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Asthma, Airway Hyperresponsiveness, and Lower Airway Obstruction in Children with Sickle Cell Disease

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Abstract

As a comorbid condition of sickle cell disease (SCD), asthma leads to increased complications and mortality. However, poor understanding of asthma phenotypes in SCD and the complex interaction with SCD-related airway inflammation, manifested by bronchial hyperresponsiveness or obstructive airway, pose a unique clinical challenge. The objective of this chapter is to provide a comprehensive review and discussion of epidemiology, pathophysiology, interactions, and clinical implications of airway hyperresponsiveness (AHR), obstructive airway, and asthma in SCD. Discussion will cover new understanding and limitations of asthma diagnosis and management in SCD. AHR, lower obstructive airway, and asthma are highly prevalent in SCD. Despite overlapping features, these entities are nonetheless distinct as demonstrated by basic science and clinical data. Diagnosis of asthma should be based on a physician assessment. We provide new unpublished data of a prospective study on diagnosing asthma in a small preschool population. Administered validated asthma-screening questionnaire to SCD children reveals good sensitivity and specificity as an asthma detection tool. It is unclear at this time if detection of bronchial lability or asthma early in life would result in better outcome of patients, or if improved control of SCD attenuates lower airway pathology. Being able to distinguish asthma from bronchial lability in the preschool age children would allow for appropriate intervention early in life.

Keywords: sickle cell disease, children, pediatrics, asthma, obstructive airway, lower airway obstruction, wheezing, hyperresponsive airway, hyperreactive airway, reactive airway disease

1. Introduction

Asthma is a heterogeneous chronic airway disease seen in 10% of children, characterized by airway hyperresponsiveness (AHR) and recurrent episodes of airway obstruction due to airway inflammation. In the general population, a physician diagnosis of asthma supported by pulmonary function testing or laboratory evidence is often sufficient to make such a diagnosis, but continues to remain an elusive topic in sickle cell disease (SCD).

As a comorbid condition of SCD, asthma may lead to increased complications and mortality. Children with SCD experience frequent concurrent wheezing, respiratory complications such as pneumonia or acute chest syndrome (ACS), airway hyper-responsiveness, and airway obstruction, attributed to SCD-related airway inflammation but not necessarily from asthma. As a result, wheezing (clinical surrogate for bronchial hyperresponsiveness), obstructive airway, and asthma are present in higher prevalence within the SCD population, with significant overlap (**Figure 1**), rendering common office procedures such as spirometry (measure of airway obstruction), methacholine challenge testing (measure of hyperresponsiveness), and exhaled nitric oxide (measure of asthma-related airway inflammation) inadequate to distinguish them apart.

Figure 1. The relationship of asthma, wheezing, and lower airway obstruction in SCD.

2. Pathophysiology (interrelationship between wheezing, asthma, and obstruction)

The mechanism by which wheezing, obstruction, and asthma develop in SCD is poorly understood. Transgenic SCD mice demonstrate higher airway resistance via an altered immunologic pulmonary response, priming the lungs to increased inflammation, and airway hyperresponsiveness after sensitization to allergens [1]. Therefore, as an inflammatory

comorbid condition, asthma likely contributes to sickle hemoglobin-induced vasculopathy and in reverse, SCD attributes to airway inflammation leading to development of asthma, obstruction, or bronchial hyperresponsiveness (**Figure 2**). How SCD subtypes variably influence the lower airways is not adequately described.

Figure 2. Interrelationship of SCD inflammation with lower airway inflammation.

Severe airway narrowing may lead to local hypoxia, promote sickling and systemic inflammation which in turn may increase airway inflammation.

2.1. Lower airway obstruction in SCD

SCD mice compared with hemoglobin A mice possess greater resistance in the airways at baseline and after allergen challenge [1]. Reversal of SCD-related inflammation through bone marrow transplant and hydroxyurea lead to improved pulmonary function, implying SCD adversely affects the lower airways. The effect of SCD on the lower airways starts early in life. Predominant lower airway obstruction (LAO) abnormality is already present in early infancy, even prior to a diagnosis of asthma [2]. Majority of older children and adolescents with SCD have either normal pattern of lung function or lower airway obstruction (LAO). Cross-sectional prevalence of lower airway obstruction estimates it being high in SCD children [3], ranging from 20 to 50%. Longitudinal studies further elaborate a tendency of lower airway obstruction development in childhood [4]. SCD LAO is not associated with increased methacholine sensitivity or eosinophilic inflammation, eluding to airway hyperresponsiveness and asthma, respectively, being distinct entities from lower airway obstruction. Increasing age, female gender, history of asthma or wheezing, tobacco smoke exposure, and high lactate dehydrogenase (LDH) are independent predictors of obstruction [5]. Clinical significance of LAO in children remains uncertain; however, some reports describe association with increased vaso-occlusive crisis [6], but not with ACS or mortality. Ongoing SCD-related airway inflammation eventually leads to LAO, which in turn increases eosinophil and collagen deposition in the lungs of SCD mice to a greater extent than control mice [1]. Whether an ongoing LAO even-

tually progresses into asthma remains uncertain, but SCD airway inflammation could have deleterious effect on asthma control. Clinically differentiating asthma from LAO poses a challenge, but respiratory symptoms or complications are primarily associated with the former. As asthma is poorly characterized in SCD, it isn't clear if a mild asthma evolves to a more severe form over time and how best to differentiate mild form of asthma from LAO. Management guidelines currently do not recommend monitoring pulmonary function routinely in all SCD children unless symptomatic [7].

2.2. Airway hyperresponsiveness in SCD

AHR is a cardinal feature of asthma in children without SCD; however, a high prevalence of up to 55–75% in the absence of asthma or reactive airway disease symptoms exists in SCD children, reaffirming that these entities are distinct [8–10]. Younger age, higher serum immunoglobulin E (IgE) concentration, eosinophilia, and a higher LDH level were independently associated with AHR [11]. The pro-inflammatory state of the SCD lung and its contribution to AHR is not completely understood but Nitric oxide (NO) metabolism dysregulation may possibly contribute to its etiology, independent of asthma. A lack of relationship between methacholine-induced AHR and either traditional symptoms or a physician diagnosis of asthma suggest a potential novel mechanism for AHR in SCD [12]. Clinical significance of AHR includes increased complications such as ACS and more frequent vaso-occlusive events [13]. The presence of elevated eicosanoids in SCD asthma is not associated with AHR. Hydroxyurea use may attenuate AHR, though more confirmatory studies are needed. Not enough data are available on the beneficial effects of bronchodilators or whether asthma anti-inflammatory controller medication is beneficial in preventing complications.

2.3. Asthma in sickle cell disease

Asthma is a multifactorial disease that manifests in illness as a final combination of heritability (genetics), triggers (environment), and immunologic alterations that promote hyperresponsiveness of the airway. This entity is diagnosed based on a physician assessment through the combination of medical history and physical examination.

A familial pattern of inheritance of asthma exists among first-degree relatives of probands with diagnosis of both SCD and asthma, suggesting that asthma is a distinct comorbid condition with SCD rather than a lung disease phenotype mimicking asthma [14]. Autopsy lung histological findings of a deceased SCD patient with asthma during an acute respiratory event are consistent with characteristic features of bronchial asthma. Pain crisis and ACS rates were increased in SCD children without a diagnosis of asthma but with a positive family history of asthma, compared with children without asthma and a negative family history. When adjusted to a diagnosis of asthma, individuals with family history of asthma had increased complications compared to those with asthma but without a family atopic risk [15]. Inflammatory genes and their corresponding mediators of asthma pathogenesis may therefore contribute to vascular inflammation.

Inflammatory mediators implicated in the pathogenesis of asthma and pain provide additional evidence suggesting that there is a common mechanism between asthma and SCD. Phospholipase A2 activity on cell membrane component arachidonic acid leads to production of leukotriene products (LTB₄, LTC₄, LTD₄, and CysLT₁) which in the lungs have effects on asthma pathogenesis and neutrophil activation (**Figure 3**). Baseline levels of leukotrienes were significantly elevated in those with SCD compared to healthy population. Among children with SCD, levels were higher in those with asthma than those without asthma [16]. Leukotriene significantly increases during pain crisis or acute chest syndrome in children with sickle cell disease [17, 18]. Although LTB₄ levels have a lesser role in the process of asthma, their actions on the activation, migration, and adhesion of neutrophils to the endothelium suggest that LTB₄ could contribute to the process of vaso-occlusion. In one study, the T-lymphocyte helper cell cytokine, interleukin (IL)-4, elevation was associated with SCD rather than asthma status [19]. Consistent with SCD-triggered inflammation leading to airway changes, we previously reported preliminary data of neutrophilia and eosinophilia systemic inflammation, inversely associated with pulmonary function in asymptomatic asthmatic SCD children [20].

Figure 3. Eicosanoid metabolism and leukotriene biosynthesis.

Histologic findings in sickle cell mice indicate SCD independently induces a baseline lung pathology that increases large and small airway resistance and primes the lungs to increased inflammation and airway hyperresponsiveness post-sensitization. Individuals with SCD may therefore have a unique, divergent phenotype, perhaps amenable to a different therapeutic approach. Among children in the general population, an elevated IgE level and aeroallergen sensitization are among the strongest risk factors for asthma. Earlier reports of elevated IgE [21] and allergen-specific IgE [22] in physician-diagnosed asthma in SCD children were not replicated subsequently. Aeroallergen sensitization in physician-diagnosed asthma SCD children was significantly higher than the non-asthma group but was of limited clinical value in detection of asthma [23].

Asthma disproportionately affects African-American children in the United States with a prevalence of about 20%. The prevalence of comorbid asthma in patients with SCD has not been well defined, as such studies require simultaneous surveillance in the general population. In children with SCD, estimates of asthma prevalence are similar to that in children of African descent as in the general population. It is not certain if SCD imparts a modest tendency to develop asthma. Without a clear definition of asthma or understanding of asthma phenotype in SCD, the epidemiological data may vary widely. It is well described that a physician's diagnosis of asthma is not synonymous with LAO or AHR, and the prevalence of asthma in multiple SCD cohorts is much lower than LAO and AHR.

Available additional tests include spirometry, methacholine challenge, and exhaled nitric oxide, for school-aged children provide additional objective measurements to support the physician's assessment to make a diagnosis of asthma in children. Potentially, signs and symptoms suggestive of asthma, such as wheezing or an obstructive pattern on pulmonary function testing, may be related to pulmonary manifestations of SCD and thus represent a different pathophysiology than asthma. A high incidence of abnormal pulmonary function findings, including LAO or a restrictive pattern in the SCD population limit its use in the diagnosis of asthma. Bronchodilatory effect of beta agonists was appreciated in many non-asthma SCD patients [3]. Similarly for AHR in SCD, methacholine challenge is unable to differentiate those who have asthma from those without [12]. Due to dysregulation of the arginine-NO metabolic pathway in SCD, fractional exhaled nitric oxide (FeNO) levels used to assess airway eosinophilia activity could be compromised. Recently, it was shown that FeNO measures were not significantly different in SCD children with a physician diagnosis of asthma from those without asthma [23].

SCD mice with experimentally induced asthma are more susceptible to death and pulmonary inflammation compared with control mice, suggesting that asthma contributes significantly to morbidity and mortality in SCD. In children with both SCD and asthma, respiratory symptoms are a risk factor for painful episodes. Several clinical studies have since confirmed that concomitant asthma increases SCD complications of vaso-occlusive events, ACS, pneumonia, and even mortality [24–27]. Children were diagnosed as asthmatic prior to onset of their first ACS episode, suggesting that asthma exacerbations may predispose to ACS episodes. Mechanisms by which asthma predisposes to increased morbidity and mortality remain unclear.

3. Physician assessment in asthma diagnosis

To date, all studies defining asthma are based on a physician's subjective assessment. The objective criteria used to make a physician diagnosis of asthma are not well defined and may vary from one physician to another. Whether a physician diagnosis of asthma in children with SCD has the same constellation of clinical features that are recognized among children without SCD is not known.

3.1. Asthma-screening questionnaire in school-aged children with SCD

In 2015, we published data that demonstrated the utility of an asthma-screening questionnaire to identify physician-diagnosed asthma in SCD children. In this study, we prospectively administered a previously validated asthma-screening questionnaire to 41 SCD children on a routine clinic visit. Prevalence of obstructive airway was high at 51.2% and physician diagnosis of asthma was lower, 33.3%. The sensitivity and specificity were high in detecting physician diagnosis of asthma in this SCD population [28].

An asthma-screening questionnaire showed to be a useful tool in identifying at-risk SCD children who may benefit from further asthma management as an effective, easy-to-administer screening tool. More importantly, as the screening questionnaire had been developed and validated in the general population, it provided new evidence that a physician diagnosis of asthma in children with and without SCD was consistent. In another study, after extensive evaluation of SCD children for respiratory symptomology, atopic risk, pulmonary function measures, and inflammatory markers; parental history of asthma, wheezing causing shortness of breath, and wheezing after exercise were predictive of development of asthma [23], indicating the importance of a proper history and physical in determining an asthma diagnosis. We did not observe a difference between parental history of asthma in SCD with the asthma and non-asthma groups, but allergic rhinitis was significantly seen in the asthma group.

3.2. Wheezing and SCD

Children with SCD are more likely to wheeze than non-SCD children in the same geographical setting [29]. Wheezing likely is a clinical surrogate of SCD inflammation-related AHR, bronchial asthma airway inflammation, or both. No age association between wheezing and asthma diagnosis exists; therefore, children with wheezing were no more likely to carry an asthma diagnosis than adults [30]. Some SCD patients have recurrent wheezing without a personal or familial history of asthma. Risk factors including upper respiratory tract infection, environmental tobacco smoke exposure, maternal history of asthma, lower socioeconomic status, excessive production of inflammatory mediators such as leukotrienes, low vitamin D level, and exposure to acetaminophen in early life were found to be associated with wheezing independent of asthma [30]. Many of these risk factors are similar to early life wheezing in the general population and asthma. The International Study of Asthma and Allergies in Childhood (ISAAC) to assess current respiratory symptoms of asthma showed that recent use of acetaminophen was associated with an exposure-dependent increased risk of asthma [31]; therefore, further work is needed in SCD due to high exposure of pain medications. Recurrent, severe wheezing regardless of asthma status was associated with increased pain crisis, ACS, and mortality. Wheezing and asthma are likely independent risk factors of SCD complications [32].

The Asthma Predictive Index (API) was developed for children less than 3 years old with recurrent wheezing. This index was created as a guide for the primary physician to determine which children would likely have asthma later in life. The API takes into consideration a combination of major and minor criteria (**Table 1**) to evaluate the patient asthma risk.

Major criteria	Minor criteria
Parental asthma	Food allergies
Physician diagnosis of atopic dermatitis	Eosinophilia >4%
Sensitization to aeroallergens	Wheezing apart from colds

Table 1. Asthma predictive index: a positive API requires ≥ 3 episodes of wheezing a year during the first 3 years of age and one of the two major criteria or two of the three minor criteria.

In preschool children aged 3–5 years, or younger, the diagnosis of asthma sometimes is a challenge. Many times, viral respiratory illnesses may mimic early asthma symptoms. Cardinal symptoms that suggest asthma include dry cough, trouble in breathing, chest tightness or pain, and wheezing, most of them are also present in SCD. Asthma could be exacerbated by weather changes, colds, emotions, or exercise. In SCD patients, diagnosis of asthma may be even harder taking into consideration the vaso-occlusive pathophysiology involved in this disease as an additional confounding factor for asthma symptoms. It is uncertain if the API can be reliably applied to the SCD population.

3.3. Asthma in the preschool SCD population

For a primary physician, diagnosis of asthma in the preschool population may be a potential challenge notwithstanding other several comorbidities that can mask asthma symptoms like in those patients with SCD.

In our unpublished 3-years prospective study, a validated asthma-screening questionnaire was administered to 12 preschool SCD children (aged 2–5 years) on a routine clinic visit. Prevalence of physician diagnosis of asthma at initial visit was 33.3% ($n = 4$). We found that the abbreviated three-question version had 100% sensitivity and 62.5% specificity in detecting asthma early in life in this subject population when followed over time. The Breathmobile Case Identification Survey (BCIS) in preschool-age children in the general population had a high sensitivity (70%) and specificity (84%) [33]. Further work is required to assess early asthma-screening approaches in SCD.

These data demonstrate that a validated asthma-screening tool intended for the general population might be relevant in preschool SCD and might be used as a screening tool for a valid asthma diagnostic approach. A validated screening tool implemented in early asthma diagnosis will help the primary physician to assess objectively and uniformly the diagnosis of asthma in preschool SCD children in order to identify individuals at risk of major complications or those with poorly controlled asthma.

It is unclear if detection of bronchial lability or asthma diagnosis earlier would result in better outcomes or if improved asthma control in SCD attenuates lower airway pathology. Identifying mild asthma would continue to remain a challenge. Previously, due to poor understanding of an asthma diagnosis in this high-risk population, clinical trials were difficult to conduct, resulting in a gap of knowledge. Future research to evaluate the impact of early asthma detection in the development of further comorbidities in SCD children should be explored.

4. Asthma management in SCD

Sickle cell disease is marked by high utilization of medical services. A history of asthma was associated with an increased risk of SCD emergency department (ED) utilization for both pain and ACS [34]. Recently, the patient-centered medical home (PCMH) emerged as a viable method to improve delivery of medical care. The American Academy of Pediatrics (AAP) currently defines a PCMH as care that is accessible, continuous, comprehensive, family-centered, coordinated, compassionate, and culturally effective. Children with SCD reported to experience comprehensive care had lower rates of ED encounters and hospitalizations after controlling for demographics and health status. SCD patients with asthma are anticipated to benefit the most in this setting.

Achievement of asthma control to reduce pulmonary complications and mortality are the goals of the National Asthma Education and Prevention Program (NAEPP) expert panel report 3 on 2007 guidelines. These guidelines focus on impairment and risk as key factors to assess asthma severity and control. Treatment recommendations are summarized in a stepwise approach for long-term asthma treatment taking into consideration the patient age and epidemiologic risk factors. Currently, physicians follow the NAEPP 2007 asthma guidelines in order to minimize future comorbidities and reduce asthma-related mortality in the pediatric population.

It is known that the pathophysiology of asthma involves several overlapping areas that affect the asthma phenotype in each patient. Also many comorbid factors can play a direct role in the development of asthma, SCD being one of them. Concerns regarding asthma management in SCD using the standard NAEPP 2007 approach have arisen, taking in consideration the hemolytic and chronic inflammatory state of this disease. Current consensus in the management of asthma in SCD agrees with the use of NAEPP 2007 guidelines to treat SCD asthma until new studies demonstrate a different approach.

Acute asthma exacerbations

- Rescue medications may include inhaled bronchodilators (albuterol and ipratropium) and systemic corticosteroids.
- Several cases have been described associating oral corticosteroid use with rebound pain and ACS. However, their use should not be withheld in the setting of an acute asthma exacerbation. A slow taper of systemic corticosteroids may decrease the risk for rebound pain.
- Admit all patients with acute asthma exacerbations requiring corticosteroids and consider a lower threshold to admit SCD patients with mild asthma exacerbations in view of the potential complications, such as ACS or pain crisis.

Long-term asthma control

- Physicians are encouraged to prescribe inhaled corticosteroids (ICS) as the first line for asthma-controlled medication and to consider additional controlled medications such as leukotriene inhibitors.

- Consult pulmonary specialist and hematologist when starting ICS in an SCD patient.
- Interval pulmonary function test in the outpatient setting is recommended.
- Asthma assessment on all SCD patients at least annually.
- A Doppler echocardiogram annually in SCD patient with asthma to screen for pulmonary hypertension.
- A baseline EKG should be completed before starting therapy with beta2 agonists due to increased risk of prolonged QTc complications in SCD.

In the following sections, we expand the available literature on asthma management in the SCD population and explore future areas of interest about this topic [35].

4.1. Oxygen therapy

As part of the management of acute asthma exacerbations in the general population, oxygen therapy plays an important role in the correction of asthma-induced hypoxemia, secondary to V/Q mismatch. In SCD, oxygen is also part of the initial management for acute chest syndrome. It is known that in SCD, the onset of erythrocyte sickling can be triggered by hypoxemia and, for instance, the development of acute chest syndrome. More studies are needed to evaluate the benefit of oxygen in SCD in the acute setting of asthma. Short-term oxygen in an acute asthma exacerbation should be initiated with SCD during a moderate to severe asthma exacerbation.

4.2. Bronchodilators

Acute hyper-responsiveness can be treated successfully with short-term inhaled bronchodilators that selectively stimulate the Beta-2 receptors in the airway and relax the smooth muscle. In SCD, the approach may be different if acute chest syndrome overlaps with an acute asthma exacerbation. On red blood cells, beta2-receptor stimulation was associated with cellular adhesion in vivo. This may theoretically promote vaso-occlusive episodes in SCD but clinically this phenomenon has not been described. Studies to evaluate the effectiveness in the treatment of asthma and acute chest syndrome in SCD have not been performed. Several Cochrane Reviews have shown consistently the lack of well-designed randomized controlled trials in this area. As a clinician, this information will be helpful to evaluate the risks of the use of inhaled bronchodilators in the therapy for acute chest syndrome and asthma in the SCD population [36].

Inhaled beta2 agonist has been related with life-threatening cardiac events in adults with long QT syndrome [37]. Prolonged QTc is a frequent finding in the SCD pediatric and young adult population. Considering this, evaluation for possible life-threatening events in SCD related to QTc prolongation after beta2 agonist use may be warranted [38]. An EKG prior to starting a beta2 agonist will provide useful information at initial evaluation in SCD asthma management to prevent additional comorbidities. A randomized control trial evaluating the risk of the use of beta2 agonists in SCD secondary to QTc prolongation needs to be explored.

Long-term bronchodilators (long-acting beta-agonists [LABAs]) are recommended for asthma control in those with moderate to severe persistent asthma as per NAEPP 2007 guidelines. In SCD, some concerns arise about the use considering the epidemiology of the disease. In the Salmeterol Multicenter Research Trial (SMART), African-American subgroup showed an increased risk for respiratory-related deaths [39], prompting the US Food and Drug Administration (USFDA) to issue a black box warning. The safety profile of LABA is currently being investigated in the pediatric population with the VRESTRI clinical trial and is expected to complete in 2017.

An alternative approach to address the risk of short-acting beta-agonists (SABA or LABA) use in the African-American SCD population for asthma management is the use of short-acting and long-acting anticholinergics. Ipratropium and tiotropium work as acetylcholine receptor antagonists, causing bronchodilation. A randomized clinical trial in 2015 has compared the effectiveness and safety of tiotropium versus LABAs. In this study, African-American adults with moderate to severe asthma were enrolled over 18 months. The combination of LABAs or tiotropium with ICS showed no significant differences in asthma exacerbations, forced expiratory volume in 1 s (FEV1), asthma control questionnaire (ACQ) scores, or patient reported outcomes [40].

An observational study evaluated the increased pulmonary capillary volume as a possible explanation for airway obstruction in SCD patients. They found that an increased pulmonary capillary volume contributes to increased airway obstruction and, for instance, may limit the effect of ipratropium in reducing airway obstruction in SCD [41].

4.3. Leukotriene's inhibitors

During acute asthma episodes, prolific release of inflammatory metabolites contributes to airway bronchoconstriction and acute exacerbations. Leukotrienes are arachidonic acid metabolites that contribute to airway inflammation in asthma and may have additional pathophysiologic roles in SCD. Lung leukotriene cascade activates and releases additional metabolites including LTA_4 , LTB_4 , LTC_4 , LTD_4 , and LTE_4 after activation of the 5-lipoxygenase, a key enzyme in the biosynthesis of leukotrienes (**Figure 3**).

Montelukast is an adjuvant therapy that works as a leukotriene receptor antagonist (LTRA) in the airway mast cells, eosinophils, and also in lung epithelial cells. Of all LTRAs, LTD_4 is the most potent bronchoconstrictive leukotriene. Additional chemo-attractive properties have been attributed to Cyst-LTs with a direct effect on lung vascular permeability, mucous secretion, and airway narrowing. Currently, under recruitment process, a phase-2 clinical trial tries to evaluate the effect of montelukast as an adjuvant medication to hydroxyurea for SCD vaso-occlusion treatment. This trial will provide valuable information about the role of leukotrienes in the SCD inflammatory state. Additional studies are needed to evaluate efficacy of LTRA inhibitors in SCD and asthma.

Zileuton is a specific 5-lipoxygenase inhibitor with a direct activity by decreasing leukotriene production. It is suggested that zileuton could have benefits in SCD considering the structural analog of hydroxyurea, and the advantage of inducing fetal hemoglobin to improve oxygen

affinity and delivery. In vitro trials have documented a potential effect in downregulating SCD inflammatory state through nitric oxide pathways in a dose-dependent effect [42]. Upregulation of IL-13 with hydroxyurea and downregulation of IL-13 with zileuton has been documented in vitro. This observation promotes the idea that zileuton is a potential drug for management of the SCD inflammatory state [43]. A phase-I trial evaluated the role and tested the safety of zileuton to reduce inflammation associated with SCD in a dose-dependent manner in children and adults [44]. Phase-II and -III clinical trials are pending to be done to explore the interactions between zileuton and hydroxyurea in SCD.

4.4. Corticosteroid

As per NAEPP 2007 guidelines, moderate to severe persistent asthma involves the introduction of an inhaled corticosteroid in order to achieve asthma control in the pediatric population. However, unclear data about the use and safety of corticosteroid in SCD children introduce challenges in the management.

Specific data regarding the use of corticosteroid in the management of asthma are needed. Some trials have evaluated systemic corticosteroids in the setting of acute chest syndrome in SCD. In a randomized trial evaluating the efficacy of dexamethasone in SCD with acute chest syndrome a beneficial effect was found [45]. Significant statistical data showed lower rates of hospitalizations, blood transfusions, duration of oxygen and analgesic medications; however, the subjects were never evaluated for pre-existing asthma diagnosis. Noteworthy here is that the rebound readmission rate in the dexamethasone group has raised some concern.

Rebound pain crisis after systemic corticosteroid use had been a concern in SCD. The potent anti-inflammatory effects of systemic corticosteroid may have a role in the management of ACS and asthma. Nevertheless, rebound pain and subsequent readmission may limit their use to an SCD sub-population [46]. It is suggested to use a longer course of systemic steroid with slow taper, but controlled clinical trials would be needed to evaluate this approach.

It is currently recommended to follow NAEPP 2007 guidelines as part of the treatment of asthma in SCD. Systemic steroid may be used in moderate to severe asthma exacerbations with a close monitoring for rebound pain. An individual approach may be considered to start inhaled corticosteroids in persistent asthma in SCD to avoid asthma-related morbidity, while upcoming clinical trials provide the clinician evidence-based guidelines about the best strategies for asthma management in SCD. However, poor understanding of asthma phenotype in SCD and additive bronchial asthma airway inflammation to underlying SCD inflammation, and its impact on asthma control has not been explored. Current clinical trials for inhaled mometasone and budesonide are being conducted to address the gap in the knowledge.

4.5. New therapy in asthma

New modes of asthma management may have beneficial effects on SCD asthma airway inflammation and asthma. However, no data are currently available on these modes of therapy. These include immunotherapy, monoclonal antibody against specific immune protein, and

bronchial thermoplasty. The role of hydroxyurea and other anti-inflammatory interventions of SCD in improving asthma control requires investigation.

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