Sickle cell disease is an autosomal recessive blood disorder that affects millions of individuals worldwide. A single mutation in the beta globin gene resulting in a single amino acid substitution underlies the pathophysiology of this highly prevalent disorder. The disease is characterized by chronic hemolysis, recurrent vaso-occlusion, predisposition to infections, and end-organ failure. Phenotypic heterogeneity characterizes sickle cell disease, with pain as the hallmark of this disease.

The past 2 decades have witnessed an influx of information that has improved our current knowledge of the molecular, clinical, and therapeutic aspects of the disease. Multiple randomized, observational, and interventional trials have demonstrated that with early diagnosis and timely introduction of modern therapy in a comprehensive care setting, the survival rates and quality of life for affected patients have remarkably improved over recent years.

Acute chest syndrome (ACS) is the most common cause of sickle cell disease (SCD)-related death, accounting for one-fourth of these fatalities. ACS is also the second most common cause of hospitalization in patients with SCD. Many patients have multiple severe episodes of ACS, and recurrent ACS events have been associated with chronic lung disease and early death.

Rapid diagnosis and administration of appropriate therapy can help reduce morbidity and mortality associated with ACS. Because of improved survival and increased numbers of SCD patients living to adulthood, it is important for primary care providers to become familiar with all of the diagnostic, therapeutic, and preventive aspects of this frequent complication.
This review comprehensively covers the epidemiology, clinical presentation, pathophysiology, risk factors, diagnosis, management, prevention, and outcome of ACS.

**EPIDEMIOLOGY OF ACS**

ACS is defined as the presence of a new pulmonary infiltrate along with fever, chest pain, respiratory distress, or new onset hypoxemia.\(^1\) Much of our current knowledge about ACS, as well as other SCD complications, has emanated from the multicenter Cooperative Study of Sickle Cell Disease (CSSCD), which prospectively followed 3,751 patients with SCD from birth to 66 years of age.\(^2\)

Data on signs and symptoms, laboratory findings, and hospital course were collected on 939 patients who experienced 1,722 ACS episodes.\(^2\)

A seasonal variation favoring a higher occurrence of ACS in winter was observed in children.\(^2\) Fifty percent of adults had a pain event in the 2 weeks preceding ACS, and children were more likely to have preceding febrile events. Even though peak incidence of ACS is in children between ages 2 and 4 years, ACS can be seen across all ages. It is, however, rarely seen in children younger than 2 years, probably because of the slower decline of fetal hemoglobin (HbF) concentrations, which could have a protective effect. As for older age groups, the decreased incidence of ACS is attributed to improved acquired immunity, which decreases the frequency of respiratory infections, which constitute a leading cause of ACS.

**CLINICAL PRESENTATION**

The clinical features of ACS are age-dependent and can overlap with other infectious causes of pulmonary infiltrates and symptoms, occasionally impeding its proper diagnosis. Children younger than 10 years of age usually have mild to moderate disease and present with fever, cough, wheezing, and isolated upper and middle lobe involvement. Additionally, ACS in this age group is often associated with an underlying infectious etiology. Adults, on the other hand, are afebrile and are more likely to present with sudden onset of shortness of breath, chills, severe pain, bilateral lower lobe involvement, pleural effusion, and rapid progression.\(^3\) Respiratory failure requiring mechanical ventilation is seen in 10% of affected patients.\(^3\)

In adults, pulmonary fat embolism is frequently a component of severe ACS.\(^2,3\)

**RISK FACTORS**

Several risk factors are associated with the occurrence of ACS in SCD. Approximately 50% of ACS cases develop during the course of hospitalization for pain.\(^2,3\) Patients undergoing an abdominal surgery such as splenectomy and/or cholecystectomy have been shown to be at a higher risk for developing ACS. The frequency of postsurgical ACS was found to be decreased by early ambulation and use of incentive spirometry.\(^4\) Airways hypersensitivity and smoking have been also demonstrated to be associated with a higher risk of developing ACS in adults,\(^5,6\) whereas atopic asthma has been shown to be more correlated with recurrent ACS episodes in children.\(^7\)

The SCD genotype is weakly associated with the incidence of ACS. The frequency of ACS is highest in hemoglobin (Hb)-SC and HbS-ß° patients. HbSS patients have a slightly higher frequency of ACS than HbS-ß° thalassemia patients.\(^1\)

Interestingly, Saudi patients with the Arab-Indian haplotype have a relatively lower ACS incidence and milder disease than those with the African haplotype.\(^8\) Additionally, the DRB1*130101-DQB1*060101 HLA haplotype has been shown to be strongly associated with ACS development compared with other haplotypes.\(^9\)

**PATHOGENESIS IN CHILDREN**

ACS has a multifactorial etiology, including a variety of inciting events that trigger deoxygenation of HbS, leading to its polymerization and to red blood cell sickling with subsequent vaso-occlusion, ischemia, and endothelial dysfunction.\(^10\) A specific cause for ACS, however, is identified in less than half of the cases despite an extensive workup.

In children, superimposed infections represent the most common etiology.\(^11\) Infection with *Mycoplasma pneumoniae* or *Chlamydia pneumoniae* is a major precipitant of ACS, leading to severe pneumonia-like clinical presentation rather than to the typical walking pneumonia encountered in healthy children.\(^11\)

Hence, differentiation of ACS from pneumonia is clinically insignificant as the management will be the same.\(^11\)

In adults, the disease is more severe and appears to be related to vascular occlusion, pulmonary thrombosis, and fat embolism. Around 50% of adult patients who develop ACS are initially admitted for vaso-occlusive crisis (VOC), particularly pain.\(^3\) Patients with VOC of the spine, ribs, or abdomen usually have severe pain necessitating opioid therapy. This therapy coupled with severe pain can lead to hypventilation and hypoxemia with decreased tidal volume and eventual drop in arterial oxygen, which initiates the sickling cascade. Airway hyper-reactivity and asthma also increase the risk of ACS in a similar manner and have been shown to be more common in children with SCD than in ethnic-matched controls.\(^7\)

Pulmonary and bone marrow infarctions as well as fat emboli have been cited as possible triggers of ACS. Specifi-
physically, pulmonary fat embolism (PFE), a usual complication of bone fracture, has been identified as a possible cause in 44% of moderate to severe ACS, including in children.\textsuperscript{1,12} Fat emboli from bone may progress to lungs, kidney, and liver, causing multiorgan damage and eventual death.\textsuperscript{11} Some studies have also shown that the incidence of deep vein thrombosis and pulmonary embolism (PE) is higher in SCD patients, both pediatric and adult, compared with the general population, suggesting that PE may be a complication of ACS rather than a cause of it.\textsuperscript{13}

\textbf{DIFFICULTIES IN DIAGNOSIS}

Diagnosis of ACS can be difficult at times and depends on the physician’s experience.\textsuperscript{14} The clinical symptoms described above should alert the physician to the possibility of ACS. Physical examination may reveal tachypnea, dyspnea, hypoxia, decreased air entry, wheezes, and rales. However, it is common not to find any of these physical signs in some young patients, particularly at ACS onset. Physical exam alone can, at times, be unreliable in the diagnosis of ACS, and up to 60% of cases are missed by clinicians without radiologic confirmation.\textsuperscript{15} As such, a chest radiograph is indicated for confirming ACS diagnosis and ensuring early initiation of treatment in any patient with SCD who presents with fever and/or chest pain. Additionally, because pain crises often herald ACS, a chest radiograph may be indicated in patients hospitalized for pain, particularly when they develop fever and/or respiratory symptoms.\textsuperscript{5} It should be noted, though, that lung infiltrates may not appear in the radiographs before 48 to 72 hours after onset of clinical symptoms.

\textbf{MANAGEMENT OF ACS}

Because the causes of ACS are largely unknown, therapy is supportive. Once a diagnosis is made, management is targeted at limiting the progression of the disease in the acute phase and later preventing its recurrence and long-term sequelaes. All ACS patients should be hospitalized and given intravenous antibiotics, bronchodilators, and analgesia. Caution in initiating hydration is warranted to avoid pulmonary edema.\textsuperscript{1,16} Oxygen supplementation to maintain adequate oxygen saturation and incentive spirometer to prevent atelactasis represent important additional aspects of management. Patients with hypoxia and/or respiratory failure need to receive immediate ventilation support. Such patients along with those showing progression of disease on treatment are best monitored and treated in an intensive care unit.\textsuperscript{11}

On admission, complete blood count, reticulocyte count, blood type and cross-match, routine chemistry, arterial blood gases, blood and sputum cultures, and seasonal viral (influenza and respiratory syncytial virus) and \textit{Mycoplasma} assays need to be performed. Hemoglobin and pulse oximetry also need to be closely monitored.\textsuperscript{17}

\textbf{Antibiotics}

All patients with ACS should receive broad-spectrum parenteral antibiotics consisting of third-generation cephalosporins and a macroleide. This antibiotic regimen may be further modified depending upon culture results and the clinical status of the patient. Vancomycin needs to be added for those having severe disease at onset or disease progression on treatment or harboring a vancomycin-sensitive organism in culture. There are no available guidelines for the optimal duration of antibiotic therapy of ACS, but a 10-day course seems to be a reasonable option.\textsuperscript{11}

\textbf{Transfusions}

Transfusions are a first-line defense for managing ACS in SCD patients, as transfused cells dilute sickle cells and alleviate pain. Two types of transfusion modalities are used: exchange transfusions and simple transfusions. Although most ACS patients respond adequately to simple transfusions, some studies have shown efficacy of exchange transfusions as first-line therapy in ACS.\textsuperscript{18} Exchange transfusions are primarily used in patients who are not sufficiently anemic; in some PFE-induced ACS cases; in persistent hypoxia; and in patients requiring mechanical ventilation and/or who are unresponsive to simple transfusions.\textsuperscript{11} Exchange transfusions have been shown to alleviate PFE-induced multiorgan failure in isolated case reports.\textsuperscript{19} Yet, the superiority of exchange transfusions over simple transfusions in several nonrandomized clinical studies could not be demonstrated.\textsuperscript{1} This is an area that merits further investigation through multicenter randomized clinical trials. Practitioners should remain vigilant for delayed hemolytic transfusion reactions that SCD patients may present with 1 week post-transfusion.

\textbf{Pain Control}

Pain leads to hypoventilation that exacerbates ACS severity. To counteract pain, opioid analgesics are often used.\textsuperscript{20} If opioids are to be used, attention should be given to proper dosing to prevent over-sedation and hypoventilation. Notably, nonsteroidal anti-inflammatory drugs, over-hydration, and overuse of opioid analgesics should be avoided because they worsen ACS pain.\textsuperscript{1} Intercostal nerve block has been attempted and was shown to alleviate chest pain for less than 24 hours.\textsuperscript{1}

For better pain control and avoidance of respiratory depression, patient-controlled analgesia (PCA) can be used.\textsuperscript{1} Although using PCA does not decrease pain episodes, it does alleviate opioid use–related nausea and constipation compared with uncontrolled analgesic usage.\textsuperscript{1} ACS patients should be monitored for exacerbation of pain episodes,
and pain scores are recommended on a daily basis to control analgesia usage. Moreover, serum sodium levels should be monitored because ACS-induced nephropathy can lead to sodium loss and hyponatremia, which can be associated with pain. Administration of sufficient sodium can prevent the development of this metabolic complication.

**Other Therapies and Considerations**

Because airway hypersensitivity is a risk factor for developing ACS, bronchodilators may be used in patients who are wheezing or show signs of airflow obstruction. Well-designed, randomized clinical trials supporting this treatment modality are still lacking. Other aspects of management include anticoagulation with unfractionated heparin or low-molecular weight heparin. This latter treatment modality has been shown to significantly reduce hospitalization days and pain crisis.

The role of corticosteroids, and specifically dexamethasone or prednisone, in the management of ACS has been controversial. Although initial studies suggested efficacy, later studies showed an increased readmission rate for pain 72 hours after corticosteroid therapy. Due to the increased risk of corticosteroid-induced fat emboli in SCD patients, caution is warranted for administering steroids in this patient setting. Although not routinely used, bronchial alveolar lavage (BAL) can be used to identify cases with suspected pulmonary fat emboli. However, complications can occur in 13% of ACS patients undergoing BAL, especially in those with dyspnea and tachypnea. Moreover, BAL would less likely change the modality of management of ACS and is not recommended.

**PREVENTIVE MEASURES**

Because HbF is a major inhibitor of HbS polymerization, it is not unexpected that hydroxyurea (HU), a potent inducer of HbF, would decrease ACS recurrence. The Multicenter Study of Hydroxyurea in SCD (MSH), a randomized, double-blind clinical trial, demonstrated that HU decreased ACS in adult patients with SCD by 50% and that there was an inverse correlation between the incidence of ACS and HbF levels. Similarly, chronic transfusion therapy was shown to reduce the incidence of ACS without alleviating the severity of the crisis in children enrolled in the Stroke Prevention Trial (STOP) trial. Incentive spirometry can be an effective prophylactic measure for exacerbations of ACS in SCD patients with minimal pulmonary complications and in those with pain and/or postsurgery. Additionally, stem cell transplantation can prevent the recurrence of ACS and is indicated for patients with ACS refractory to HU.

**CONCLUSIONS**

ACS is a common and debilitating complication of SCD. It is the leading cause of death in SCD patients and accounts for around one-fourth of SCD-related mortality. The death rate in patients with ACS is 1.1% in children and 4.3% in adults. According to the CSSCD, adults have more severe disease with a higher hospitalization and fatality rate than children.

Early diagnosis and optimal management of this highly prevalent complication are necessary for improving outcome and minimizing associated morbidity and mortality. Physicians caring for SCD patients need to be aware of the early symptoms and signs of ACS and of its optimal preventive and therapeutic modalities. Educating affected patients and their families about the clinical features of early ACS, the seriousness of this complication, and the need to seek immediate medical attention is vital.

Treatment of ACS remains supportive; close monitoring for disease progression and/or increasing hypoxia and impending pulmonary failure is warranted. The identification of novel predictors for ACS development and severity may help in earlier diagnosis and better management of this highly morbid and prevalent condition. The efficacy of therapeutic regimens such as anticoagulation, steroids, and bronchodilators still needs to be demonstrated in future prospective randomized trials.

**REFERENCES**

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