

Acute Chest Syndrome and Other Pulmonary Manifestations of Sickle Cell Disease

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ABSTRACT

- **Objective:** To review the diagnosis, treatment, and prevention of acute chest syndrome (ACS).
- **Methods:** Review of the literature.
- **Results:** Sickle cell disease is a genetic disease of the hematopoietic system with diverse pulmonary manifestations and complications, including ACS. ACS occurs in approximately 48% of patients with sickle cell disease and is a leading cause of morbidity and mortality. Treatment of ACS is based on the recognition of common etiologies; after initial supportive measures, therapy includes antibiotics covering atypical and routine pathogens, hydration, transfusion as indicated, and mechanical ventilation if required. For spontaneously breathing patients, incentive spirometry can both prevent ACS as well as prevent worsening of an episode already in progress. Despite recent advances in our understanding of this syndrome, treatment remains challenging and mortality is substantial. Successful management does not preclude future events or the development of pulmonary hypertension.
- **Conclusion:** Future research in the field should help us to better understand and manage this disease.

Sickle cell disease (SCD) is an inherited disorder of the hematopoietic system that affects approximately 250 million people globally, making it one of the most prevalent genetic diseases worldwide [1]. The highest prevalence of SCD is found in Sub-Saharan Africa, South and Central America, Saudi Arabia, and Mediterranean countries [2–4]. In the United States, the disease occurs at a rate of 1 in 500 births among African Americans and 1 in up to 1400 births among Hispanic Americans [5].

The sickle-shaped red blood cells that characterize SCD are the result of a single gene mutation in hemoglobin A that causes the formation of abnormal hemoglobin chains (ie, hemoglobin S) that polymerize when deoxygenated. These deformed cells may obstruct blood vessels, causing pain, tissue death, and severe injury in the major organs in the event of vaso-occlusive crisis. Obstruction in the blood vessels of the lungs related to the effects of these vaso-occlusive

events can cause lung injury and infarction, a complication known as *acute chest syndrome* (ACS) [6]. ACS occurs in approximately 48% of people with SCD, with an incidence rate of 14 episodes per 100 patient-years [7]. It is a leading cause of morbidity and is the most common cause of mortality among patients with SCD [8,9].

Variants of SCD

The SCD variants result from different hemoglobin gene mutations and differ substantially in terms of their clinical manifestations. The most common types are homozygous SCD, sickle hemoglobin C disease, and the sickle β thalassemias. Homozygous SCD occurs when the gene for hemoglobin S, or sickle hemoglobin, is inherited from both parents. In sickle hemoglobin C disease, the hemoglobin S gene is inherited from one parent and the hemoglobin C gene is inherited from the other. The sickle β thalassemias result from the inheritance of a hemoglobin S gene and a thalassemia gene. β Thalassemia genes produce reduced amounts of normal hemoglobin, with the amount produced varying from patient to patient. In sickle cell/ β^0 thalassemia, no normal hemoglobin is produced, and the clinical manifestations are comparable to homozygous SCD. In sickle cell/ β^+ thalassemia, small amounts of normal hemoglobin are produced, which can mitigate the effects of hemoglobin S. Homozygous SCD and sickle cell/ β^0 thalassemia are generally considered the more severe forms of the disease, with sickle hemoglobin C disease and sickle cell/ β^+ thalassemia tending to be less severe.

Epidemiology

The incidence of ACS differs among the forms of SCD as demonstrated by the Cooperative Study of Sickle Cell Disease (CSSCD), a prospective study that followed 3751 patients for 19,867 patient-years [8]. In the CSSCD, the incidence of ACS was highest among patients with homozygous SCD at 12.8 cases per 100 patient-years, followed by sickle cell/ β^0 thalassemia (9.4 cases/100 patient-yr), sickle hemoglobin C disease (5.2 cases/100 patient-yr), and sickle cell/ β^+ thalas-

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semia (3.9 cases/100 patient-yr). This study also noted that the incidence of sickle cell complications is inversely related to age, with the incidence of vaso-occlusive pain crisis or ACS decreasing steadily from childhood to adulthood. Insight into other clinical aspects of ACS episodes was provided by the National Acute Chest Syndrome Study Group (NACSSG), which evaluated 671 episodes of ACS in 538 adult and pediatric patients over a 4-year period among 30 centers [10]. Nearly half of the patients were admitted for reasons other than ACS, most commonly pain, and went on to develop the syndrome later in their hospital course. Approximately 18% of patients had frequent admissions due to recurrent episodes of this syndrome, which may result in long-term sequelae. The CSSCD found that ACS was the second most common reason for hospitalization after vaso-occlusive pain crisis (12.8 hospitalizations/100 patient-yr) [11]. The mean duration of hospitalization ranges from 6.4 days [10] to 10.5 days [11]. The incidence of death from ACS also has varied in different studies, ranging from 1.8% in the NACSSG report to 3% in the CSSCD. [10,11]. Patients older than 19 years of age have a higher mortality rate, up to 4.3%, and the main cause of death was respiratory failure [11]. Clinical features may also have a link to survival. Patients with leukocytosis exceeding 15,000 cells/ μ L at baseline may be at higher risk for mortality (2.2 versus 1.2 deaths per 100 person-yr) [12].

Pathogenesis

Red cell sickling is the primary cellular event leading to the clinical pathophysiology in SCD [13]. SCD results from a single gene defect in which valine is substituted for glutamic acid in the β -globin subunit of hemoglobin A, resulting in the formation of hemoglobin S. When deoxygenated, hemoglobin S polymerizes in the cell, distorting the cell's shape and causing it to stiffen and become less pliable [14]. The distorted shape and inflexibility of sickled red blood cells make them prone to obstruct arterioles and capillaries, leading to ischemia and tissue damage. Other factors that contribute to the pathogenesis of ACS include increased expression of adhesion molecules on sickle cells and endothelium, reduced levels of nitric oxide (NO), and release of inflammatory mediators. Hypoxia enhances the ability of sickle cells to adhere to vessel endothelium via interaction between very late activation antigen 4 (VLA4) on red blood cells and the vascular cell adhesion molecule-1 (VCAM-1) on vessel wall [15,16]. Hypoxia also has been shown to decrease production of NO, which under normal conditions is produced by the endothelium and inhibits VCAM-1 up-regulation [15,16]. In addition, free hemoglobin released during acute and chronic hemolysis reacts with NO to form methemoglobin and nitrate, inhibiting its bioactivity and resulting in up-regulation of VCAM-1 [16]. Atelectasis worsens sickling locally due to hypoxia, leading to local

release of mediators of inflammation and ultimately micro-infarction. Recently, researchers have suggested that human platelet antigen-5b allele may be a genetic risk factor for the development of occlusive vascular complications, such as ACS, in SCD [17]. This allele may ultimately lead to enhanced therapy or the prevention of occlusive syndromes.

Etiology

A single event or multiple events can trigger the pathogenic mechanisms of ACS (ie, hypoxia, hemoglobin S deoxygenation and polymerization, red cell sickling, and microvasculature occlusion), which evolve through a final pathway where hypoxia causes further sickling, leading to a self-perpetuating cycle. Initiating processes include pulmonary infection, fat and bone marrow embolism, pulmonary infarction, thromboembolism, or in situ thrombosis. In addition to these processes, atelectasis from poor chest movement secondary to pain from thoracic bone infarction and decreased respiratory stimulation due to opiates can worsen the hypoxia, inducing further red cell sickling. These specific etiologies result in syndromes that are clinically similar and best described as ACS.

The most common causes of the syndrome are infection and pulmonary fat embolism, although a specific cause often is not identified. Contrary to the prior reports of gram-positive bacterial infections causing ACS [6,18], current studies suggest that atypical organisms may be the more likely culprit [10,19]. The most common infective organisms found in recent studies are *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* followed by respiratory syncytial virus [10,19]. Up to 27 pathogens have been implicated as etiologic factors in ACS. The incidence of streptococcal infection has been decreasing, likely secondary to prophylactic vaccination in patients with SCD.

During vaso-occlusive crisis, bone ischemia can lead to infarction and necrosis of bone marrow and release of the marrow contents, including fat, into the blood stream. Pulmonary fat emboli resulting from this pathologic process is presumed to be most frequent single recognizable cause of ACS. Patients with fat embolism are usually older [11]. Thoracic bone infarction also contributes to the development of the syndrome as it can lead to splinting and atelectasis, which may result in ineffective clearance of secretions, promoting infection. As shown by bone scans in a study by Bellet et al [20], thoracic bone infarction (ribs and vertebrae) occurs in up to 39.5% of sickle cell patients hospitalized due to acute chest or back pain.

Thromboembolism or in situ thrombus are etiologic considerations in ACS [21] given the hypercoagulable state induced by hypoxia and decreased levels of NO and the higher incidence of thromboembolism in patients with SCD. Pulmonary infarction is the diagnosis of exclusion when other specific etiologies are eliminated.

Recent studies have linked asthma to ACS among patients with SCD. Sylvester et al [22] in his study showed that 18% of the children with a history of ACS were taking medications to help with their asthma compared to only 5% with no history ACS. These children on medications for their asthma had been diagnosed with asthma approximately 3.5 years before the onset of ACS [1]. Children with asthma and SCD also have more vaso-occlusive complications, including ACS [23]. These findings may suggest an association between the 2 diseases or that asthma, prevalent among inner-city African-American populations, may simply exacerbate SCD and trigger ACS. Evidence underscoring the link between the 2 diseases was recently published showing that patients with SCD diagnosed with asthma have a higher incidence of ACS [24]. Furthermore patients with asthma and SCD have a greater risk of death after adjusting for known risk factors [25].

Diagnosis

ACS is diagnosed clinically. It is defined as a new infiltrate on chest radiograph in combination with 1 other new symptom or sign: chest pain, cough, wheezing, tachypnea, and/or fever ($> 38.5^{\circ}\text{C}$) in a patient with SCD [26]. The most common presenting symptoms include fever, cough, and chest pain, with shortness of breath, wheezing, hemoptysis, chills, and productive cough occurring less commonly [11]. The symptoms of ACS are age-dependent, with younger patients presenting more often with wheezing, cough, and fever, and older patients presenting with vague pains in their extremities [10,11]. Physical findings such as increased pulse rate, elevated respiratory rate, and high temperature also are more prominent in children than adults [27]. Pulmonary signs usually noted are crackles on examination [10,27].

Diagnostic Testing

Diagnostic testing for the ACS includes a complete blood count (CBC), chest radiograph, arterial blood gas analysis, and measurement of phospholipase A_2 . Compression ultrasonography of the extremities can help exclude deep vein thrombosis (DVT), obviating the need for anticoagulation. However, ruling out pulmonary embolism can be quite challenging. CBC is performed routinely in all patients, and on average, the hemoglobin declines by 0.7 g/dL and the white blood cell count increases by 70% [11]. A platelet count below 200,000 cells/ μL is noteworthy as a multivariate analysis performed by the NACSSG found that neurologic complications, which occurred in 11% of the study patients, were more common in patients with a platelet count below this value [10]. A daily metabolic profile is helpful in patients with ACS as it allows for early detection of electrolyte abnormalities, worsening renal function, elevated lactate dehydrogenase due to acute hemolysis, and increasing bilirubin levels.

Chest radiograph remains the initial radiologic test for evaluation of the patient with complications of SCD. The presence of airspace disease or air bronchogram and consolidation are typical for ACS. However, the findings can vary among sickle cell patients, with younger children having more upper lobe involvement and adults having more of a multifocal presentation [11,28].

Pulse oximetry should be monitored continuously. It is important to note that the accuracy of pulse oximetry is decreased in vaso-occlusive pain crisis or ACS [29]. If needed, blood gas analysis should be performed with a co-oximetry panel [30].

Secretory phospholipase A_2 plays an important role in generation of proinflammatory mediators, which in turn release free fatty acids responsible for lung injury in fat embolism. Increased serum levels of secretory phospholipase A_2 may be a reliable marker that can help in early identification of present or incipient ACS or vaso-occlusive crisis and minimize complications [31,32]. Although C-reactive protein (CRP) has been evaluated as a marker for predicting the development of ACS, it lacks diagnostic accuracy as elevated CRP levels occur in other conditions [33].

Other Evaluations

Blood and sputum cultures should be obtained in all patients. Bronchoscopy with bronchoalveolar lavage (BAL) may be helpful if sputum cultures are negative. In the NACSSG [10], up to 13% of patients who underwent this procedure experienced an adverse event, which ranged from respiratory failure to episodic hypoxia [10]. Although half of these events were episodic hypoxia, caution is required. The diagnosis of pulmonary fat embolism is usually suggested by BAL or induced sputum samples showing fat droplets in greater than 5% of alveolar macrophages [34,35]. Godeau et al [35] initially demonstrated that BAL has a sensitivity of 60% for diagnosis of fat embolism associated with ACS when using a cut-off of more than 5% of macrophages containing fatty droplets. Subsequently, Lechapt et al [34] determined that analysis of induced sputum for fatty macrophages is a reliable test for detecting fat embolism, demonstrating a correlation of 0.65 between analysis using induced sputum versus BAL samples ($P < 0.018$). In these studies, the oil red O method was used to detect fat droplets. The sputum samples were pretreated with 0.1% dithiothreitol in PBS, and then the suspensions were filtered and a hemocytometer was used to calculate the nonsquamous cells. Smears were prepared with centrifuged samples and stained with oil red O, a specific neutral fat stain [35].

Ventilation-perfusion scan is not reliable and usually is not employed for diagnosis of ACS. However, it can be useful in suggesting the diagnosis in patients who have symptoms of the syndrome but have a normal chest radio-

Table 1. Treatment of the Acute Chest Syndrome

	Comments
Supportive measures	
Hydration	Up to 2–3 L of fluids. Oral route should be encouraged if patient can tolerate PO.
Analgesics	Provide optimum pain control to minimize complications and maximize comfort
Oxygen	Maintain oxygen saturations above 97%
Specific therapy	
Incentive spirometry	Prevents atelectasis and its complications
Bronchodilators	May benefit a subset of patients with underlying bronchospasm
Antibiotics	Always cover for atypical bacteria; use local antibiograms
Blood transfusion	Decreases hemoglobin S levels in anemic patients
Exchange transfusion	Reserved for patients with severe ACS, initial hemoglobin concentrations > 9 g/dL, or vaso-occlusive crisis
Corticosteroids	May benefit patients with underlying bronchospasm
Experimental therapies	
Tinzaparin	Not recommended at this time
Purified poloxamer 188	In phase I trials
Inhaled nitric oxide	Case reports show benefit; randomized trial completed, awaiting results
Arginine	Potential future agent as precursor of nitric oxide

graph [36,37]. This modality also may suggest the presence of thromboembolic disease or pulmonary infarction, but specific diagnosis can be difficult.

Management

Initial Supportive Measures

The initial management of ACS is hydration, pain control, and oxygen supplementation (Table 1). Fluid replacement and analgesics for pain control must be used judiciously as overhydration and narcotic analgesics can lead to pulmonary edema [38]. Oral hydration is preferred, but aspiration precautions should be maintained as these patients are often on high doses of narcotics. Selection of a pain control medication is a critical step in the management of ACS or any form of vaso-occlusive pain crisis. Even oral morphine has been shown to cause or worsen ACS [39].

A recent study of morphine continuous infusion with co-infusion of naloxone reported a decreased incidence of itching in the high-dose naloxone group [40]. Patient-controlled analgesia has resulted in a lower morphine dose with adequate pain relief but has shown no effect on hospital stay [41]. There have been case reports of successful use of dexmedetomidine in relieving ACS pain, but these findings have not been evaluated in a randomized controlled trial [42].

Oxygen via face mask or nasal cannula is routinely administered to all patients with ACS. The results of pulse oximetry should be interpreted with care since baseline pulse oximetry values vary in patients with SCD [29]. In addition, although higher oxygen saturation reduces erythrocyte sickling, it does not affect pain medication requirements or hospital stay [43,44]. Therefore, we recommend keeping oxygen saturation above 97% with or without supplemental oxygen.

Incentive spirometry is one of the most beneficial treatments that can be offered to patients with ACS. Bendixen and colleagues [45] have shown that healthy individuals take deep breaths 9 to 10 times per hour to prevent alveolar collapse. Incentive spirometry can take the place of deep breathing that is lacking in sickle patients with chest pain or back pain and counteract the effects of splinting. The efficacy of incentive spirometry in preventing acute pulmonary complications in SCD was demonstrated in a prospective randomized trial involving 29 patients with 38 hospital admissions assigned to spirometry or no spirometry. Only 1 of 19 admissions in the incentive spirometry arm had pulmonary complications as compared with 8 of 19 admissions in the nonspirometry group [20].

Because some patients with SCD may have occult or undiagnosed asthma or have been diagnosed with asthma prior to the diagnosis of ACS [46,47], bronchodilators should be used in all patients and continued depending upon clinical response. β_2 agonist nebulizers have been shown to improve symptoms in some patients with ACS. In the NACCSG report, 61% of patients were treated with bronchodilators, and nearly 20% of these patients had a clinical response, defined as a 15% improvement in forced expiratory volume in 1 second [10].

Specific Therapy

Antibiotics. Antibiotic therapy in ACS is critical and should always include coverage for atypical pathogens as these have been found to be a major etiologic factor in multiple studies [10,19]. Antibiotic coverage should be broadened to cover hospital pathogens in patients with a history of frequent hospital care. Surprisingly, there have been no randomized controlled trials regarding the use of antibiotics in treating ACS [48].

Corticosteroids. Some evidence suggests a beneficial effect of high-dose systemic corticosteroid therapy on outcomes in patients with ACS, including the results of a randomized controlled trial that showed a decrease in hospital days and incidence of blood transfusion with corticosteroids as compared with placebo [49]. Similar effects were shown in an earlier study by Isaacs et al [50] in which patients with recurrent sickle cell crisis who were given steroids had improved pack-cell volumes. However, other studies have shown worse outcomes with steroid use, including hemorrhagic stroke [51] and increased risk of readmission [52]. At this point, we do not recommend routine use of steroids with sickle cell crisis unless there is active underlying asthma.

Blood transfusion. Blood transfusion remains the cornerstone of treatment in SCD patients who have hemolysis, symptomatic anemia, or signs of hypovolemia. In ACS patients with a hemoglobin level less than 10 g/dL, blood transfusion can swiftly resolve the pulmonary event. Blood transfusion was used to treat 72% of the patients in the NACSSG's multicenter study of outcomes in ACS (68% receiving simple transfusion), and resulted in a significant improvement in oxygenation [10]. There was no difference in oxygenation in patients receiving simple transfusion or red cell exchange transfusion. The indications for blood transfusion in ACS are usually to raise the hemoglobin to increase the oxygen-carrying capacity in cases of symptomatic, severe anemia seen in associated aplastic crisis, sequestration crisis, accelerated hemolysis, or blood loss. Patient selection for transfusion has become more stringent due to increased recognition of transfusion-related reactions as reported in multiple studies, including the NACSSG study and case reports [10,53].

As demonstrated in the NACSSG, simple transfusion and exchange transfusion result in similar levels of oxygenation. To avoid increasing the risk of vaso-occlusion due to the effects of increased blood viscosity, the hemoglobin level should not be increased higher than approximately 11 g/dL (hematocrit of 35%) after transfusion, and an exchange transfusion should be attempted if concerns of increased hematocrit or viscosity arise [54]. However, the mean hemoglobin level in patients with ACS is 7.7 g/dL, which allows for simple transfusion of 2 to 4 units of packed red blood cells that decreases the hemoglobin S levels without the complications associated with increased blood viscosity. In severe cases, maintenance of hemoglobin between 10 and 11 g/dL may be acceptable with simple transfusion. We recommend reserving exchange transfusions for patients with severe ACS or in patients with initial hemoglobin concentrations greater than 9 g/dL. Patients with severe, progressive ACS are at risk for respiratory failure manifested by increased respiratory

rate, worsening hypoxia, and bilateral alveolar infiltrates on chest radiograph [54]. The advantages of red cell exchange are that it results in dramatic resolution of the episode of ACS, minimizes the development of iron overload, and rapidly decreases hemoglobin S and hematocrit levels [55]. Exchange transfusion lowers white blood cell count, absolute neutrophil count, platelets, and VCAM-1 levels, but these effects are short-lived [56]. A double-volume red cell exchange transfusion can be performed to decrease the percentage of hemoglobin S-containing red blood cells to less than 20%, which improves vascular perfusion. Some series have demonstrated that patients with a hemoglobin S level between 20% and 30% have better outcomes [55], and this is the cut-off value for exchange transfusion in most institutions.

The risk for transfusion-related complications must be considered when deciding whether to treat patients with blood transfusion. Delayed transfusion reaction is common among patients with SCD. Allo-antibodies against minor red cell membrane, such as Rh and Kell, are usually implicated in these reactions [57,58], and these antibodies can occur in up to 47% of adults with SCD who receive transfusion [59]. Delayed transfusion reactions in most instances do not have clinically serious outcomes, but they can cause severe hemolytic anemia 3 to 5 days after transfusion, which can result in a drop of hemoglobin to 2 to 3 g/dL, a phenomenon sometimes referred to as "bystander hemolysis." Delayed transfusion reactions can also precipitate vaso-occlusive pain crisis or cause death [59]. Some centers recommended routinely matching for Rh and Kell antigens to minimize allo-antibody formation [57,60]. The management of delayed transfusion reaction is usually supportive. Typing of patients with minor antigens and increasing the use of African-American donors because of similarity of antigen may minimize the incidence of delayed transfusion reactions in sickle cell patients [61].

Newer and Experimental Treatments

New approaches to treating complications associated with SCD include anticoagulation, inhaled NO, and arginine therapy. A randomized double-blind clinical trial that evaluated the low-molecular-weight heparin tinzaparin for the management of acute vaso-occlusive pain crisis demonstrated that tinzaparin administered according to its approved treatment regimen reduced the severity and duration of acute crisis of SCD [62]. At this point, we do not recommend routine use of anticoagulation with tinzaparin for sickle cell crisis. Also, a phase I evaluation of purified poloxamer 188 (a non-ionic surfactant) found the drug to be safe to administer to patients with ACS, and preliminary data suggest that it may shorten the duration of hospitalization in a dose-related manner [63].

Table 2. Pulmonary Complications of Sickle Cell Disease

Acute complications

Hypoxia
Acute chest syndrome
Acute respiratory distress syndrome
Thromboembolic disease
Respiratory failure
Death

Chronic complications

Pulmonary hypertension
Interstitial lung disease
Sleep-related disorder

Case reports supporting the use of inhaled NO therapy have been published [64,65]. A Cochrane database meta-analysis did not find any trials to include in their analysis, and the authors concluded that upcoming research should provide clear evidence to make informed decisions about whether NO is effective [66]. However, randomized studies [67,68] of patients with vaso-occlusive crisis demonstrated that patients who received inhaled NO had statistically significant decreases in hourly pain scores [67,68] and morphine use [67]. Further data on clinical effectiveness were lacking. A multicenter, randomized, placebo-controlled trial of inhaled NO for vaso-occlusive crisis has been completed recently and benefit was not seen [69]. Arginine may be another potential agent for treatment of ACS as it is a precursor of NO [70,71]. Morris and colleagues [72] recently showed that the addition of arginine to hydroxyurea might be more beneficial than hydroxyurea alone and improve the bioavailability of NO. Arginine supplementation enhanced lymphocytic blastogenesis in SCD patients, which may improve immune function [71].

Other therapies that have been attempted with limited success include extracorporeal membrane oxygenation [73–75] in ACS and transfusion of polymerized blood products for acute vaso-occlusive pain crisis [76].

Prophylaxis and Prevention

All patients with SCD should receive penicillin V prophylaxis until the age of 5 years, regardless of immunization status [77]. It is considered safe to stop ongoing antibiotics after the child's sixth birthday if they have been vaccinated and have no evidence of asplenia. Also, all children should be immunized with heptavalent pneumococcal vaccine, preferably before 24 months of age [77]. Adamkiewicz et al [78] have shown that administering the vaccine up to 10 years of age may provide herd immunity and recommend that children should be vaccinated even after age 4 years.

Hydroxyurea is a cytotoxic drug that inhibits DNA synthesis by means of inhibiting ribonucleotide reductase. It causes an increase in hemoglobin F, which in turn decreases hemoglobin S polymers. Hydroxyurea also has been shown to increase the water content of red blood cells, improve successful microvascular navigation of sickle cells, and alter the adhesion of red blood cells to endothelium by decreasing the expression of endothelium adhesion molecules [79]. A randomized placebo-controlled trial of hydroxyurea therapy in patients with at least 3 sickle cell crises per year [80] showed an approximately 50% decrease in acute crises among the treatment group [81,82]. A subsequent study that evaluated whether hydroxyurea reduces mortality in patients with SCD showed a cumulative mortality at 9 years of 28% when hemoglobin F was less than 0.5 mg/dL versus 15% when hemoglobin F was greater than 0.5 mg/dL. It also showed a 40% decline in mortality with hydroxyurea use [82]. These mortality benefits have been replicated in a 17-year-long trial in different variants of SCD [83].

Chronic simple transfusion every 2 to 4 weeks can be used to maintain a hemoglobin A level of 60% to 70% or a hemoglobin S level of approximately 30%. This strategy is usually tried in patients who do not benefit from hydroxyurea. In the Stroke Prevention Trial, chronic transfusion statistically significantly reduced the incidence of ACS to 2.2 events/100 patient-years compared to 15.7 events/100 patient-years [84]. Although evidence supports that transfusion reduces sickle cell complications like ACS, its role remains restricted because of danger of transfusion reaction, alloimmunization, and iron overload.

Allogeneic hematopoietic cell transplantation (HCT) is currently the only curative treatment option for patients with SCD. Approximately 84% of patients who undergo human leukocyte antigen (HLA)-identical sibling donor HCT survive disease-free. However, this therapy carries significant risk of transplant-related morbidity and mortality and is typically reserved for patients with serious complications of SCD [85].

Complications of ACS

Acute Complications

Acute complications of SCD in addition to ACS include respiratory failure, acute respiratory distress syndrome, thromboembolic disease, and hypoxia (Table 2). The need for respiratory support with mechanical ventilation in ACS varies among studies. In the NACSS, approximately 13% of patients required mechanical ventilation for a mean duration of 4.6 days, and 81% of these patients had a favorable outcome [10]. The mode of ventilation used should be aimed at minimizing injury to the lung. Respiratory failure and other complications are more common in older patients with recurrent episodes. The independent predictors of respira-

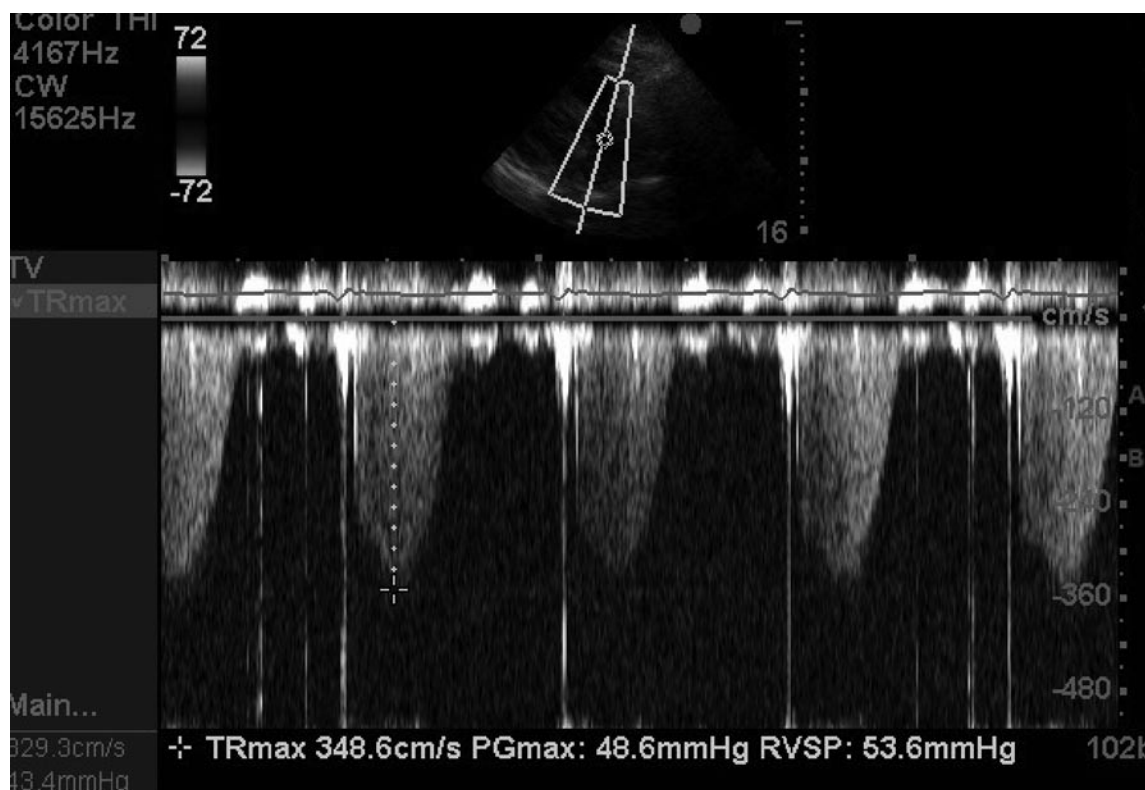


Figure. Doppler echocardiography showing elevated pulmonary artery pressure (high tricuspid regurgitation jet velocity). A value of 348 cm/s of jet correlates with right ventricular systolic pressure of 53.6 mm Hg.

tory failure in a multivariate analysis in the NACSS were multifocal disease, platelet count less than 200,000 cells/ μ L at diagnosis, and history of cardiovascular disease [10].

Thromboembolic episodes are known to cause mortality in patients with ACS. The prevalence of pulmonary embolism is higher in hospitalized patients with SCD as compared other hospitalized patients [21]. Vascular occlusion in SCD usually is consistent with thrombus in situ whose extent is limited to arterioles and pulmonary artery branches less than 1 mm in size and which cannot be identified by spiral computed tomography scans. Furthermore, injected radio-opaque contrast used in imaging can induce sickling [86]. Pulmonary embolism, although uncommon, can occur in patients with SCD, and the risk of imaging should be considered before proceeding with this test. Over time, thromboembolic disease can also contribute to pulmonary hypertension.

Chronic Pulmonary Complications

Chronic effects include pulmonary hypertension, interstitial lung disease causing restrictive lung disease on pulmonary function testing, and sleep-related disorders. The most

common abnormal echocardiographic finding in patients with SCD is elevated pulmonary artery pressure, which is seen among more than half of these patients and is more pronounced in those with a history of ACS [9]. Pulmonary hypertension is seen frequently in patients with SCD, and those with pulmonary hypertension have a higher mortality than patients with SCD and normal pulmonary arterial pressures [87,88]. Gladwin et al [87] found a prevalence of pulmonary hypertension of 32% in 195 consecutive patients with SCD. In this study, a history of renal or cardiac disease, hypertension, high levels of lactate dehydrogenase and alkaline phosphatase, and low transferrin levels were independent correlates of pulmonary hypertension. A recent study showed that the incidence of pulmonary hypertension can rise to up to 60% in patients with an episode of severe ACS [89]. In this study, the incidence of severe pulmonary hypertension or cor pulmonale was 13%, and ACS with higher pulmonary pressures and elevated cardiac markers translated into a higher risk for respiratory failure and death. Furthermore, Ataga et al [90] showed that patients with pulmonary hypertension have an increased risk for mortality (relative risk, 9.24), and that hydroxyurea therapy

may decrease the incidence of pulmonary hypertension.

Lower levels of fetal hemoglobin are associated with pulmonary hypertension [91]. Nitrogen oxide scavenging by free hemoglobin can result in up-regulation of VCAM-1 and E-selectin, and it also induces endothelin-1, which is a potent vasoconstrictor [92]. Elevated levels of endothelin-1 have been demonstrated in patients with SCD and primary pulmonary hypertension [93,94]. In a recent study [95], N-terminal probrain natriuretic peptide levels of 160 pg/mL or greater had a 78% positive predictive value for the diagnosis of pulmonary hypertension and were an independent predictor of mortality, with a risk ratio of 5.1 (95% confidence interval, 2.1–12.5).

All patients with SCD with an ACS episode should be screened with a cardiac echocardiogram. If right heart dysfunction or severe pulmonary hypertension (defined as tricuspid regurgitation jet of ≥ 3 m/sec) is present, close monitoring and further workup is critical. Although echocardiogram is an adequate screening test for pulmonary hypertension in SCD, further testing, including right heart catheterization, should be done before beginning therapy (Figure).

Further trials are needed to help guide treatment of pulmonary hypertension secondary to SCD. Although patients with SCD and pulmonary hypertension have a lower pulmonary artery pressure and higher cardiac output than patients with primary pulmonary hypertension, they have a shorter median survival [96–98]. In a study in which 8 patients were given short-term prostacyclin infusions, all patients had a reduction in pulmonary artery pressures (mean reduction, 34%) [88]. Since endothelin-1 is elevated in SCD, endothelin receptor antagonists such as bosentan and ambrisentan might be helpful. A recent cohort study of a small number SCD patients with pulmonary hypertension had improvement in 6-minute walk, amino-terminal brain natriuretic peptide, tricuspid regurgitation velocity, and pulmonary artery mean pressures with treatment with endothelin receptor antagonists [99]. Bosentan was also well tolerated in ASSET 1 and 2 [100]. Further large placebo-controlled clinical trials are needed to provide evidence to guide the use of drugs such as bosentan and prostacyclin in clinical practice.

Chronic interstitial lung disease and abnormal results on pulmonary function testing occur frequently in patients with SCD. Up to 90% of adults with SCD have abnormal results on pulmonary function testing. Common abnormalities include decreased diffusing capacity of the lung for carbon monoxide and a restrictive pattern [101], although patients can also have features of hypoxemia and obstructive disease [102,103]. Episodes of ACS may be a risk factor for the development of fibrosis and restrictive lung disease. The incidence of obstructive sleep apnea syndrome (OSA) may be the same among patients with SCD and those without

SCD, but the severity of OSA in terms of desaturation and hypercapnia is higher among the former [104]. Moreover, up to 40% of children screened have nocturnal desaturations, which are associated with a higher rate of vaso-occlusive crisis [105,106].

Conclusion

SCD is a genetic disease of the hematopoietic system with diverse pulmonary manifestations and complications. The treatment of ACS is based upon recognition of common etiologies; after initial supportive measures, therapy includes antibiotics covering atypical and routine pathogens, hydration, transfusion as indicated, and mechanical ventilation, if required. For spontaneously breathing patients, incentive spirometry can both prevent ACS as well as prevent worsening of an episode already in progress. Despite recent advances in our understanding of this syndrome, treatment remains challenging and mortality is substantial. Successful management does not preclude future events or the development of pulmonary hypertension. Further investigation into the pulmonary manifestations, which have a major impact on quality of life, is needed. As we know, ACS or acute sickle cell crisis are the cause of death in 78% of patients with SCD [12]. Future research in this field should help us to better understand and manage this disease.

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