Review Article

Challenges of Management of Sickle Cell Disease with Pulmonary Hypertension in Resource Scarce Settings

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ABSTRACT

Sickle cell disease (SCD) is a genetic hemoglobinopathy endemic to sub-Saharan Africa, parts of the Middle East, and other resource-scarce areas worldwide. Pulmonary hypertension (PH) is now one of the most severe complications of SCD, affecting 6-30% of adult patients. SCD-PH carries high morbidity and mortality. The past decade has been marked by significant advances in understanding the epidemiology, pathophysiology, diagnosis, and management of SCD-PH. However, much work remains to be done to improve outcomes for patients with SCD-PH who reside in resource-limited areas. This narrative review will cover the epidemiology, pathophysiology, diagnosis, and treatment of SCD-PH, with a focus on the unique challenges in these settings. Diagnosis and screening remain poor in these areas, and confirmatory testing with right heart catheterization is often limited. Access to disease-modifying therapies such as hydroxyurea is poor, and PH-specific therapies are not available. These gaps in care present several opportunities for task-sharing, decentralization of care, adaptation of novel screening algorithms, and policy change.

Introduction

SCD is among the most common inherited diseases worldwide. Sub-Saharan Africa bears the greatest disease burden as SCD is endemic to this region [1]. PH in the setting of SCD is defined by a mean pulmonary artery pressure ≥25 mmHg on right heart catheterization (RHC). Doppler echocardiography with tricuspid regurgitant jet velocity (TRV ≥2.5 m/s) is commonly used to screen patients [5], [6]. Pulmonary hypertension (PH) is a well-known complication of Sickle Cell Disease. It contributes heavily to illness and death in adults. PH development in sickle cell disease is complex and involves multiple mechanisms described by the World Health Organization's classification. SCD-related PH is usually grouped under Group 5 (multifactorial mechanisms), but it often overlaps with other groups. Chronic haemolysis releases free haemoglobin and arginase. These reduce nitric oxide and increase endothelin-1, leading to changes like those seen in Group 1 pulmonary arterial hypertension. Chronic anaemia causes high cardiac output. This may result in left ventricular changes and post-capillary PH, as seen in Group 2 disease. Pulmonary issues such as recurrent chest syndrome, hypoxemia, restrictive lung disease, and sleep disorders contribute to Group 3 PH. SCD's hypercoagulability can lead to blood clots, which can cause Group 4 PH. As a result, PH in sickle cell disease often includes mixed forms with overlapping causes.

Studies link higher tricuspid regurgitant velocity and PH with increased death in adults with SCD. This stresses the need for early and thorough heart-lung evaluations. PH associated with SCD (SCD-PH) poses unique diagnostic and therapeutic challenges in resource-limited settings. Many patients with SCD reside in these areas; however, provider expertise, diagnostics, and medications are limited. In these resource-scarce contexts, clinicians can take practical first steps such as focusing on symptom-based screening for unexplained shortness of breath, exercise intolerance, or signs of right heart strain. Basic laboratory tests, including a complete blood count and markers of hemolysis, may help identify at-risk patients. Targeted echocardiography for those with suggestive symptoms or risk factors, when available, can further guide management. High out-of-pocket costs for medicines and investigations, weak health systems, and low SCD research capacity are also contributory factors [10], [11]. The purpose of this review is to summarize

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what is currently known about SCD-PH in resource-limited settings, highlight knowledge gaps, and propose potential solutions.

Epidemiology and Burden of SCD-PH in Resource-Scarce Settings

Each year, there are an estimated 300,000 children born worldwide with SCD [2]. The vast majority (>75%) of these births occur in sub-Saharan Africa. Conversely, approximately 100,000 people in the United States live with SCD [2]. The prevalence of PH among patients with SCD varies widely by geographic location based on several factors such as age, disease severity, survival biases, and diagnostic methodology. A systematic review and meta-analysis were performed to better understand the global prevalence of elevated TRV among patients with SCD [7]. Investigators found a pooled prevalence of elevated TRV of 23.5% (95% CI 19.5–27.4%) and did not observe a significant difference between children (20.7%) and adults (24.4%). However, there remains controversy regarding the true prevalence of TRV ≥2.5 m/s in resource-limited countries, as estimates are highly variable, with lower bounds ranging from 5.7% to 23.9% across studies [4], [12], [13].

The variation may be attributed not only to differences in access to care and diagnostic techniques, but also to differing diagnostic thresholds, study methodologies, patient selection criteria, and possible reporting biases. For example, while one study from Sudan reported a prevalence of pulmonary hypertension (TRV ≥3.4 m/s) of 29% with pulmonary artery systolic pressures between 41 and 85 mmHg [5], other studies using different thresholds have yielded much lower estimates. Such disparities complicate efforts to accurately gauge the global burden of SCD-PH and raise ongoing debate about the most appropriate screening and diagnostic criteria. Children are not spared from SCD-PH; in Ghana, investigators found a PH prevalence of 11% among children aged 5–18 years [6]. PH was independently associated with increasing age and markers of hemolysis (reticulocytosis, increased total bilirubin and LDH), leukocytosis, thrombocytopenia, anaemia, and receipt of recent blood transfusions.

The impact of SCD-PH extends well beyond its prevalence, resulting in marked reductions in patients' functional capacity. Decreased six-minute walking distance in affected individuals, which correlates inversely with tricuspid regurgitant velocity (TRV) and predicted pulmonary artery pressure, reflects significant physical limitations that directly affect quality of life and daily functioning [4], [14]. Beyond diminished exercise tolerance, SCD-PH is also associated with increased health care utilization, frequent hospitalizations, and elevated risk of right heart failure. Mortality rates for patients with both SCD and PH remain high, and PH has emerged as a leading cause of premature death in this population, underscoring its role as a major determinant of poor long-term outcomes despite advances in overall SCD care [8], [15].

Pathophysiology and Risk Factors

The pathogenesis of PH in SCD is complex and multifactorial. Thought to be initiated by haemolysis, other mechanisms include endothelial dysfunction, inflammation, hypercoagulability, hypoxemia, and genetic factors [16], [17]. Chronic intravascular haemolysis results in excess free haemoglobin in the circulation. Free haemoglobin binds nitric oxide (NO), a potent vasodilator and regulator of vascular tone [18]. Loss of NO leads to vasoconstriction and platelet aggregation. Additionally, free haemoglobin induces concomitant release of arginase, which depletes L-arginine, the substrate necessary for NO synthesis, leading to further endothelial dysfunction [16], [18]. Other mechanisms that have been proposed include functional asplenia with resultant inflammatory cytokines in the circulation, recurrent pulmonary thromboembolism, chronic lung disease due to repeated acute chest syndrome, left ventricular diastolic dysfunction causing post-capillary PH, and iron overload secondary to chronic transfusion therapy [9], [17].

Right-heart catheterization data show PH to be pre-, post-, or mixed in these patients [15]. Risk factors that have been identified include older age, female sex, obesity, systemic hypertension, hypoxemia, anaemia, renal impairment, and laboratory values consistent with haemolysis such as high LDH, bilirubin, and reticulocyte count [6], [12], [14]. Independent risk factors among children include age, reticulocyte count, and frequent blood transfusions [6]. Interestingly, a study out of Sudan demonstrated cigarette smoking to be significantly associated with PH [5]. There is still uncertainty as to whether hydroxyurea use decreases the incidence or severity of PH. A multicentre trial in Nigeria found no significant difference in PH prevalence between hydroxyurea users and non-users [4]. Investigators postulated that this may be secondary to underdosing or poor adherence. Similarly, Khalil et al. found no significant difference in PH rates between hydroxyurea users and matched controls [6]. Larger studies are needed to better understand the impact, if any, of hydroxyurea on SCD-PH [5].

Diagnostic Challenges in Resource-Limited Settings

Pulmonary hypertension (PH) in people with Sickle Cell Disease is challenging to diagnose because its symptoms are often non-specific and overlap with other cardiac and pulmonary conditions associated with the disease. Although right heart catheterization (RHC) is the gold standard for confirming PH and for distinguishing pre-capillary, post-capillary, or mixed hemodynamic profiles [15], it is rarely available in resource-constrained countries due to the need for specialized personnel, equipped catheterization laboratories, and the associated

high costs. In the absence of RHC, clinicians in such settings may adopt a pragmatic diagnostic algorithm: initial screening with clinical history and physical examination to identify unexplained dyspnea, exercise intolerance, or signs of right heart dysfunction; followed, when feasible, by targeted echocardiography to estimate pulmonary pressures via tricuspid regurgitant velocity (TRV). Patients presenting with both symptoms and elevated TRV (usually ≥2.5 m/s) may then be presumed to have probable PH, and undergo further non-invasive evaluation for hemolysis and other risk factors, in place of definitive RHC. This approach enables risk stratification and guides management, though many patients remain without confirmatory diagnosis in the absence of catheterisation.

Transthoracic echocardiography is a common screening method, but current evidence does not support screening every patient with SCD. Instead, doctors should focus on those showing clinical signs or risk factors. Echocardiography is advised for patients with unexplained or worsening shortness of breath, trouble exercising, reduced function, chest pain, fainting, low oxygen levels at rest or during activity, or signs of strain on the right side of the heart. Other clues include elevated biomarkers such as N-terminal pro-brain natriuretic peptide (NT-proBNP), signs of hemolysis (e.g., high lactate dehydrogenase, bilirubin, or reticulocytes), dropping oxygen saturation, or a history of recurrent blood clots. In these cases, echocardiography estimates pulmonary artery pressure by measuring tricuspid regurgitant velocity (TRV) and checks the size and function of the right heart.

Patients with high TRV (usually 2.5 to 3.0 m/s or more) or other signs of pulmonary vascular disease should have a right heart catheterization, which is the definitive test for PH. Access to echocardiography in resource-limited settings is challenging and constrained by a lack of equipment, poor machine maintenance, unreliable electricity, and a shortage of trained sonographers [1], [2], [11]. Screening also appears to be highly variable among pregnant women with SCD, despite them being at increased risk [1]. Screening asymptomatic patients is also difficult, as low-cost tools with adequate sensitivity and specificity have not been validated.

Besides echocardiography, a comprehensive diagnostic workup is important to identify the cause of PH and to rule out other heart and lung conditions common in SCD. This usually includes lung function tests to assess how well oxygen moves through the lungs, blood gas analysis, chest imaging, such as high-resolution CT scans when needed, and tests for blood clots, such as ventilation–perfusion scans or CT pulmonary angiography. Blood tests for hemolysis markers and natriuretic peptides also help with risk assessment and monitoring. Because many patients have overlapping conditions, identifying other lung or heart issues can greatly influence treatment decisions.

Many people with SCD have chronic dyspnea for reasons other than pulmonary hypertension. This can be due to chronic anaemia that increases the heart's workload, lung problems from recurrent acute chest syndrome episodes, pulmonary fibrosis, asthma-like airway hyperresponsiveness, chronic blood clots in the lungs, or left ventricular heart problems. Sleep-related breathing issues and low oxygen levels at night are also common and can make heart and lung disease worse in SCD. These overlapping conditions make it harder to spot PH and complicate the evaluation of patients suspected of having pulmonary vascular problems. Diagnosing PH in SCD requires a careful, team-based approach that includes clinical evaluation, echocardiography for selected patients, and confirmatory tests, such as hemodynamic studies when necessary. Using a clear strategy to identify high-risk patients, especially those with unexplained shortness of breath, signs of haemolysis, or worsening function, can help detect PH earlier and distinguish it from other lung problems common in sickle cell disease.

Management Challenges

Management of pulmonary hypertension (PH) in patients with Sickle Cell Disease is multifaceted and generally involves three broad domains: optimizing sickle cell disease control, treating pulmonary vascular disease, and aggressively managing comorbid cardiopulmonary conditions. Because PH in SCD often reflects overlapping mechanisms rather than a single disease category, treatment strategies must be individualized and directed toward both the underlying hemolytic disorder and the pulmonary vascular consequences.

Optimisation of SCD-directed therapy remains the cornerstone of management. Chronic hemolysis contributes significantly to endothelial dysfunction and pulmonary vasculopathy; therefore, therapies that reduce hemolytic burden may attenuate vascular injury. The most widely used disease-modifying therapy is hydroxyurea, which increases fetal haemoglobin levels, reduces Vaso-occlusive crises, and improves nitric oxide bioavailability. In selected patients, chronic transfusion therapy may further reduce haemolysis and improve oxygen delivery, particularly in those with severe anaemia or recurrent complications. Newer agents, including voxelotor, crizanlizumab, and L-glutamine—have expanded therapeutic options by targeting haemoglobin polymerization, endothelial adhesion, and oxidative stress, although their availability remains limited in many low- and middle-income countries, particularly across sub-Saharan Africa.

Targeted pulmonary hypertension therapies may be considered in selected patients with confirmed pre-capillary disease. Agents developed for pulmonary arterial hypertension include phosphodiesterase-5 inhibitors such as sildenafil, endothelin receptor antagonists such as bosentan or ambrisentan, and prostacyclin pathway agents such as epoprostenol or

treprostinil. However, the availability of these advanced therapies in resource-limited settings is often extremely limited or nonexistent due to high costs and the lack of supply chains. Among these, sildenafil is most likely to be available in some settings, though it may not be widely accessible outside tertiary centres. Where these agents are unavailable, management should focus on optimised SCD-directed therapy, supportive care, and aggressive management of comorbid cardiopulmonary conditions. The evidence supporting the use of pulmonary arterial hypertension therapies in SCD-associated PH is less robust than in idiopathic pulmonary arterial hypertension, and treatment should ideally follow haemodynamic confirmation with right heart catheterization when feasible. Careful patient selection is essential because earlier trials of sildenafil reported increased vaso-occlusive pain episodes in some patients.

Supportive care remains one of the most impactful—and often most accessible—components of management. Oxygen therapy should be provided for patients with resting or exertional hypoxemia. Diuretics may be beneficial for right heart failure or volume overload. Anticoagulation should be considered in patients with confirmed thromboembolic disease, particularly those with or at risk for Chronic Thromboembolic Pulmonary Hypertension.

Equally important is the aggressive management of coexisting pulmonary conditions that may exacerbate pulmonary vascular disease. These include recurrent acute chest syndrome, restrictive lung disease, airway hyperreactivity, sleep-disordered breathing, and chronic thromboembolism. Screening and treatment for nocturnal hypoxemia or obstructive sleep apnea may reduce pulmonary vascular stress and improve functional status. Vaccination against respiratory pathogens and early treatment of infections are also essential preventive strategies [4], [12], [14]. Chronic dyspnoea is common in SCD and often results from multiple overlapping mechanisms, including severe anaemia, high-output cardiac physiology, pulmonary fibrosis, left ventricular diastolic dysfunction, and pulmonary hypertension itself. Careful evaluation is therefore necessary to identify the dominant cause of symptoms and guide therapy.

In many high-burden regions, particularly in sub-Saharan Africa, practical interventions such as hydroxyurea therapy, optimized supportive care, oxygen therapy, and improved screening for cardiopulmonary complications remain the most feasible strategies. For example, in Nigeria, community-based programs have successfully increased access to hydroxyurea by decentralizing prescribing and educating community health workers, resulting in improved disease control. Similarly, pilot echocardiographic screening initiatives in Ghana have demonstrated the feasibility of integrating heart-lung evaluation into routine SCD clinics, enabling earlier detection of pulmonary complications. Strengthening diagnostic capacity, expanding access to essential therapies, and integrating cardiopulmonary evaluation into routine SCD care will be critical to improving outcomes in this population.

Therapeutic Realities in Resource-Limited Settings

Despite the expanding therapeutic armamentarium globally, only a fraction of these interventions is readily accessible in many high-burden regions. In many sub-Saharan African countries, the most practical and scalable interventions remain hydroxyurea therapy, optimized supportive care, oxygen therapy, and management of comorbid cardiopulmonary disease. Advanced pulmonary hypertension therapies, right heart catheterization, and novel SCD medications are often limited to tertiary centres or remain financially inaccessible. Weak health systems, poor insurance coverage, lack of coordinated multidisciplinary care, insufficient policy-making, and severe workforce shortages impact almost every aspect of care for SCD-PH [2], [11]. The lack of nationwide SCD registries affects care by making it difficult to plan services and adequately assessing the care being delivered [6]. Addressing this gap will require coordinated health policy initiatives, expansion of specialized cardiopulmonary services, improved access to essential medications, and integration of PH screening within established sickle cell clinics.

Strategies for Improving Care

To improve care for patients with SCD-PH, we must take a comprehensive approach. Screening all patients with SCD for PH should be implemented and incorporated into both routine SCD follow-up and antenatal care clinics [1], [3], [6], [11]. Task-sharing or training providers who do not typically care for patients with SCD to recognize and manage these patients is another potential solution [16]. Concrete steps for effective task-sharing may include short, targeted training for primary care providers or nurses on recognizing common SCD-PH symptoms and management strategies; developing and disseminating standardized treatment protocols and clinical algorithms; and setting up regular mentorship or case discussion sessions between non-specialist providers and specialists, either in person or via telemedicine. Supportive supervision and the use of simple checklists can further empower non-specialists to deliver evidence-based care. Decentralizing hydroxyurea therapy and continuing to develop simplified diagnostic algorithms can help increase access to care. The use of digital health, telemedicine, and the establishment of electronic registries where they do not exist can also help improve care [10]. Lastly, policy changes that acknowledge SCD as a public health crisis, the addition of hydroxyurea and PH therapies to national drug formularies, and the development of context-specific treatment guidelines can have a major impact [2]. International collaboration with low- and middle-income

countries can also improve care by fostering research and clinical networks.

Future Directions and Research Needs

There are several avenues for future research in patients with SCD-PH in resource-limited settings. Standardized epidemiologic studies are needed to better characterize the global burden of SCD-PH. Data on longitudinal outcomes are needed, as is evaluation of genetic and environmental modifiers of disease. Low-cost and sensitive screening tools are necessary, as is research into affordable targeted therapies for pulmonary hypertension [5], [15], [16]. Implementation research and health systems science can help determine how best to provide care to these patients.

Conclusion

PH is a severe complication of SCD and is now recognized as one of the leading causes of morbidity and premature death among adults. Resource-limited settings bear the greatest disease burden of SCD, and many unique challenges to care exist. Providers in these areas are limited, as are diagnostics and medications. Despite these challenges, there are many areas in which we can improve care. Specific, actionable recommendations include increasing access to echocardiography and basic laboratory testing for at-risk populations, decentralizing hydroxyurea prescription and education programs to primary care centers, expanding targeted provider training on SCD-PH diagnosis and management, and integrating PH screening into routine SCD and antenatal clinics. In addition, establishing national SCD registries, advocating for the inclusion of essential PH therapies on national drug formularies, and fostering collaboration between local health workers and specialists through telemedicine are important steps. Tailoring these interventions to the local context through policy and community engagement can improve outcomes for individuals living with SCD and PH.

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