Management of chronic respiratory complications in children and adolescents with sickle cell disease

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ABSTRACT   Sickle cell disease (SCD) is a life-threatening hereditary blood disorder that affects millions of people worldwide, especially in sub-Saharan Africa. This condition has a multi-organ involvement and highly vascularised organs, such as the lungs, are particularly affected. Chronic respiratory complications of SCD involve pulmonary vascular, parenchymal and airways alterations. A progressive decline of lung function often begins in childhood. Asthma, sleep-disordered breathing and chronic hypoxaemia are common and associated with increased morbidity. Pulmonary hypertension is a serious complication, more common in adults than in children. Although there is a growing attention towards respiratory care of patients with SCD, evidence regarding the prognostic meaning and optimal management of pulmonary issues in children with this condition is limited.   This narrative review presents state-of-the-art evidence regarding the epidemiology, pathophysiology and therapeutic options for chronic respiratory complications commonly seen in paediatric patients with SCD. Furthermore, it highlights the gaps in the current knowledge and indicates future directions for studies that aim to improve our understanding of chronic respiratory complications in children with SCD.

Introduction

Sickle cell disease (SCD) is the most common hereditary blood disorder in people of African ancestry, affecting around 14 000 people in the UK alone [1].

In this condition, recurrent episodes of red blood cell sickling, haemolysis and microvascular occlusion trigger a cascade of events resulting in a wide range of symptoms, as well as chronic vasculopathy and multiple end-organ damage [2]. Highly vascularised organs, such as brain, kidneys, spleen and the lungs, are particularly affected. Respiratory disease is among the leading causes of morbidity and mortality in SCD, with death most commonly occurring in the context of severe acute chest syndrome, pulmonary embolism and/or pulmonary hypertension [3]. There is increasing focus on respiratory care of patients with SCD, and the number of studies investigating respiratory complications has markedly increased in recent years [4].

These complications often begin in childhood [5], and most of them are also associated with a more severe course of disease. Therefore, it is important that paediatricians are aware of and recognise precocious respiratory signs/symptoms that necessitate appropriate assessment and management in children with SCD.

In this narrative review, we aim to provide a brief overview of chronic respiratory issues in children with SCD and a practical understanding of how to investigate and manage conditions such as asthma, lung function abnormalities, sleep-disordered breathing (SDB), hypoxaemia, pulmonary hypertension and reduced exercise capacity in this group. Given that the most severe manifestations of SCD and most of the published evidence concern people with haemoglobin SS disease or sickle β-zero thalassaemia, we will focus on these phenotypes.

Findings from relevant studies in the field will be presented and will be integrated with the authors' intuitive, experiential and explicit perspectives in the areas where evidence is missing. An extensive literature search was carried out at this scope and was limited to PubMed. However, since this was not a systematic review, we cannot dismiss that some relevant studies may have been omitted.

Lung function abnormalities

Lung function abnormalities are frequently noted in children and adolescents with SCD, who may have a progressive decline of lung function with age [6, 7]. Comparison of results between older studies is hindered by the fact that many different reference values and criteria for defining lung function abnormalities have been used, as previously reviewed by KOUMBOURLIS et al. [8]. Nowadays, the availability of the 2012 Global Lung Initiative reference values for spirometry [9], including prediction equations for African–Americans that have also been validated in sub-Saharan Africa [10], provides a useful tool to compare lung function in patients with SCD from different countries. When interpreting lung function results in this group, it is important that the lower limit of normal (LLN) is established at the 5th percentile (-1.64 z-scores) of the reference population instead of using a fixed cut-off (e.g. 80% of predicted), which can lead to misclassification of the lung function pattern [8, 11]. Combining the results of dynamic and static lung volume measures (i.e. spirometry and body plethysmography), it is then possible to identify five different respiratory patterns in patients with SCD: normal, restrictive, obstructive, mixed and nonspecific (figure 1) [12]. Using such classification, COHEN et al. [12] reported an abnormal lung function in 30% of children and adolescents with SCD (16% obstruction, 7% restriction, 1% mixed and 6% nonspecific pattern).

In paediatric patients with SCD from high-income countries, an obstructive physiology (forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio <LLN (<5th percentile) and total lung capacity (TLC) ⩾LLN) is the most frequent lung function alteration, noted in approximately 15–20% of the cases [12, 13]. In low- to middle-income countries, however, cross-sectional spirometry data in children with SCD aged 6–19 years showed that 25–30% of participants had reduced FEV_1 and FVC <5th percentile
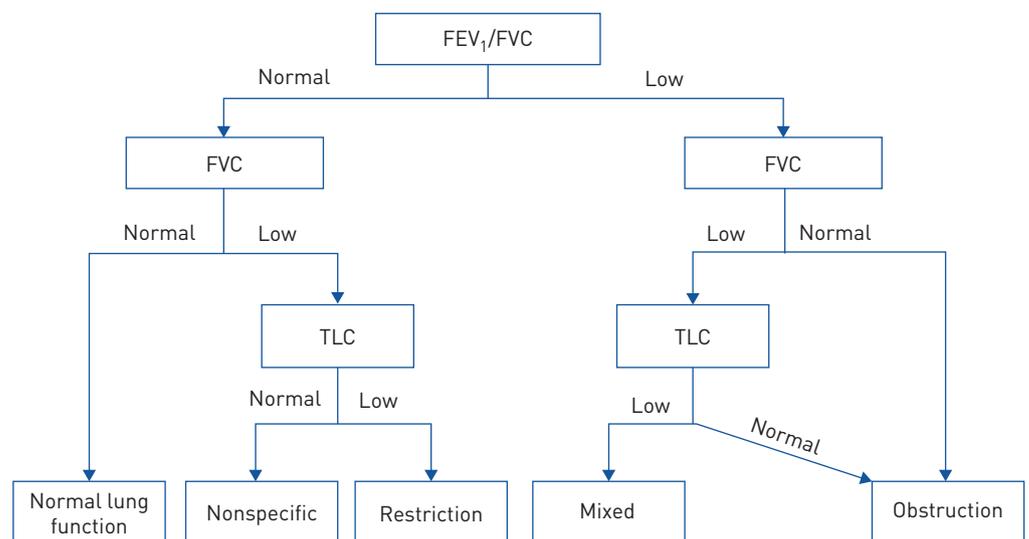

FIGURE 1 Diagnostic algorithm to assess lung function abnormalities in children with sickle cell disease. FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; TLC: total lung capacity; low: lower limit of normal (5th percentile of the reference population); normal: ⩾5th percentile. Reproduced from [12] with permission of the American Thoracic Society.

with preserved FEV_1/FVC ratio, possibly indicating a restrictive (TLC <LLN) or nonspecific pattern (TLC ⩾LLN) [14, 15]. Diffusing capacity (adjusted for haemoglobin values) can also be impaired in paediatric patients with SCD [13], more often in adolescents with a restrictive physiology [16].

It is not clear whether any intervention is able to slow down the deterioration of lung function with age that is often seen in people with this condition. However, a retrospective analysis of 56 children and adolescents with SCD aged >5 years showed that, after starting hydroxyurea, the annual rate of decline in FEV_1 was less pronounced in the study group than in 75 patients who did not receive this therapy [17].

The pathophysiology of lung function abnormalities in children with SCD is still not well defined. Obstructive physiology (figure 1) is not limited to patients with asthma [12, 13]. An alternative mechanism may be the compression of small airways by congested peripheral pulmonary vessels, as suggested by the correlation between pulmonary capillary blood volume and airflow limitation [18].

On the other hand, in adult SCD patients with a restrictive lung function pattern (figure 1), reduced spirometry indices and TLC correlated with lobar volume loss on high-resolution computed tomography [19], which is common in fibrotic lung disease. FIELD et al. [20] demonstrated higher levels of circulating activated fibrocytes in SCD patients with impaired FEV_1 and FVC, which could contribute to the pathogenesis of lung fibrosis [21]. However, interstitial pulmonary fibrosis does not seem to be the only mechanism responsible for loss of lung volume in this group [22].

In the authors' opinion, different lung function patterns in paediatric patients with SCD, except for an obstructive physiology associated with allergic asthma, do not necessarily identify different phenotypes but rather represent the spectrum of SCD-related chronic lung disease, which affects airways, parenchyma or pulmonary vasculature. Longitudinal prospective data show, however, that even in the paediatric population, the incidence of restrictive lung function alterations in individuals with SCD increases with age [7], probably as a result of the progression of pulmonary end-organ damage.

The clinical and prognostic meaning of lung function alterations in children with SCD is uncertain, due to the paucity of long-term longitudinal data and the use of various interpretative strategies across different studies [4]. Abnormal lung function patterns are not associated with past or future rates of pain [12], whereas there is conflicting data regarding the relationship with future acute chest syndrome episodes [7, 12]. Provided that in adults with SCD a reduced FEV_1 is associated with earlier mortality [23], we suggest that paediatric patients with this condition undergo annual spirometry from the age of 6 years [5], with more frequent assessments and static lung volume measurements for those with abnormal lung function and/or asthma. These latter subjects should also be periodically evaluated by a paediatric pulmonologist. A chest computed tomography scan to assess the degree of pulmonary fibrosis may be considered in patients with moderate/severe restrictive or mixed lung function pattern.

Asthma and wheezing

In a large prospective cohort study, a doctor diagnosis of asthma was reported in 17–28% of children with SCD [24–26] and was associated with a higher risk of vaso-occlusive pain crises [24, 25], acute chest syndrome [24–26] and premature death [27]. The mechanisms linking asthma and increased morbidity in SCD have not been elucidated to date. MILLER et al. [28] proposed that asthma-induced ventilation–perfusion mismatch may cause local tissue hypoxia and subsequent sickling of the red cells, triggering the cascade of pathophysiology events leading to SCD respiratory complications.

Asthma is far more common in paediatric SCD patients with allergies than in those without: in an unselected cohort of 187 children and adolescents with SCD, 45% of those with a physician diagnosis of asthma had at least two skin prick tests positive for common aeroallergens, compared with only 15% of participants without asthma [26]. However, chronic airway inflammation and airway remodelling may also develop simply due to SCD pathophysiology, causing asthma or isolated recurrent wheezing [26], airway hyperresponsiveness [29] or obstructive lung function [12]. Evidence from animal and human studies suggests that several mechanisms are involved in SCD airway disease, including exaggerated allergic airway inflammation after sensitisation [30] and activation of inflammatory pathways following ischaemia-reperfusion injury in the lung [31]. Moreover, downstream products of the haemolytic arginine-nitric oxide pathway may contribute to asthma and airway remodelling [32], as well as the increased levels of cysteinyl leukotrienes and leukotriene B_4 in SCD patients (involved in eosinophilic asthma and neutrophilic inflammation, respectively) [33, 34]. Overall, these mechanisms result in increased levels of T-helper 1, T-helper 2 and monocytic inflammatory markers in patients with SCD and asthma or asthma-like features compared with non-SCD subjects with atopic asthma [35].

The overlap of wheezing phenotypes makes the diagnosis of asthma in children with SCD challenging. STRUNK et al. [26] reported that almost half of SCD paediatric patients without an asthma diagnosis had

experienced wheezing in the past, whereas the presence of at least two characteristics among having a parent with asthma, wheezing with exercise and wheezing causing shortness of breath had a sensitivity of 100% for doctor diagnosis of asthma [26]. The demonstration of airflow obstruction reversible with bronchodilators supports the diagnosis but non-reversible lower airway obstruction can also be found as part of the SCD-related chronic airway disease [36]. Exhaled nitric oxide fraction (F_{ENO}) has been reported at higher, lower or similar levels compared with control subjects [37–39]. COHEN et al. [40] found that in 131 children with SCD, higher F_{ENO} levels were associated with atopic features (positive skin-prick test, raised immunoglobulin-E levels and peripheral blood eosinophil count) but not wheeze, baseline spirometric indices or bronchodilator response. An allergy assessment including history and skin prick tests (or blood radioallergosorbent test) for aeroallergens should be performed in SCD patients with suspicion of asthma [26]. Finally, an asthma diagnosis should be ruled out in patients with recurrent episodes of acute respiratory distress interpreted as acute chest syndrome despite negative chest radiograph findings, given the overlap of symptoms between the two conditions (e.g. wheezing, cough, chest pain, shortness of breath) [41].

There is a lack of evidence regarding acute and chronic asthma treatment for patients with SCD. For those with an acute asthma attack, in our practice we apply a low threshold for hospital admission and chest radiography, in light of the differential with acute chest syndrome. Hypoxaemia compared to the baseline should be promptly treated as it triggers red cell sickling and, potentially, further complications [42]. Apart from short-acting β_2-agonists, oral corticosteroids can be administered for moderate or severe exacerbations, although they should be used with caution due to a reported association with vaso-occlusive pain [43]. When needed, we suggest a 3-day course of $1\ mg\cdot kg^{-1}$ per day (max 40 mg) of prednisolone-equivalent dose.

For SCD patients with frequent asthma symptoms that require regular preventer therapy, we follow a step-wise therapeutic approach based on national and international guidelines for the management of asthma in children [44, 45]. A poor clinical response to escalating doses of inhaled corticosteroids (ICS) in SCD patients with asthma may depend on inadequate delivery of ICS to lungs (e.g. poor compliance to ICS, use of wrong inhaler, poor inhaler technique), comorbidities (e.g. allergic rhinitis, dysfunctional breathing) or the presence of a predominant non-eosinophilic component of airway inflammation [35], or may indicate the need to reconsider the appropriateness of diagnosis. Given the potential role of the leukotriene pathway in the pathogenesis of SCD-related morbidity [46], we often use cysteinyl leukotriene receptor antagonist (montelukast) for chronic asthma prophylaxis in this group. A higher risk of neuropsychiatric adverse effects (including irritability, aggressiveness and sleep disturbances) was reported with montelukast than with ICS in children with asthma (relative risk 12.0, 95% CI 1.60–90.2) [47]. These symptoms usually appear in the first week of therapy [48], in which case the drug should be stopped.

The routine use of spirometry along with standardised asthma control questionnaires [49] can be useful to evaluate the response to treatment, although these tools have not been validated for such scope in the SCD population.

SDB and hypoxaemia

SDB with nocturnal hypoxaemia is common in children with SCD. Obstructive sleep apnoea (OSA) affects approximately 40% of children of African ancestry with SCD when using an obstructive apnoea–hypopnoea index cut-off point ⩾1 at polysomnography (PSG) or 10% at cut-off point ⩾5 [50]. Over one-third of children with SCD will also have sustained daytime hypoxaemia (oxygen saturation measured by pulse oximetry (S_{pO_2}) <96%) [51, 52], which can depend on the variable combination of lung parenchyma, airways and vasculature alterations leading to reduced gas-exchange and ventilation–perfusion mismatch. Moreover, the polymerisation of haemoglobin S (HbS) causes a right-shift of the oxyhaemoglobin dissociation curve (i.e. decreased haemoglobin oxygen affinity) [53], determining an oxyhaemoglobin saturation at a given arterial partial pressure of oxygen lower than predicted by a normal oxyhaemoglobin dissociation curve [42].

The gold standard measure of oxyhaemoglobin saturation in patients with SCD is arterial blood gas analysis with co-oximeter or, as an alternative, noninvasive pulse co-oximetry. The use of co-oximetry allows measurement of the fractional oxyhaemoglobin saturation, which is the proportion of total haemoglobin oxygenated [42]. The oxyhaemoglobin saturation obtained by conventional two-wavelength pulse oximetry presents less discrepancies with co-oximetry than traditional arterial blood gas [54], where oxyhaemoglobin saturation is calculated from the arterial oxygen tension and the oxyhaemoglobin dissociation curve of haemoglobin A, which is not applicable to individuals with SCD.

However, the use of two-wavelength pulse oximetry in SCD presents some caveats, mainly because of the increased levels of carboxyhaemoglobin and methaemoglobin in these patients [55]. Such dysfunctional

haemoglobins are unable to carry oxygen but adsorb light at similar wavelengths as oxygenated and deoxygenated haemoglobin, affecting S_{pO_2} readings [42]. Of note, low S_{pO_2} values during pulse oximetry in patients with SCD may be simply due to digit hypoperfusion (*i.e.* acute dactylitis). Therefore, in cases of low S_{pO_2} it is always advisable to obtain a second reading from another site (*e.g.* earlobe) to confirm the finding. Moreover, it should be kept in mind that oxyhaemoglobin saturation is only one of the determinants of the total amount of oxygen that can reach the tissues, with haemoglobin concentration, cardiovascular function and oxygen release from haemoglobin also playing an important role [56].

Oxyhaemoglobin desaturation triggers HbS polymerisation, which is the first of a chain of events culminating in SCD complications [2]. Moreover, in the presence of SDB, the repeated cycles of hypoxia and re-oxygenation enhance the oxidative stress and pro-inflammatory signalling pathways that contribute to cause SCD-related acute and chronic manifestations [57].

Current evidence suggests that children with SCD and nocturnal hypoxaemia are at higher risk of intracranial arteriopathy [58] and central nervous system events [59], while a lower daytime S_{pO_2} resulted in an increased risk of stroke [60]. A higher frequency of left ventricular diastolic dysfunction has been reported in those with both asleep and waking oxygen desaturation [61], and there is evidence of increased risk of pulmonary hypertension, as suggested by a tricuspid regurgitation velocity (TRV) >2.5 m·s^{-1} at Doppler echocardiography in paediatric patients with lower awake S_{pO_2} [62, 63]. Enuresis is more frequent in SCD children with OSA [50], whereas most recent prospective studies did not find an association between overnight [52, 64] or daytime [52, 65] S_{pO_2} and the incidence of vaso-occlusive pain crises and acute chest syndrome in paediatric SCD patients.

Given the clinical implications of nocturnal hypoxaemia in children with SCD, it is important to specifically investigate the presence of SDB symptoms in these patients, such as snoring, daytime somnolence, morning headaches, hyperactivity or behavioural disturbance, enuresis continuing after 6 years of age and observed apnoeas during sleep. In the presence of such symptoms, we suggest undertaking a sleep study, possibly a PSG. Recent British guidelines recommend investigating overnight oxygen saturation in SCD paediatric patients with spot daytime S_{pO_2} <95% [66]. Those with mean overnight S_{pO_2} <95% should then undergo PSG, assessment for cerebrovascular disease, and static and dynamic lung volumes measurement, and they should be considered for echocardiography [66].

Furthermore, we usually perform a hypoxia challenge test in SCD patients with waking S_{pO_2} <95% when fitness to fly is requested. In fact, during commercial flights in pressurised aircrafts, pressure of oxygen falls to the equivalent of breathing 15% oxygen (instead of 21%) at sea level [67]. As a consequence, patients with SCD and low baseline S_{pO_2} may develop severe in-flight hypoxaemia, potentially triggering vaso-occlusive pain crises and other SCD-related complications [68].

Management of OSA in children with SCD includes conservative therapeutic attempts with nasal corticosteroids and/or montelukast administered for 6–12 weeks, tonsillectomy and adenoidectomy and the use of nocturnal continuous positive airway pressure [69].

Hydroxyurea significantly improved both overnight and daytime S_{pO_2} [70] in a retrospective cohort of 43 paediatric SCD patients, and it is currently indicated for treating chronic hypoxaemia in the UK (grade 1C) [71]. Nocturnal home oxygen therapy is an alternative option for SCD patients with chronic severe hypoxaemia. The recent American Thoracic Society guidelines for home oxygen therapy in children indicated that oxygen supplementation at home should be considered for SCD patients who have at least 5% of recording time spent with an S_{pO_2} <90% during a sleep study or at least three separate spot daytime S_{pO_2} records at steady state <90% (conditional recommendation) [72]. There are concerns about the safety of long-term home oxygen therapy in patients with SCD, especially in terms of possible erythropoiesis suppression. In fact, oxygen may inhibit the hypoxia-inducible transcription factors which trigger erythropoietin production in kidney and liver and enhance maturation of erythroid progenitors in the bone marrow [73]. Some previous reports showed indeed impaired erythropoiesis when administering continuous high flow oxygen for several days in acutely ill patients with SCD [74, 75]. However, more recently, two retrospective reviews of adults [76] and children (unpublished data) with SCD undergoing long-term nocturnal home oxygen therapy demonstrated a good safety profile without detrimental effects on erythropoiesis.

Exercise tolerance

Children with SCD may have reduced tolerance of both moderate (6-min walk distance (6MWD)) [62, 77] and maximal exercise [78, 79]. Factors associated with poor cardiorespiratory fitness in SCD include the degree of anaemia and low fetal haemoglobin levels [77], the presence of left ventricular diastolic dysfunction [80] and restrictive lung disease [81], whereas a TRV ⩾2.5 m·s^{-1} at echocardiography is associated with a greater decline by time of age-standardised 6MWD [82]. Exercise-induced

bronchospasm/asthma can also cause poor exercise tolerance, and an exercise bronchial challenge test could highlight this.

There have been concerns regarding possible adverse effects of high-intensity exercise in patients with SCD as it induces changes that could trigger red blood cell sickling, such as dehydration, moderate temperature changes, lactic acid production, acute inflammation and oxidative stress [83]. However, though evidence is still limited, a regular moderate exercise programme in SCD patients (excluding contact sports, especially in those with splenomegaly) might have several positive effects, including favouring social inclusion and improving overall inflammation and oxidative stress [84].

Given these premises and pending further evidence, we generally suggest that paediatric patients with SCD undertake regular non-intensive exercise activity, and recommend that: 1) they avoid contact sports and exposure to extreme temperatures; 2) they start the exercise gradually and interrupt it if they are tired; 3) they keep well hydrated before, during and after the sport activity; and 4) a pre-exercise treatment with bronchodilator is used for those with exercise-induced bronchospasm.

Pulmonary hypertension

Pulmonary hypertension (PH) is a known risk factor for earlier mortality in adults with SCD [85, 86]. The transthoracic echocardiogram is the most important noninvasive screening tool for PH, though the definitive diagnosis requires right heart catheterisation with the demonstration of a mean pulmonary artery pressure (mPAP) >20 mmHg [87]. Previous studies reported a frequency of mPAP $\geqslant$25 mmHg (previous cut-off for PH) in 6–10% of adults with SCD [85, 86], whereas there are no right heart catheterisation data in paediatric patients with SCD.

Haemodynamically, subjects with SCD may have mainly pre-capillary PH with thickened pulmonary arteriolar walls, or post-capillary PH, secondary to left heart dysfunction [88]. Affected patients frequently have haemodynamic features of both components [89]. Alongside a mPAP >20 mmHg, pre-capillary PH is characterised by increased pulmonary vascular resistance (PVR; >3 Wood Units) and pulmonary artery wedge pressure $\leqslant$15 mmHg, as opposed to post-capillary PH [87]. However, it should be borne in mind that baseline PVR values in individuals with SCD are lower than normal due to anaemia-induced increased cardiac output [88], and a PVR value >2 Wood Units is often considered high in these patients [89]. The aetiology of pre-capillary PH in SCD is multifactorial, potentially involving vasculopathy secondary to haemolysis, nitric oxide deficiency and hypoxia, besides chronic pulmonary thromboembolism [88]. Symptoms of PH are nonspecific and may include fatigue, dyspnoea (particularly on exertion), chest pain and syncope, whereas signs of right heart failure at physical examination will only appear at advanced stages of disease. Accompanying desaturation with exertion would increase suspicion of PH.

The echocardiographic screening is based on a combined assessment of TRV measurement (threshold 2.8 m·s^{-1}) and signs suggestive of PH, such as right atrial enlargement, right ventricular dilation or hypertrophy, right-to-left septum shift and enlarged inferior cava diameter with decreased inspiratory collapse [90].

In a prospective cohort study including 160 HbSS individuals aged 3–20 years, a TRV >2.5 m·s^{-1} at baseline was reported in 14% of cases and was associated with greater haemolysis and oxygen desaturation at baseline, as well as with increased odds of decline in exercise capacity at a median follow-up of 22 months [82].

The American Thoracic Society guidelines suggest screening for PH patients with SCD between 8 and 18 years of age through a one-time Doppler echocardiography [89]. Those with an echocardiographic probability of PH that is intermediate to high should be referred to a PH centre experienced in SCD [90].

There is no evidence regarding the most adequate treatment for paediatric patients with SCD and PH [89]. Supplemental oxygen is given for hypoxaemia, aiming to obtain a S_{pO_2} $\geqslant$90% at rest, during exertion and sleep [89]. Treatment of eventual respiratory comorbidities, such as asthma or OSA, seems to have a beneficial effect also on TRV [91]. The use of hydroxyurea as first-line treatment, with chronic transfusions as an alternative, is recommended [89].

Future directions

Long-term prospective follow-up studies in children with SCD and chronic respiratory issues are needed in order to clarify the prognostic meaning of specific conditions, such as lung function abnormalities, chronic hypoxaemia or elevated TRV at echocardiography, and whether therapeutic interventions, such as hydroxyurea, and new emerging disease-modifying therapies [92], have an impact on clinical outcomes and survival. Further, mechanistic studies are desirable to clarify the pathophysiology of asthma and

obstructive airway disease in SCD. In this regard, the effectiveness of cysteinyl leukotriene receptor antagonist for asthma treatment in patients with SCD should be specifically addressed. Mechanistic studies and clinical trials are also needed to evaluate the effects of 5-lipoxygenase inhibitors on airway inflammation and airway hyperreactivity. Finally, the risk and benefits of regular moderate exercise activity in SCD patients should also be further investigated.

Conclusion

Chronic respiratory complications have a high burden in children with SCD and are generally associated with a more severe course of disease. Regularly investigating the presence of chronic respiratory symptoms or sleep disturbances, together with performing basic cardiorespiratory screening in the general paediatric SCD population (*i.e.* annual spirometry, nocturnal oximetry or PSG in patients with chronic hypoxaemia or SDB, and at least one echocardiogram before 18 years of age), might help to identify patients with early chronic respiratory complications who require further and specialist assessments. This can be particularly useful in an era of emerging disease-modifying drugs that might possibly improve also respiratory complications of patients with SCD.

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