

Considerations for Care: Management of Asthma in the Child with Sickle Cell Disease

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Asthma is difficult to diagnose in the child with sickle cell disease because symptoms and pulmonary function abnormalities are similar to the spectrum of pulmonary manifestations in sickle cell disease. There are no published reports of controlled trials of asthma medications in children with sickle cell disease. Thus, treatment decisions should be guided by the Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma (www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf). However, issues specific to children with sickle cell disease should be considered. Initial strategies should focus on control of environmental triggers, as effectiveness on asthma outcomes is proven and the cost for implementation can be low. Use of short- and long-acting β_2 -agonists may prolong QTc, particularly in this population of children who already have a higher prevalence of prolonged QTc than the general population. Long-acting β_2 -agonist use has been associated with life-threatening asthma exacerbations with potentially higher risks in African Americans. Montelukast has been reported to increase suicidal thinking and behavior, and persons with asthma and sickle cell disease are already at risk for these events. Oral corticosteroids in the treatment of acute chest syndrome may increase risk of readmission even in children with asthma. The lack of prospective controlled trials of asthma drug treatment in children with asthma and sickle cell disease compels us to move this issue forward.

ALTHOUGH THE ACTUAL prevalence is not known, sickle cell disease is believed to affect up to 100,000 persons in the United States,^{1,2} and occurs in approximately 1 in 350 African Americans, 1 in every 32,000 Hispanic Americans (western states), and 1 in 1,000 Hispanic Americans (eastern states).^{1,3} Asthma affects nearly 18 million adults and 7 million children in the United States (8.2% of the population). In the pediatric population, African Americans have a greater prevalence than whites (16% vs. 8.2% respectively),⁴ which is larger than the racial differences seen in adults (11.1% vs. 7.8% respectively).⁵

There is ample evidence that “asthma” is a commonly occurring comorbidity in children with sickle cell disease^{6–12} with a reported prevalence varying from 2% to 45%.^{6–11,13,14} However, it is not clear what respiratory characteristics in the child with sickle cell disease are appropriately attributed to underlying asthma as defined in the guidelines¹⁵ as opposed to being caused by the pathology that contributes to sickle cell disease associated pulmonary dysfunction.¹⁶ It is clear that those children with asthma or asthma-like symptoms are at increased risk of morbidity associated with higher rates of acute chest syndrome, vaso-occlusive events, stroke, pain, as well as death.^{16–18} It is hoped that the National Heart, Lung,

and Blood Institute (NHLBI) Expert Panel Report for the Management of Sickle Cell Disease, made briefly available for public review in August 2012, will include clarification of asthma diagnosis and treatment when released (www.nhlbi.nih.gov/guidelines/scd/index.htm). In the meantime, it is reasonable to suggest that a child with a familial history of asthma accompanied by symptoms of atopy and a history of wheezing or coughing should be evaluated for asthma. If the diagnosis of asthma can be reasonably confirmed, then management should conform to the established guidelines for treatment of acute and persistent symptoms.¹⁵

Management of asthma symptoms should begin with control of environmental triggers. Strategies to reduce dust-mite exposure can include using allergen-impermeable covers on mattresses and pillows, removing carpet or upholstered furniture particularly in the child’s bedroom, and washing bedding and stuffed toys weekly in the washer’s hot-water cycle. Simple measures for cockroach or rodent control include using trash cans with lids to seal contents, removing potential food and water sources, cleaning food scraps from preparation areas including floors, and sealing entry points and using baits. Pets may need to be removed from indoors or at least kept out of the child’s bedroom and

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closet. Second-hand tobacco smoke is also a significant trigger for asthma symptoms, and cessation counseling for individuals caring for the child should be included at each encounter with a healthcare provider. A multipronged approach to controlling environmental triggers has been shown to reduce missed school days, decrease acute care visits, improve quality of life, and have positive economic value.^{19,20}

Asthma medications are categorized as quick-relief or long-term control and include short-acting β_2 -agonists (SABA), short-acting anticholinergics, and systemic corticosteroids for the former, and inhaled corticosteroids with or without long-acting β_2 -agonists (LABA), leukotriene modifiers (with or without inhaled corticosteroids), omalizumab, and, less often, theophylline and cromolyn for the latter.¹⁵ The National Heart, Lung, and Blood Institute Guidelines for the Diagnosis and Management of Asthma provides details on classification of asthma severity and treatment strategies for children aged 0 to 4 years, 5 to 11 years and adolescents 12 years and older.¹⁵ The reader is referred to the guidelines for in depth coverage of these issues (www.nhlbi.nih.gov/guidelines/asthma/index.htm). No prospective controlled trials evaluating drug treatments for asthma symptoms in patients who have both sickle cell disease and asthma have been published,^{13,16,21} and there are certain caveats to consider when prescribing these medications to children with sickle cell disease that are described in this update.

Treatment of Persistent Asthma in Children with Sickle Cell Disease

Inhaled corticosteroids

The preferred treatment for long-term control of persistent asthma symptoms is inhaled corticosteroids.¹⁵ Other than typical issues relating to proper techniques for inhaling drug from powder devices and pressurized metered-dose inhalers, and using the lowest effective dose to minimize effects on growth, there are no concerns unique to children with sickle cell disease and asthma that would preclude use in this population. Discussion of issues related to systemic corticosteroid use is included in the section "Treatment of Acute Asthma in Patients with Sickle Cell Disease."

Inhaled long-acting β_2 -agonists

LABA (salmeterol and formoterol) have been associated with an elevated risk profile, including rare respiratory life-threatening experiences and asthma-related deaths in African Americans compared with whites,^{22,23} though some of this difference may be driven by underuse of inhaled corticosteroids in African Americans.²⁴ These risks appear to be even greater in children and adolescents compared to adults based upon results presented at a Food and Drug Administration (FDA) Advisory Committee meeting in 2008, although too few children were available to stratify analysis by race.²⁴ LABA are only to be used with an anti-inflammatory drug (preferably inhaled corticosteroids).

Several studies have attempted to determine specific characteristics that increase susceptibility to these risks. In a retrospective cohort study of nearly 1 million Medicaid patients <40 years old with asthma (82% were children and 39% were African American), African American race as well as alcohol substance abuse disorder, pregnancy, and obesity contributed to an increased risk of a serious asthma exacerbation with LABA use.²³ Other than obesity,^{25,26} no other characteristic

would be a relevant risk factor in children with sickle cell disease prescribed LABA therapy. A small pharmacogenetic study in adults ($n=87$) found in the subgroup analysis of African Americans that those who were homozygous for arginine (at amino acid position 16 in the β_2 -adrenergic receptor gene, *ADRB2*) had poorer peak expiratory flow response to LABA (given with ICS) compared to those homozygous for glycine.²⁷ Although this was a small study, African Americans are more likely to be homozygous Arg16 (23%–30% of the population) compared to whites (14%–16%).²⁸ To evaluate risks of LABA, several large multicenter trials ($n=46,800$ adolescents and adults; $n=6,200$ children 4 to 11 years), mandated by the FDA to examine the safety of LABA with ICS, began in 2011 and results are expected in 2017.²⁹ Results from these trials may clarify risk factors in African Americans.

An additional risk relevant to the use of LABA in sickle cell disease is the prevalence of prolonged QTc reported this population.^{30,31} Rarely, β_2 -agonists increase atrial or ventricular ectopy and prolongation of the QTc interval.^{32,33} In patients with prolonged QTc, the the risk of cardiac events is doubled with the use of β_2 -agonists, and risk is greatest in the first year of use.³² Thus, a screening electrocardiogram (ECG) may be useful prior to prescribing LABA.¹⁶

Leukotriene modifiers

Leukotriene modifiers may be particularly useful in asthma management in children with sickle cell disease. Evidence from both in vitro and clinical studies suggests that the leukotriene pathway is upregulated in children with sickle cell disease. Induced asthma in a murine model of sickle cell disease results in increased lung levels of eosinophils, a major source of leukotrienes in asthma.³⁴ Expression of key leukotriene pathway enzymes, 5-lipoxygenase and 5-lipoxygenase activating protein, are elevated in peripheral blood mononuclear cells from patients with sickle cell disease, and levels of placenta growth factor which stimulates expression is associated with disease severity.^{35,36} Clinically, urinary leukotriene E4 levels, a measure of whole body leukotriene production,³⁷ are elevated in children with sickle cell disease, and higher levels are associated with an increased rate of pain and ACS episodes.^{38–40}

Montelukast is the preferred leukotriene modifier in patients with asthma and sickle cell disease because of its well-established effects on the improvements of asthma symptoms, once daily dosing, and its safety record (similar to placebo) that extends over 10 years of use in millions of patients.⁴¹ However, montelukast use has been associated with behavior changes, which may be relevant when considering use in the child with sickle cell disease. Agitation, aggressive behavior or hostility, anxiousness, depression, dream abnormalities, hallucinations, insomnia, irritability, restlessness, somnambulism, suicidal thinking and behavior (including suicide), and tremor may occur with montelukast use.²⁰ Patients with asthma as well as patients with sickle cell disease are already at risk for suicide ideation and attempted suicide and depression.^{42,43} Montelukast should not be withheld if clinically indicated, but monitoring for these adverse effects in patients with sickle cell disease would be reasonable.

Other therapies for long-term control in persistent asthma

The addition of theophylline to optimal-dose inhaled corticosteroids may be beneficial in children who remain poorly

controlled despite efforts to reduce exposure to environmental triggers and treatment with montelukast, inhaled corticosteroid alone, or inhaled corticosteroid with montelukast. However, because theophylline can cause nausea, nervousness, and poor appetite early in treatment, even at low doses (serum concentrations <7 mg/L),⁴⁴ it may be a less suitable choice in children with sickle cell disease who may already be taking hydroxyurea and codeine, both of which can cause nausea and vomiting. Cromolyn, now rarely used, is available only by nebulizer and must be administered four times daily. Likewise, omalizumab, which is an add-on option for a specific subset of patients, is rarely a suitable option in the child with sickle cell disease. Omalizumab is associated with a risk of anaphylaxis after the first dose, and also after a patient has received regular injections, even after a year or more. Anaphylaxis in the child with sickle cell disease could have devastating consequences. In addition, omalizumab must be given by subcutaneous injection (one to three injections) every 2 or 4 weeks in a physician's office. However, in the carefully selected child with sickle cell disease, omalizumab may be beneficial in reducing asthma exacerbations and thus the associated complications of pain episodes and acute chest syndrome in this population.

Treatment of Acute Asthma in Children with Sickle Cell Disease

Emergency department and hospital-based pharmacologic care of asthma includes the use of frequent inhaled SABA treatment with or without inhaled anticholinergics, and includes oral (or intravenous, if hospitalized) corticosteroids.¹⁵

African Americans may respond less well to SABA (compared to whites) in the acute setting and thus higher doses may be required.^{45,46} The primary risk associated with high doses of inhaled SABA is prolongation of the QTc as described previously for LABA.¹⁶ There is no expectation that anticholinergic efficacy or toxicity would be any different for children with sickle cell disease than any other pediatric population.

Systemic corticosteroid treatment for acute chest syndrome has been associated with rebound pain and increased early (within 2 weeks) readmission rates in many but not all studies.^{47–51} In one study, readmission rates after treatment with corticosteroids for acute chest syndrome in patients with asthma (50%) were no different than rates for all patients (58%).⁵⁰ However, readmission rates were higher, though not statistically significant, in patients given a corticosteroid taper. It is possible that the increased risk of readmission was actually due to underdosing of corticosteroid during the treatment or taper period, resulting in inadequate resolution of symptoms prior to discontinuation of corticosteroid treatment.⁵⁰ The asthma guidelines state that treatment with adequate prednisone doses (1–2 mg/kg/day, maximum 60 mg/day) should continue until symptoms resolve (3 to 10 days or occasionally longer); there are no data that support adding a taper following improvement in symptom control and pulmonary function to prevent a relapse of asthma exacerbations.¹⁵ Courses less than 10 days do not require a subsequent taper to reduce the risk of hypothalamic–pituitary–adrenal axis suppression.¹⁵ Similarly, analysis of claims data for more than 5,000 admissions for acute chest syndrome in more than 3,000 individuals found that the odds ratio for readmission

was significantly greater in those receiving corticosteroids, and even when examining only those with asthma, the relative risk of readmission was larger in those who received corticosteroids.⁴⁸ The increase in relative risk is perhaps due to the undertreatment with corticosteroid therapy, as only 48% of patients with asthma received corticosteroid treatment or possibly a reflection of more severe acute chest syndrome events in patients with asthma. As such, available evidence suggests that even in patients with asthma, systemic corticosteroid treatment is not without risk. Nonetheless, without more substantive data, patients with asthma should receive standard guideline appropriate care,¹⁵ which would include aggressive use of bronchodilators with systemic corticosteroid treatment and consideration for a sufficiently long taper to resolve symptoms completely.

Future Areas for Research: Vitamin D and Childhood Use of Acetaminophen

There are now many reports of an epidemiological association between hypovitaminosis D (either insufficiency or deficiency) and asthma.⁵² In addition, studies have also reported an association between patients with asthma who have deficient/insufficient vitamin D levels and higher rates of hospitalizations, greater risk of severe exacerbations, and greater airway hyperresponsiveness.^{53,54} Hypovitaminosis D among African American youths is greater in individuals with asthma (86%) compared to controls without asthma (19%)⁵⁵ and between 33% and 76% of children with sickle cell disease are classified as vitamin D deficient (from <10 to 12 ng/mL).^{56–58} It is possible that low vitamin D levels children with both sickle cell disease and asthma contributes to the significantly increased morbidity and mortality that is observed in this population. Thus, it may be appropriate to measure serum vitamin D in this high-risk group.⁵² Clinical trials enrolling several hundred participants are ongoing to evaluate vitamin D supplementation in patients with asthma (<http://clinicaltrials.gov>).

There are now many reports of an association between exposure to acetaminophen in utero, in childhood, and in adolescence with the subsequent development of asthma.^{59–62} Putative mechanisms relate to reactive intermediates generating a pro-inflammatory environment or shifting the Th1/Th2 balance.^{60,63} In addition, a genetic variant in the acetaminophen metabolic pathway associates with susceptibility to asthma and is more common in African Americans.⁶⁴ Research is needed to explore whether any association exists between acetaminophen use in childhood for the management of sickle cell disease pain and risk for subsequent asthma.

Summary

Asthma symptoms and exacerbations are associated with pain and acute chest syndrome episodes. Thus, keeping asthma under good control is of particular importance in children with sickle cell disease. The principles for asthma management outlined in the Guidelines for the Diagnosis and Management of Asthma are appropriate, but strategies for managing risks associated with SABA or LABA use, montelukast, theophylline, omalizumab, and systemic corticosteroids should be considered. Prospective research is needed in this understudied population of children who suffer from significant morbidity and mortality.

Author Disclosure Statement

No competing financial interests exist.

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