Acute chest syndrome: Getting down to the basics

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Abstract: Acute chest syndrome (ACS) is one of the most common causes of death and hospitalization among patients with a sickle hemoglobinopathy. The clinical presentation is characterized by the appearance of a new infiltrate on a chest radiograph, with 1 or more new symptoms, including fever, cough, chest pain, and dyspnea. Additional findings include leukocytosis, hypoxemia, and auscultatory signs of consolidation. The differential diagnosis includes pneumonia, pulmonary infarction, fat embolism syndrome, pulmonary edema, and bone infarction. Treatment of ACS involves supportive care, empiric antibiotic therapy, and red blood cell transfusion when indicated. The decision of whether to use simple or exchange transfusions depends on the severity of illness and the risk of acute respiratory failure. Currently, hydroxyurea is the only FDA-approved drug designated as a preventive therapy. (J Respir Dis. 2005;26(12):529-534)

Sickle cell disease (SCD) is a hereditary hematologic disorder caused by a single amino-acid substitution of valine for glutamic acid in the sixth position of the β chain of the hemoglobin (Hb) tetramer. In the United States, SCD is seen primarily in persons of African ancestry. Outside the United States and Africa, this gene mutation has been reported in India, Greece, Saudi Arabia, Sicily, Italy, Israel, Turkey, Iran, Central America, Brazil, the United Kingdom, France, Belgium, Germany, and the Netherlands.1

In the United States, SCD affects about 70,000 persons; this number is likely to increase as the life expectancy of persons with this disease rises.2 Despite significant advances that have led to improved survival in patients with SCD, the median life expectancy is only 42 years for men and 48 years for women. In persons with Hb SC, the median life expectancy is in the 60s.

Acute chest syndrome (ACS) is the most common cause of death and the second most common cause of hospitalization in patients with SCD.3 ACS is defined by the appearance of a new infiltrate on a chest radiograph, involving at least one bronchopulmonary segment, in a person with a sickle hemoglobinopathy such as Hb SS, Hb SC, or Hb S-β thalassemia. Atelectasis and isolated pleural effusion do not meet the criteria for making a diagnosis of ACS in sickle hemoglobinopathies. In addition, patients with ACS have 1 or more new symptoms, such as fever, cough, chest pain, or dyspnea.

In this article, we will review the clinical presentation, diagnosis, and management of ACS.

RISK FACTORS

The Hb S genotype was demonstrated by Castro and associates4 to be a risk factor for ACS. In descending order, the incidence of ACS in SCD is the following: Hb SS, Hb S-β0 thalassemia, Hb SC, and Hb S-β+ thalassemia. ACS occurs in about 50% of patients with SCD, and approximately 80% of patients with ACS experience a recurrence. The rate of ACS decreases with increasing age and fetal Hb concentrations and increases with higher baseline steady-state Hb concentrations and white blood cell (WBC) counts.

ACS occurs more commonly in the winter, after major surgery, and in association with avascular necrosis. The occurrence of ACS in the first 2 years of life is a predictor of early death after the age of 20.2 ACS is also a risk factor for sickle cell chronic lung disease. Most deaths among patients with SCD and chronic lung disease result from pulmonary hypertension and cor pulmonale.

In patients with SCD, signs of pulmonary hypertension are often lacking at baseline and manifest during an episode of ACS.5 In an autopsy study of patients with SCD and underlying pulmonary hypertension, ACS has been causally associated with mortality.6

PATHOGENESIS

ACS may be the result of one process or the interaction of numerous processes, such as nonembolic microvascular occlusion, atelectasis, fat embolism preceded by bone marrow infarction, thromboembolism, inflammation, and infection. Obstruction of the pulmonary microvasculature secondary to increased adhesivity of the erythrocyte to vascular endothelium, polymerization of Hb S, and sickling is central to the pathophysiology of ACS.

Mechanical obstruction of the pulmonary microvasculature by the erythrocyte results in tissue hypoxia with parenchymal damage distal to the site of obstruction. Increased sickle erythrocyte
adhesivity to microvascular endothelium results in prolongation of the erythrocytetransit time through the pulmonary capillaries, thereby facilitating the unloading of oxygen by Hb S and the subsequent sickling of the erythrocyte.\textsuperscript{7} Commonly studied sickle erythrocyte membrane-adhesion molecules capable of adhering to vascular endothelium are the α4β1 integrin, which binds the endothelial cell vascular cell adhesion molecule-1 (VCAM-1), and the thrombospondin receptor, CD36. Hypoxia not only triggers erythrocyte sickling; it also up-regulates VCAM-1. This process enhances erythrocyte α4β1 binding to endothelial cell VCAM-1.\textsuperscript{8}

In addition to adhesion molecules, the anionic phospholipid phosphatidylserine on the sickle erythrocyte surface has been found to increase sickle erythrocyte adhesion to vascular endothelium.\textsuperscript{9} Unlike the α4β1 integrin and CD36, which are found primarily on stress reticulocytes, phosphatidylserine exposure may facilitate the adhesion of reticulocytes and mature sickle erythrocytes to the vascular endothelium.\textsuperscript{9}

Increasing evidence, based on clinical observations in which a WBC count of more than 15,000/μL has been associated with an increased incidence of ACS,\textsuperscript{10} suggests that WBCs and inflammation play a significant role in the pathogenesis of ACS. Also, patients receiving hydroxyurea frequently demonstrate a decreased incidence of pain crisis and ACS when the WBC count is lowered without increases in fetal Hb. These observations further support a role for inflammation in triggering ACS.\textsuperscript{11} The high level of cytokines noted in patients with SCD suggests a chronic and perpetually activated polymorphonuclear leukocyte state, which may stimulate the activation of an inflammatory cascade and the release of soluble inflammatory products, such as platelet-activating factor (PAF) and leukotriene B\textsubscript{4}.\textsuperscript{12} This results in increased endothelial permeability and the adhesion of neutrophils and sickle erythrocytes to the pulmonary endothelium. We have reported data that support this model.\textsuperscript{12} Bone marrow infarction with subsequent fat embolism plays a major role in the pathophysiology of ACS.\textsuperscript{3,10,13} Endothelial injury that directly results from phospholipid hydrolysis by phospholipase A\textsubscript{2} to arachidonate and lyso-PAF may lead to nonhydrostatic pulmonary edema. In fact, elevated serum phospholipase A\textsubscript{2} levels have been shown to correlate with the onset of ACS.\textsuperscript{14}

**PRESENTATION AND DIAGNOSIS**

To date, there is no single confirmatory test for diagnosing ACS. It remains a clinical diagnosis that requires a high index of suspicion (Table 1). When ACS is diagnosed, it is important to recognize that there are many possible causes, some of which can occur simultaneously. The differential diagnosis includes pneumonia; pulmonary infarction; fat embolism syndrome; pulmonary edema; and bone infarction leading to hypoventilation and intrapulmonary sickling.

Distinguishing the exact single or multiple causes of an ACS episode is often difficult. We have previously used cultures of lower airway specimens obtained by fiberscope and quantitative bacteriology to determine the role of bacterial pathogens in ACS. A bacterial pathogen was isolated in 4 (21%) of 19 patients with ACS. *Streptococcus pneumoniae* was isolated in 2 patients, and mixed aerobic and anaerobic bacteria were isolated in 2 others. This led us to conclude that bacterial pneumonia is an uncommon cause of ACS.\textsuperscript{15}

Bronchoscopy is potentially useful in assessing the cause of ACS. However, clinicians must be careful neither to delay implementation of empiric antibiotics nor to assume that other causes of ACS, such as fat embolism or infarction, are not concomitantly involved. In fact, autopsy findings have revealed infection, infarction, and fat embolism in the same lung. Blood cultures should be obtained from all patients with ACS. A positive blood culture remains the gold standard for diagnosing bacteremic pneumonia. Bronchoalveolar lavage (BAL) performed during ACS episodes has identified alveolar macrophages containing fat droplets in 77% of cases, supporting a diagnosis of fat embolism.\textsuperscript{16} The presence of lipid-laden macrophages lacks specificity, and the therapy for fat embolism is primarily supportive. Therefore, we do not recommend that BAL be routinely performed to support a clinical suspicion of fat embolism as the cause of ACS. Sputum specimens obtained for culture and stains are infrequently beneficial in dictating care; it is our view that sputum testing in this manner is not cost-effective.

ACS is characterized by a new infiltrate on the chest radiograph in a person with SCD. Fever (80%), cough (74%), chest pain (57%), dyspnea (41%), leukocytosis, and hypoxemia are common associated findings. The incidence of the associated signs and symptoms is somewhat influenced by the patient's age. Although any of these findings may be seen in patients with ACS, fever and cough are more common in children younger than 20 years and chest pain is more common in children older than 9 years and in adults. Bronchospasm appears to be more common in children than in adults.

Pain crisis may be the admitting diagnosis in as many as one third of patients in whom ACS develops.
2 to 3 days after admission. Chest radiographic abnormalities range from segmental infiltrates to diffuse bilateral infiltrates (Figure). A lower lobe predominance of infiltrates is the most common distribution. About one third of patients have a small pleural effusion associated with airspace disease.\(^\text{16,17}\)

Clinically, patients with ACS may appear acutely ill with fever (temperature up to 40°C [104°F]). Chest pain can be pleuritic or nonpleuritic. Tenderness may be present over the ribs, sternum, or vertebral secondary to bone infarcts. Auscultation and percussion of the chest commonly show findings consistent with consolidation. Hypoxemia is common, and its degree of severity reflects the extent of ventilation-perfusion inequality and/or shunt fraction. It is important to remember that the oxygen-hemoglobin dissociation curve for Hb S is shifted to the right of Hb A. Thus, calculation of oxygen saturation based on Hb A can yield an erroneously high oxygen saturation value in patients with SCD.\(^\text{18,19}\)

Thrombocytopenia should raise clinical suspicion of possible fat embolism syndrome and/or parvovirus B19 infection.\(^\text{20}\) A 2 g/dL drop in Hb level from baseline often precedes signs of disease progression on the chest radiograph and acute respiratory failure. Multilobar involvement, thrombocytopenia, and a history of cardiac disease are all independent risk factors for acute respiratory failure.\(^\text{17}\) Should this occur, patients must be closely monitored and aggressive therapy must be implemented.

**THERAPY**

The treatment of ACS involves a combination of supportive care, empiric antibiotic therapy, and red blood cell transfusion when indicated (Table 2). General management

Regardless of the cause of ACS, hypoxemia should be treated with supplemental oxygen to maintain an oxygen saturation of at least 94%. There is no evidence that maintenance of supraphysiologic oxygen saturation is beneficial. In severe respiratory failure refractory to supplemental oxygen, intubation and mechanical ventilation with continuous positive airway pressure or positive end-expiratory pressure may be indicated. Although there are no published data on noninvasive positive pressure ventilation in the treatment of hypoxic respiratory failure in SCD, in our experience, it can be effective.

In the absence of volume contraction, hydration with a glucose-containing hypotonic solution is indicated. We recommend volume replacement to maintain a euvolemic state. Excessive hydration may result in hydrostatic pulmonary edema, especially in vascular beds predisposed to injury. Until the patient is ambulatory, deep venous thrombosis prophylaxis with heparin, 5000 U subcutaneously every 12 hours, or enoxaparin, 30 mg subcutaneously once a day, should be given.

In patients who present with chest wall pain and ACS, incentive spirometry should be started. This is a simple way to minimize atelectasis secondary to splinting with subsequent development and/or progression of ACS.\(^\text{21}\)

For patients with bronchospasm, use of an inhaled β\(_2\)-agonist is beneficial, particularly in children.\(^\text{11}\) In patients who present with pain crisis, opioid analgesics are usually required. Undertreatment of pain, particularly that involving the chest, can result in splinting and atelectasis, and overtreatment can result in respiratory depression, hypoventilation, and sickling. The approach to pain management must be balanced.

**Antibiotic therapy**

Although an infectious cause of ACS is identified in approximately one third of patients, we recommend that all patients be treated empirically for community-acquired pneumonia. Autopsy findings clearly demonstrate that infections, infarction, and fat embolism can occur simultaneously.\(^\text{3}\)

In a study by Vichinsky and associates,\(^\text{17}\) *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* were the microorganisms most frequently associated with ACS, followed by viruses and common bacteria such as *S pneumoniae* and *Haemophilus influenzae*.

Therefore, our approach is to cover both typical and atypical bacteria, either with dual antibiotic therapy consisting of a third-generation cephalosporin, such as ceftriaxone or cefotaxime, plus a macrolide, or with monotherapy with a broad-spectrum third- or fourth-generation fluoroquinolone, such as levofloxacin, gatifloxacin, or moxifloxacin.

**Transfusion therapy**

The most effective treatment modality for ACS is early intervention with transfusion therapy using packed red blood cells that are sickle-negative, leukocyte-depleted, extended, and antigen-matched.

Clinical severity and the risk of acute respiratory failure dictate whether simple or exchange transfusion is used. Improvement in oxygenation can be seen with both types of transfusions. A simple transfusion may be helpful in patients who have worsening anemia and hypoxemia. Exchange transfusion should be initiated if a patient with a high baseline Hb level has worsening hypoxemia, multilobar involvement, or thrombocytopenia and appears to be clinically deteriorating.

The goal of exchange transfusion is to reduce the Hb S concentration to 30% or lower while maintaining a hematocrit value of approximately 30%. Although data from prospective randomized
trials are lacking, exchange transfusion remains the single most effective treatment for noninfectious causes of ACS. Other therapeutic interventions

Inhaled nitric oxide and intravenous corticosteroids may have clinical benefit in the treatment of ACS. While evidence-based studies demonstrating the efficacy of inhaled nitric oxide are lacking, anecdotal experience and case reports suggest potential benefit. The possible therapeutic benefits of inhaled nitric oxide in ACS are the lowering of pulmonary artery pressure, improvement in ventilation and perfusion matching, improvement in oxygenation, and reduction of ischemia-reperfusion injury. Clinical studies are under way to determine whether inhaled nitric oxide will reduce morbidity and mortality associated with ACS.

Elevated serum phospholipase A sub 2 levels have been shown to correlate with the onset of ACS. Corticosteroids have been shown to reduce the production of inflammatory cytokines and to influence arachidonic acid metabolism through the inhibition of phospholipase A sub 2; intravenous corticosteroids may therefore have a role in the management of ACS.

Bernini and associates conducted a study in which dexamethasone, 0.3 mg/kg intravenously every 12 hours for 4 doses, was compared with placebo in children with mild to moderately severe ACS. There were statistically significant reductions in the duration of opioid analgesia, duration of hospitalization, duration of oxygen supplementation, need for transfusion, and clinical deterioration. However, there is concern about disease recurrence after tapering of the dexamethasone. Although these data are interesting and suggest a potential positive impact on outcome, more studies that include all age groups are required. Prevention

Hydroxyurea is the only drug to date that is FDA-approved as a preventive therapy for ACS. In the Multicenter Study of Hydroxyurea in Sickle Cell Anemia, the frequency of ACS episodes was reduced by approximately 50% in two thirds of patients. Like other patients who have chronic disease, patients who have SCD should receive the pneumococcal and influenza vaccines.

References: REFERENCES