responsive to bronchodilators and associated with worsening over time. A multidisciplinary approach is required in the management and prevention of asthma involving a pulmonologist and other supporting services, as well as adoption of asthma prevention strategies such as environmental controls, the use of asthma coaches and scheduled hospital follow-up following admission for SCD-related vaso-occlusive or asthma exacerbation. Children with SCD and asthma should receive comprehensive care that includes at least a biannual visit to the pulmonologist and hematologist as well as an annual PFT.

Five-year view

The future of SCD research will focus on treatment strategies geared towards identifying optimal modalities of treatment. Leukotriene modifiers, an effective adjuvant therapy for the treatment of asthma, offer such targeted therapy and need to be studied in randomized control trials, perhaps comparing effectiveness to other asthma medications such as inhaled corticosteroids. Price *et al.* recently published a multi-institutional parallel study in individuals with asthma but without SCD to evaluate the real-world effectiveness of leukotriene inhibitors in comparison to inhaled corticosteroids as first-line therapy or a long-acting β_2 agonist as add-on therapy in individuals already receiving inhaled corticosteroids as first-line therapy had different results [71]. At 2 months, leukotriene inhibitors were equivalent to inhaled corticosteroids and to long acting β_2 agonist as add-on therapy to inhaled corticosteroids with respect to mini asthma quality-of-life questionnaire scores but resulted in lower scores at 2 years [71]. Median adherence to medications was better in the leukotriene group compared with the inhaled corticosteroid group, especially when medication adherence is of particular importance in individuals with SCD. Another area of research is the role of early viral infections in later outcomes of SCD, first in terms of asthma development and abnormal lung function. As early viral infection has been deemed important for the pathogenesis of asthma in the general population understanding the implications of the same infection may prove to be critical in the management of SCD. For example, rhinovirus infection in childhood is associated with about ten-times increased risk of wheezing at 3 years of age and wheezing at 3 years of age is also associated with a diagnosis of asthma at 6 years (OR: 25.6) [72,73]. Understanding the implications for the pathogenesis in lung disease related to SCD is critical for identifying modifiable treatment strategies. Chronic lung disease is associated with increased mortality in SCD [74]. As such, identification of patient factors that are associated with development of abnormal lung function will go a long way in stratifying patients to determine those at risk of increased mortality. This will lead to treatment strategies aimed at halting this process. Other areas for future study include the relationship between early infections and other markers of inflammation as well as the progression of lung function from childhood to adulthood through prospective longitudinal studies. In children with asthma but without SCD, nitric oxide synthase does play a role in AHR [75]. However, this has not been studied fully in children with SCD. We do know that a positive methacholine challenge test is associated with elevated LDH a marker of hemolysis which corresponds to nitric oxide depletion. Although Field *et al.* did not find any association between exhaled nitric oxide and AHR [43], future studies further exploring the effects of exhaled nitric oxide will aid in our understanding of AHR in this cohort.

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• of interest

•• of considerable interest

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Key issues

- Prevalence of asthma in children with sickle cell disease (SCD) appears to be approximately the same as it is in the general population; although no large-scale direct comparison has been made.
- Asthma in SCD is associated with increased episodes of pain and acute chest syndrome.
- All cause mortality in SCD is increased more than twofold in the presence of asthma as a comorbid condition.
- Presence of bronchial hyper-responsiveness is not equivalent to a diagnosis of asthma in SCD.
- Diagnosis of asthma is clinical and particularly difficult in children younger than 5 years of age.
- Guidelines for treatment of asthma in SCD have not been established.
- Systemic corticosteroids should be appropriately used, but with caution, in individuals with SCD and asthma.

Table 1

Differences in definition and prevalence of asthma in children with sickle cell disease.

Study (year)	Study design	Asthma definition used in study	Study cohort with asthma (%)	Ref.
Boyd *et al.* (2006)	CSSCD prospective infant cohort study of 291 SCD-SS children, self designated as African–Americans, enrolled before 6 months and followed beyond 5 years	ICD 9 code of asthma – parental report of a clinical diagnosis of asthma	17	[18]
Bryant *et al.* (2005)	Retrospective descriptive chart review of 60 children, age range 1.5–17 years with history of SCD and ACS	History of asthma (recurrent wheezing with inhaled bronchodilator response); abnormal PFT	53	[76]
Knight-Madden *et al.* (2005)	Modified ISAAC questionnaire administered to 80 children with SCD randomly selected by a computer and 80 ethnically matched healthy controls residing within their immediate community	Modified ISAAC questionnaire • Touch of asthma' • Wheeze: ever/current • Dry cough >7 days (not associated with URI) • Current or previous inhaled BD or inhaled steroid use	History of asthma ever: 48 Current history of asthma: 41	[16]
Koumbourlis *et al.* (1997)	20 infants aged 3–30 months with a record of routine PFT as part of their evaluation	Clinical records for history of asthma and family history of asthma	30	[50]
Field *et al.* (2008)	Single-institution retrospective cohort of a convenience sample of 79 children with SCD-SS with at least two PFTs	Physician diagnosis of asthma	36	[77]
Field *et al.* (2008)	Prospective CSSCD infant cohort study of 211 African–American children with SCD-SS, classifiable for family history of asthma enrolled before 6 months and followed beyond 5 years	A physician diagnosis of asthma in chart during a visit, ICD 9 code or use of asthma medications; family history of asthma in siblings or parents	20	[78]
Bernaudin *et al.* (2008)	Retrospective cohort study to determine the association between asthma and SCD morbidity in children with SCD SS with (n = 25) and without (n = 272) history of asthma in France	Physician diagnosis of asthma	8	[21]
Sylvester *et al.* (2006)	Prospective case–control study of 20 children with SCD and ACS; 20 children with SCD but without ACS, aged 6–17 years	A history of asthma in medical record	Overall asthma: 20 Asthma in non-ACS: 10 Asthma in ACS: 30	[79]

ACS: Acute chest syndrome; BD: Bronchodilator; CSSCD: Cooperative Study of Sickle Cell Disease; ICD: International classification of diseases; ISAAC: International Study of Asthma and Allergies in Childhood; PFT: Pulmonary function test; SCD: Sickle cell disease; SS: Hemoglobin SS; URI: Upper respiratory infection.

Table 2

Comparison of bronchodilator response and asthma prevalence in children with sickle cell disease and asthma.

Study (year)	Study design/description	Asthma (%)	Positive BD response (%)	Comment	Ref.
Leong *et al*. (1997)	Prospective study comparing BD response in 40 consecutive children with SCD-(SS, SC, Sβ+ thal) age range 6–19 years with ten healthy controls of siblings of study patients without history of reactive airway disease	40	12.5	No BD response in controls	[44]
Koumbourlis *et al.* (2001)	Retrospective evaluation of lung function in 63 children aged 5–18 years with SCD-SS to determine association between ACS, sickle cell pain and BD response	22	54	No association between BD response and VOC, ACS or abnormal lung function	[80]
Sylvester *et al.* (2006)	Prospective study of 40 children with SCD-SS, with and without ACS comparing BD response between the two groups	20	12.5	No difference in BD response between ACS and non-ACS	[79]
Ozbek *et al*. (2007)	Prospective study comparing BD response in 31 children aged 6–16 years with SCD (SS, SC, Sβ + thal) and in steady state to 30 healthy controls	6.5	9.7	No BD response in controls	[42]
Field *et al*. (2010)	Prospective study of 99 children with SCD without regard to past SCD morbidity or physician diagnosis of asthma examining the relationship between BD response and methacholine)	22	15	No association between BD response and methacholine challenge	[43]

ACS: Acute chest syndrome; BD: Bronchodilator; SCD: Sickle cell disease; Sβ+ thal: Sickle cell with β+ thalassemia; SCD-SS: Hemoglobin SS sickle cell disease; VOC: Vaso-occlusive crisis.

Table 3

Comparison of airway hyper-responsiveness and asthma prevalence in sickle cell disease.

Study (year)	Study design/description	Asthma (%)	Mode of AHR assessment (% with positive test)	Comments	Ref.
Leong *et al*. (1997)	Prospective study comparing AHR in 40 consecutive children with SCD with and without history of reactive airway disease age range 6–19 years	40	Cold air (60)	SCD AHR: 60%; SCD and asthma: 85%; SCD without asthma: 68%; controls: 0	[44]
Knight-Madden *et al.* (2005)	Chart review for history of ACS in 80 children with SCD between 5–10 years of age randomly selected and looking at the relationship between asthma and AHR	41	Exercise (45)	AHR between recurrent ACS and single ACS not significant	[16]
Ozbek *et al*. (2007)	Prospective study of AHR prevalence in 31 children 6–16 years with SCD-SS, -SC, -Sβ+ thal	6.5	Methacholine (78); PC_{20} <16 mg/ml	No difference on MCT in children with and without ACS	[42]
Sylvester *et al.* (2007)	Prospective study of 42 children with SCD-SS, 6–17 years of age to determine the prevalence of AHR in children with and without ACS	9.5	Cold air (14)	Positive result seen only in children without ACS	[41]
Field *et al*. (2010)	Prospective study of 99 children with SCD without regard to past SCD morbidity or physician diagnosis of asthma examining the relationship between BD response and methacholine	22	Methacholine (60); PC_{20} ≤8 mg/ml	No association between positive methacholine challenge and asthma; positive methacholine challenge test associated with lower age, higher IgE levels and high LDH a marker of hemolysis	[43]

ACS: Acute chest syndrome; AHR: Airway hyper-responsiveness; BD: Bronchodilator; LDH: Lactate dehydrogenase; MCT: Methacholine challenge test; PC_{20}: Provocative concentration of methacholine that caused a 20% decrease in the forced expiratory volume in 1 s; Sβ+ thal: Sickle cell with β+ thalassemia; SC: Hemoglobin SC SCD: Sickle cell disease; SS: Hemoglobin SS.