

Acute Chest Syndrome of Sickle Cell Disease

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The acute chest syndrome (ACS) is an acute pulmonary illness that occurs in patients with sickle cell disease. ACS is currently defined as a new infiltrate on chest radiograph in conjunction with 1 other new symptom or sign: chest pain, cough, wheezing, tachypnea, and/or fever ($> 38.5^{\circ}\text{C}$).¹ The term *acute chest syndrome* was first suggested in 1979 by Charache et al² and was developed to reflect the unique nature of acute pulmonary illness in patients with sickle cell disease. ACS can be caused by a variety of mechanisms, both infectious and noninfectious. Diagnostic considerations and treatment modalities are not typical of any other specific pulmonary illness experienced by the general population. Furthermore, the typical course, possible complications, and outcomes are unique. For these reasons, the terminology persists and remains useful for both research purposes and effective clinical communication.

As a leading cause of hospitalization and death in adults with sickle cell disease, the importance of ACS in sickle cell patients cannot be overstated.³ Emergency physicians, family practitioners, pediatricians, internists, and hematologists who encounter these patients on a regular basis have the potential to prevent significant morbidity and mortality through early recognition and aggressive treatment of ACS. This article reviews the etiology, pathogenesis, clinical characteristics, treatment, and prevention of ACS.

EPIDEMIOLOGY

The incidence of ACS in patients with homozygous sickle cell disease is 12.8 episodes per 100 patient years.⁴ Incidence is inversely related to age, with children aged 2 through 4 years having the highest incidence (25.3 episodes/100 patient-years). ACS is associated with all genotypes but occurs most frequently in patients with homozygous disease. Hematologic risk factors for the development of ACS include a high steady-state leukocyte count, low steady-state hemoglobin F concentration, and a high steady-state hemoglobin level.⁴ The risk for developing an ACS episode appears to be increased following surgery, with an average time to development of ACS of 3 days postsurgery.⁵ Children

TAKE HOME POINTS

- Acute chest syndrome (ACS) is a pulmonary illness defined by a new infiltrate on chest radiograph in combination with at least 1 clinical sign or symptom (chest pain, cough, wheezing, tachypnea, fever).
- Fever and cough are the most common presenting symptoms in children, while chest pain, shortness of breath, and chills are common in adults.
- Rales is the most common physical examination finding at diagnosis, but a normal examination is the second most likely presentation.
- The radiographic findings of ACS can lag behind the clinical findings; if ACS is clinically suspected, a positive chest radiograph defines the disease, but a single negative radiograph cannot exclude it.
- Treatment involves supportive care, incentive spirometry, broad-spectrum antibiotics, bronchodilators, and early transfusion when indicated.
- Patients admitted to the hospital for painful crisis should be considered to be in the prodromal phase of ACS, monitored closely for development, and treated with incentive spirometry.

often have a febrile episode preceding the event and are more likely to have an episode in the winter. Finally, both children and adults frequently have a painful event preceding the development of ACS.⁶

ETIOLOGY

There is not one specific cause of ACS but rather several pathologic processes capable of triggering the disease (**Table 1**). In reviewing 671 episodes of ACS, the National Acute Chest Syndrome Study Group

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Table I. Causes of Acute Chest Syndrome

Common causes	Possible causes
Pulmonary infection	Thromboemboli
Fat emboli	In situ thrombosis
Rib infarction	Iatrogenic mechanisms
	Excessive hydration
	Excessive narcotic use

(NACSSG) determined that infection and fat emboli were the most common identifiable causes.⁷ Infection appears to be more common in children, whereas fat embolism occurs more often in adults.^{6–8}

Infection

Infection has long been recognized as a cause of ACS. Initially *Streptococcus pneumoniae* was considered the most common infectious agent,^{9,10} but subsequent research has consistently reported lower rates of pneumococcal disease.^{2,7,11–15} This apparent change may be the result of more rigorous research methodology or therapies developed specifically to prevent pneumococcal disease such as prophylactic penicillin and vaccine administration.^{13,16,17} *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* are now the most common documented infectious causes of ACS.^{7,13,18,19} Other viral and bacterial organisms that have been linked to ACS include *Haemophilus influenzae*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, adenovirus, influenza viruses, parainfluenza viruses, respiratory syncytial virus, parvovirus B19, and cytomegalovirus.^{6,7,9–15,18–20}

Fat Emboli

Pulmonary vascular occlusion has long been suspected as a cause of ACS, but its exact role remains unclear. It was first considered as a cause of ACS after alveolar wall necrosis, pulmonary arterial thrombosis, and pulmonary infarction were found on postmortem evaluations.^{8,21,22} Further supporting evidence was provided by perfusion defects identified during ACS by computed tomography, angiography, and nuclear ventilation and perfusion (V/Q) scans.^{23–27} Although it is suspected that pulmonary vascular occlusion by in situ thrombosis and thromboembolism account for some of these perfusion defects, current evidence suggests that many of these defects are due to fat emboli^{3,7,14,21,22,28–35} that originate from bone marrow that becomes infarcted during vaso-occlusive crises. Reduced blood flow to bone marrow during these crises can cause painful ischemia and necrosis of the marrow, and necrotic pieces of marrow that break loose can

become emboli. Postmortem studies have found fatty necrotic bone marrow in the pulmonary vasculature.^{21,22} In addition, some have noted clinical similarities between the fat emboli syndrome of trauma patients and ACS and have used this as supportive evidence.^{28–30} More recently, investigators have identified fat droplets within cells recovered by bronchoscopy with bronchoalveolar lavage, confirming an association between fat embolism and ACS.^{7,14,31,32} Finally, increased serum levels of free fatty acids and the enzyme secretory phospholipase A₂ that occur during the syndrome are similar to the levels seen in the fat emboli syndrome.^{3,33–35}

Rib Infarction

Another likely cause of ACS is infarction of the ribs and other bones of the thorax. Infarction has been documented during sickle cell vaso-occlusive crisis and ACS by nuclear medicine techniques, and these infarctions are often in proximity to infiltrates on chest radiograph.^{36–38} It is proposed that bone infarction during vaso-occlusive crisis leads to localized splinting, atelectasis, radiographic infiltrates, and ACS.

Iatrogenic Causes

Excessive narcotic use and excessive hydration have been proposed as 2 possible iatrogenic causes of ACS; however, both have limited supporting evidence. In a model similar to rib infarction, it has been suggested that atelectasis secondary to hypoventilation and poor respiratory effort with narcotic use might lead to ACS.^{11,39,40} In addition, it has been suggested that patients admitted for sickle cell pain crisis may develop pulmonary edema and subsequently ACS if hydration strategies are too aggressive.⁴¹

PATHOGENESIS

These varied causes of ACS have in common the ability to create regional hypoxia and lung injury, which are followed by a cascade of events made possible by the inherent pathophysiology of sickle cell disease. Regional hypoxia prevents reoxygenation of red blood cells returning to the lung and leaves them in their sickled form. Sickled red blood cells, with polymerized hemoglobin, are presumed to have difficulty passing through small vascular beds both because of their deformed shape and inflexibility and because of expression of adhesion molecules on the cell wall.^{1,22,42} The injured lung and hypoxia promote upregulation of adhesion molecules on the vasculature endothelium, causing sickled red blood cells to adhere to the endothelium.^{43–48} Inflammatory mediators,^{34,35,49} free radical species,⁵⁰ and

Table 2. Clinical Presentation of Acute Chest Syndrome

Possible symptoms	Physical examination findings
Fever	Rales
Cough	Normal examination
Chest pain	Fever
Shortness of breath	Tachypnea
Pain in arms or legs	Wheezing

interactions between red blood cells and white blood cells⁵¹ are also induced by hypoxia and lung injury. Failure to reoxygenate, vascular stasis, and inflammation are suspected to create further red blood cell sickling, microvascular occlusion,²³ and pulmonary infarction.^{1,42} A cycle of injury is also promoted by the development of shunt physiology, which creates more hypoxia.^{46,47} This cascade of events is believed to cause ACS from a precipitant as simple as atelectasis.

CLINICAL PRESENTATION

The clinical presentation of ACS varies (**Table 2**). The most common symptoms at diagnosis in all age groups are fever, cough, and chest pain.^{6,7} Other less common presenting symptoms have been documented, including shortness of breath, productive cough, wheezing, and hemoptysis. The symptoms appear to be age-related, with fever and cough occurring most commonly in children and becoming less common with increasing age. Chest pain, shortness of breath, and chills, on the other hand, are less common in childhood and become more common with increasing age. Tachycardia, tachypnea, and hypoxia are variably seen on presentation. The most common physical examination finding is rales, but notably, the second most common finding is a normal physical examination. Furthermore, no clinical finding is predictive of the degree of hypoxia. The presenting symptoms in a patient's first event are predictive of symptoms during subsequent events.^{6,7}

Notably, up to 50% of patients diagnosed with ACS are initially admitted to the hospital for other reasons and subsequently develop the disease. The reason for admission in these cases is most often vaso-occlusive crisis. The average time to development of ACS after hospitalization is 2.5 days.^{6,7}

DIAGNOSTIC TESTING

Chest Radiograph

The chest radiograph remains the cornerstone diagnostic test for ACS (**Table 3**). The radiograph when positive reveals a new infiltrate most often involving the lower lobe, but any lobe can be affected.

Table 3. Diagnostic Testing in Acute Chest Syndrome

Serial chest radiographs
Consider ventilation and perfusion imaging
Serial hematologic testing
Complete blood count
Reticulocyte count
Secretory phospholipase A ₂ measurement if available
Arterial blood gas with co-oximetry
Blood cultures
Consider bronchoscopy



Figure. Chest radiograph demonstrating multilobar disease in a patient with acute chest syndrome.

Multilobar involvement is also common, and effusions can be present (**Figure**).^{6,7,11} It also cannot be overstated that a large number of patients will be admitted with a normal chest radiograph and subsequently develop infiltrate and ACS.^{6,7} Another limitation of the chest radiograph is that the clinical severity of disease and the degree of hypoxia may not be appreciated on the initial study.²³ Radiographic findings often progress with time.^{6,7,11} In this regard, serial radiographs may help guide therapy during hospitalization. Finally, 1 report of a study of pediatric patients suggested that in cases of ACS with documented infections, the radiographic findings take a longer time to resolve compared to cases without documented infections.⁵² The clinical significance of this finding is limited because of the retrospective nature of the study.

In patients with sickle cell disease, a chest radiograph for diagnostic purposes may be indicated in situations other than obvious respiratory illness. It has

been demonstrated that any pediatric patient with sickle cell disease and fever who presents to the emergency department or clinic would benefit from a chest radiograph, as the clinical assessment of such patients was inadequate to identify ACS in many cases.⁵³ One study of adults suggests that routine chest radiography of patients presenting to the emergency department in sickle cell pain crisis will at times reveal a pulmonary infiltrate not suspected by history or physical examination alone.⁵⁴ Subsequent research has not supported this finding, however.⁵⁵ As such, a reasonable approach is to have a low clinical threshold for ordering chest radiography in patients with sickle cell disease.

Advanced radiographic imaging is not commonly used in patients with suspected or documented ACS, but it can at times provide useful information. V/Q imaging may have a role in patients presenting with worsening hypoxia and a normal chest radiograph, a situation that may represent thromboembolism or alternatively early ACS prior to development of infiltrates on chest radiograph. V/Q imaging also may be useful in recognizing ventilation changes not appreciated on standard radiograph. A finding of ventilation defect without perfusion defect should raise suspicion for ACS. Unfortunately, V/Q imaging is complicated by the fact that patients may have pulmonary vascular occlusion from undocumented or subclinical events in the past.^{21,22} Review of prior imaging results, if available, for comparison may be helpful in such situations. Venous duplex scanning may be useful for further clarification. If a patient has positive V/Q imaging in the setting of positive venous duplex scanning, acute thromboembolism is favored over in situ thrombosis or chronic disease. The dye load used in computed tomography pulmonary angiograms and traditional angiograms may precipitate further sickling of red blood cells, but this concern should not prevent imaging if clinically necessary.^{23–27}

Laboratory Evaluation

There are well documented hematologic changes associated with ACS. Patients with ACS typically present with a hemoglobin level that is decreased on average 0.7 g/dL below baseline.⁶ Furthermore, progressive anemia during the course of ACS is the norm, and serial monitoring is necessary. These patients typically have a white blood cell count that is increased 69% above baseline on average at presentation. A platelet count below baseline is expected initially, and levels below $199 \times 10^3/\mu\text{L}$ are associated with worse outcomes.^{6,7,56} Lactate dehydrogenase and bilirubin levels are useful to follow for evidence of ongoing hemolysis.

Despite these well documented changes, the prospective value of routine blood tests for diagnostic purposes has never been demonstrated in the literature.^{57–59} Patients presenting with fever and abnormal vital signs or those who are clinically toxic appearing should have hematologic testing done. Clinical judgment can guide decision making on other patients to avoid unnecessary testing. Hematologic tests should be obtained and followed once the diagnosis of ACS is established as it may guide therapy.

Although currently not available at most institutions, measurement of secretory phospholipase A₂ may have a role in the diagnosis of ACS in the future. It appears that elevations in this enzyme often precede either clinical or radiographic evidence of ACS. Preliminary research has suggested that this test can detect impending ACS both in the emergency department and inpatient settings.^{3,33–35} If these results are confirmed, measurement of secretory phospholipase A₂ may one day guide early transfusion therapy, which may prevent the onset of the syndrome.

Arterial Blood Gas Analysis

Arterial blood gas testing with co-oximetry is recommended when oxygenation status is in question. Conflicting reports on the accuracy of pulse oximetry in sickle cell patients appear to be the result of testing methodology, a shifted oxygen dissociation curve, and variable presence of other forms of hemoglobin such as carboxyhemoglobin.^{60–64} The fractional hemoglobin saturation obtained from co-oximetry testing is the most accurate initial assessment. Pulse oximetry can be used to noninvasively follow trends in oxygenation once supplemental oxygen is provided.

Culture and Bronchoscopy

Testing for infectious etiologies may include blood cultures and/or bronchoscopy. Blood cultures are likely to be positive in 3.5% of patients with ACS, but the rate can be as high as 14% in patients younger than 2 years.⁷ Bronchoscopy will produce better quality microbiology samples than sputum collections and can also be used to diagnose fat embolism. The clinician must weigh these benefits with a complication rate documented as high as 13% in ACS patients.^{6,14,15,31,32}

MANAGEMENT

Supportive Measures

The treatment of ACS begins with close attention to supportive measures (**Table 4**). Close monitoring in the first 48 hours for respiratory deterioration and the need for mechanical ventilation is important.⁶

Supplemental oxygen should be reserved for patients with hypoxia. Establishing and maintaining hydration requires attention as excessive hydration may worsen pulmonary status.⁴¹ Pain control to prevent thoracic splinting and encourage good pulmonary toilet is important, but care must be taken to avoid excessive sedation that results in decreased ventilatory effort.^{11,36–40} The efficacy of supervised incentive spirometry in the treatment of atelectasis and prevention of ACS has been well documented, and spirometry should be used routinely to mitigate this problem.³⁸ Spirometry exercises performed 10 times every 2 hours between 8:00 AM and 10:00 PM and while the patient is awake overnight have been shown to decrease the incidence of pulmonary infiltrates while in the hospital.³⁸

Antibiotics

All patients with ACS should receive antibiotics at presentation, which should include a third-generation cephalosporin to cover *S. pneumoniae*, *H. influenzae*, and *K. pneumoniae*, and a macrolide to cover *M. pneumoniae* and *C. pneumoniae*.^{6,7,9–15} Risk factors for more virulent organisms and culture results can guide further therapy. Because of the inherent limitations of blood cultures and the established difficulty of clinically excluding an infectious etiology, a full course of antibiotics is recommended regardless of culture results.⁶⁵

Bronchodilators

It appears that ACS includes a reactive airway component that often responds to treatment, which may be partly attributed to the high prevalence of asthma in the sickle cell population. The mean forced expiratory volume for patients with ACS has been documented as 53% of predicted normal. In the NACSSG, 20% of patients demonstrated clinical improvement with administration of bronchodilators.⁷ Regardless of the presence or absence of audible wheezes, treatment with bronchodilators should be routine at presentation and continued if response is noted.

Transfusion Therapy

Transfusion therapy is often used in the treatment of ACS, with 72% of patients in the NACSSG receiving some form of transfusion.⁷ Reports of dramatic improvement in clinical condition after initiation of transfusion are well documented in the literature.^{12,66–69} In addition, both the partial pressure of arterial oxygen and oxygen saturation have been shown to significantly improve with transfusion.^{7,70} The mechanism by which this therapy works is not entirely known, but it is likely related to improved oxygenation and lowering

Table 4. Therapeutic Modalities for Acute Chest Syndrome

Supportive measures
Oxygen for hypoxia
Appropriate hydration
Appropriate pain control
Incentive spirometry
Antibiotics: third-generation cephalosporin, macrolides
Transfusion therapy
Simple transfusion
Exchange transfusion
Experimental therapy
Nitric oxide
Corticosteroids

the hemoglobin S concentration. The latter mechanism may promote blood flow through the pulmonary vasculature. Transfusion also may have an effect on the inflammatory mediators of disease.

Decisions about initiating transfusion therapy can be difficult. Experienced physicians should try to balance the immediate medical needs of the patient and the risks associated with treatment, which include transfusion reaction, alloimmunization, and infection. The options for transfusion include simple or exchange technique. The method by which to transfuse patients is also a difficult decision because no randomized controlled trials comparing simple versus exchange transfusion for ACS have been done. The degree of improvement of oxygenation does not differ depending on transfusion technique.⁷ For this reason, physician experience and local practice often guide therapy.

One author recommends the use of simple transfusion in patients with mild events associated with severe anemia.¹ Exchange transfusion is then reserved for those with deteriorating conditions or need for transfusion with a less severe anemia. Simple transfusion should be avoided if the hematocrit is expected to rise above 35% following therapy as this level will worsen blood viscosity.⁷¹ The use of phenotypically matched units is also important to consider as it can decrease the rate of new red blood cell antibody formation from 5% of patients to 1%.⁷

Experimental Treatments

Nitric oxide therapy and corticosteroids are 2 experimental treatments for ACS. Case reports supporting the use of nitric oxide therapy have been published, but no clinical trials have been reported to date.^{72,73} Nitric oxide therapy has the theoretical benefits of

reducing pulmonary pressures, improving oxygenation, decreasing expression of adhesion molecules, and improving hemoglobin saturation.^{46–48} The use of corticosteroids in the treatment of ACS has been evaluated in only 1 small study of pediatric patients.⁷⁴ In this study, corticosteroids were associated with a reduction in the length of hospitalization for children with mild to moderate disease and resulted in a reduction in the length of oxygen and opioid therapy, need for transfusion, and duration of fever. Concerns about rebound crisis and the need for rehospitalization after discharge limit widespread clinical use until further research is done.^{74,75} Corticosteroids are perhaps most appropriate in patients with a known history of asthma and current reactive airway symptoms.

HOSPITAL COURSE AND OUTCOMES

The average length of stay for ACS has been reported to be as short as 5.4 days in children and as long as 10.5 days in adults.^{6,7} Approximately 10% of children and 22% of adults with ACS will require mechanical ventilation for an average of 4.6 days. Independent predictors of respiratory failure requiring mechanical ventilation include a history of cardiac disease, multilobar involvement, and lower platelet counts ($< 199 \times 10^3/\mu\text{L}$).^{6,7}

Neurologic events are frequent occurrences in patients hospitalized for ACS, with as many as 11% of patients having some event.⁷ The most common events are altered mental status, seizure, and neuromuscular abnormality, while significant events such as anoxic brain injury, infarction, and hemorrhage also may occur. Prolonged hospital stay, respiratory failure, and death are more common in patients with neurologic events complicating ACS. Platelet counts less than $199 \times 10^3/\mu\text{L}$ again were an independent predictor of neurologic complication.⁷

The death rate for adults hospitalized with ACS in the Cooperative Study of Sickle Cell Disease⁶ was 4.3%, while the rate for children was far lower. Although the primary cause of death in these patients is respiratory failure, 81% who require a ventilator will survive. Other causes of death reported in patients hospitalized with ACS include cor pulmonale, hypovolemic shock from splenic sequestration, sepsis, intracranial hemorrhage, and seizure.^{6,7}

PREVENTION

Prevention of ACS is possible and is essential to the long-term health of patients with sickle cell disease. Each episode of ACS places the patient at risk for event-related mortality and long-term lung injury. Recurrent episodes are thought to contribute to chronic lung disease, pulmonary hypertension, and cor pulmonale.⁷⁶

Patients admitted to the hospital for painful crisis should be considered to be in the prodromal phase of ACS and should be monitored closely.⁶ In the future, routine monitoring of secretory phospholipase A₂ may help physicians recognize impending ACS and allow for the initiation of therapies prior to the development of clinically apparent disease.^{34,35} Treatment of pain crisis should include incentive spirometry.³⁸ Patients admitted for painful crisis should have hydration therapy and analgesia therapy monitored closely to prevent possible iatrogenic causes of ACS.^{11,39–41}

Patients with sickle cell disease admitted for surgery also should be monitored closely because of their increased risk of developing ACS postoperatively. Preoperative transfusion for significant surgical procedures, careful intraoperative anesthesia, and postoperative incentive spirometry are critical.^{5,77–82}

Chronic transfusion has been considered as a preventive strategy for many complications of sickle cell anemia, including ACS. Despite evidence of efficacy in preventing illness, including ACS, its role is limited by the risks of transfusion reactions, infection, alloimmunization, and iron accumulation.^{83–85} Bone marrow transplantation as a preventive strategy for subsets of patients with sickle cell disease is a developing therapy as well.⁸⁶

Hydroxyurea is a relatively new treatment option available for patients with sickle cell disease. Hydroxyurea is a ribonuclease reductase inhibitor with many physiologic effects, including increasing fetal hemoglobin production, decreasing white blood cell counts, and altering adhesion molecules on reticulocytes. Use of this medication has been associated with fewer episodes of pain crises and ACS, decreased need for transfusion, and lower mortality.^{87–91} Patients on this medication need to be monitored for cytopenias. The primary concern with this medication is a questionable association with leukemia that was noted when hydroxyurea was used in patients with myeloproliferative diseases. Preliminary work in sickle cell patients of all age-groups has not demonstrated any statistical risk, but long-term data are still needed.^{88–91} For this reason, firm guidelines for its use are not available, and its risks and benefits should be evaluated on an individual basis.

Finally, patients with sickle cell disease should receive comprehensive care, which includes the use of prophylactic penicillin to decrease the incidence of infections by *S. pneumoniae*.⁹² Patients should receive penicillin until age 5 years.¹⁷ It is safe to withdraw penicillin at this age if the patient has had no pneumococcal infections, has not undergone splenectomy, and has received appropriate vaccination.⁹³ One report

suggests that prophylactic penicillin may not be necessary in patients with sickle hemoglobin C and sickle β^+ -thalassemia disease.⁹⁴

Vaccination against *S. pneumoniae* is also an important part of comprehensive care. Pneumococcal polysaccharide vaccine was the first pneumococcal immunization developed.^{16,95} The effectiveness of the vaccine is limited by a poor antibody response in children younger than 2 years. Recently, the heptavalent pneumococcal conjugate vaccine Prevnar (Lederle Laboratories, Pearl River, NY) was approved for use in children starting at 2 months of age. This vaccine promotes a protective antibody response when administered to the very young. Current recommendations support the use of both Prevnar and the 23-valent pneumococcal polysaccharide vaccine in children with sickle cell disease.^{96–98} Other routine childhood vaccinations that should be given include the *H. influenzae* type b conjugate vaccine and meningococcal vaccine. In addition, annual influenza vaccination is recommended for patients with sickle cell disease.⁹⁸

CONCLUSION

ACS is a common complication of sickle cell disease and a frequent cause of death. Its pathophysiology is complex, making targeted therapy difficult. The clinical presentation can be subtle and the disease often presents only after admission to the hospital for seemingly unrelated reasons. As the understanding of this process develops, new therapies will emerge along with better outcomes. For now, heightened vigilance around detection and aggressive treatment with available options has the potential to prevent significant morbidity and mortality in patients with sickle cell disease. **HP**

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