Acute chest syndrome is an acute pulmonary illness in patients with sickle cell disease. It is a common problem, causing significant morbidity and mortality. Many factors may cause this syndrome. Treatment is primarily supportive. Therapy includes hydration, analgesia, supplemental oxygen, antibiotics, blood transfusion and mechanical ventilation. Early detection and aggressive management may limit its severity and prevent its complications. This article reviews the current information for its definition, frequency, pathogenesis, clinical features, complications, investigations, management and prevention. Recent advances in management of acute and recurrent attacks will be discussed.

**Keywords:** Sickle cell disease, acute chest syndrome, pulmonary complication.

**Saudi Med J 2002; Vol. 23 (9): 1037-1044**
over hydration and hypventilation from narcotic analgesics administered to combat pain in the chest or elsewhere or hypventilation from chest, back and abdominal pain. In the early 1970s, Barret-Conner suggested that most of the episodes of ACS (up to 80%) are due to bacterial infections especially in children. Subsequent studies in children and adults proved that bacterial infection occur in minority of these patients (<20%). One possible exception to this is in the population <5 years of age in whom Pneumococcal bacteremia is most prevalent. Another possible exception is that in certain area such as Ghana, in which infection may be more common than infarction. The differentiation of the 2 conditions (infarction versus infection) is extremely difficult, and may be only academic, since primarily infective lesions may develop areas of secondary infarction, and primarily infective lesions are likely to become secondarily infected. Microvascular infarction, and primarily infarctive lesions are likely infective lesions may develop areas of secondary sickling. It was suggested aggregates of sickle cells, make the lung one of the most propensive sites for proved that bacterial infection occurs in minority of SCD patients. It is likely that tissue necrosis may be a common cause of ACS. It was reported in both pediatric and adult populations, chlamydia pneumonia can be a common cause of ACS. Viral infection such as parvovirus B19, and cytomegalovirus may cause fatal ACS.

Clinical features. Onset. The onset of ACS is usually sudden but may be insidious. The symptoms and signs of pulmonary disease present either at admission, or hours to several days later. The presenting complaints of patients admitted without pulmonary involvement are abdominal pain, back pain, limb pain and fever. Acute chest syndrome may also develop after surgery (splenectomy, cholecystectomy, and so forth) and during episodes of cholecystitis or trauma.

Symptoms and signs. Most patients with ACS present with history of fever. Fever usually persists for a few days despite appropriate management. Cough is a common symptom. It may be productive or non-productive. Sputum may be whitish, greenish, bloody or yellowish. (Figure
1. Chest pain and dyspnea are common symptoms. Physical examination in patients with ACS is variable. Patients may be mildly affected with or without mild respiratory distress. On the other hand, they may be severely affected, ill looking, in severe respiratory distress and progressing rapidly to respiratory failure. They may be febrile (temperature >38°C), tachypneic, with intercostal and subcostal retractions. There may be tenderness of ribs and sternum in the area of chest pain. Auscultation may reveal decreased breath sounds, rales (unilaterally or bilaterally) and pleural rub.

Degree of clinical severity. A simple scoring system to grade the clinical severity of the disease was developed on the basis of physical examination findings. Score “0” is made when there is no respiratory distress and will indicate mild disease. Score “1” is made when there is tachypnea (age adjusted) and will indicate moderate severity. Score “2” is made when there are tachypnea and retractions and will indicates severe disease. These scores can be used to assess these patients and may help in giving the appropriate management.

Radiographic features (Table 1). Radiographic abnormalities in ACS are: patchy infiltrates, florid consolidation, linear atelectasis, pleural effusion and pulmonary edema. These abnormalities nearly always involve the lower lobes. Upper lobes, middle lobes and lingula may be involved. Bilateral involvement occurred in around one third of patients. Characteristic of the radiographic course is the rapid change (extension or resolution) that paralleled the variable clinical course. (Figures 2 & 3).

Hematological features. Hemoglobin level. The hemoglobin level in ACS frequently falls by 25% or more. The fall in hemoglobin level occurred significantly in patients with thrombocytosis. The cause of anemia is uncertain, but may be in part due to increased hemolysis unrelated to glucose-6-phosphate dehydrogenase (G6PD) deficiency. Life-threatening anemia associated with cold agglutinins of anti-I specificity may also occur in association with mycoplasm infection.

White blood cell count. White blood cell count is usually elevated in ACS. This elevation may continue for a few days despite appropriate management.

Platelet count. Platelet count may fall initially on admission. By the end of first week of illness, there may be an abrupt and significant increase in platelet count. The thrombocytosis usually develops after the temperature returns to normal and the patient has been discharged from the hospital.

Blister cells. Blister cells were defined as red blood cells having a large vacuole at one end and resembling a round or conical basket and include cells with bilateral, thinned, hemoglobin free areas with intact cell membranes. These cells were found to be suggestive of pulmonary embolism in patients with sickle cell anemia by some authors but were unreliable to predict the cause of the pulmonary insult by others. Whether this feature is diagnostic of pulmonary thromboembolism remains to be seen.

Evaluation of anemia. Arterial blood gases should be obtained from all patients with ACS at the time of presentation. Arterial blood gases should be monitored carefully even in those patients who appear to "look good", because cyanosis is not a useful physical finding in anemia. Arterial oxygen/tension (PaO2) has reportedly ranged from 46 to 73mm Hg in patients with ACS. Pulse oximetry has become a popular means of assessing oxygenation. It is not affected by sickle hemoglobin.

A simple way to correlate saturation to oxygen tension is the "40-50-60/70-80-90" rule: a PaO2 of 40mm Hg corresponds approximately to a saturation of 70%, a PaO2 of 50mm Hg to a saturation of 80% and a PaO2 of 60mm Hg to a saturation of 90%.

Alveolar-arterial oxygen gradient. Alveolar-arterial oxygen gradient [(A-a) PO2] can be calculated for patients whose arterial blood gas values were obtained while they were breathing room air at the time of diagnosis of ACS, using the following formula: (A-a) PO2 = (7.13 x FIO2) - (PaCO2 x 1.2)-PaO2, where FIO2 is the fraction of inspired oxygen, PaCO2 is the partial pressure of carbon dioxide in arterial blood and PaO2 is the partial pressure of oxygen in arterial blood. It was found that elevation of the (A-a) PO2 is a predictor of an adverse clinical course, particularly in patients with homozygous sickle cell anemia. An elevated gradient is strongly associated with a higher clinical severity score. Patients with an (A-a) PO2 >30mm Hg are significantly more likely to undergo blood transfusion.

Search for infection. Blood, throat and sputum (if possible) cultures should be carried out for all patients with ACS. Patients with bacteremia are likely to have pneumonia in presence or absence of pulmonary infarction. The role of positive throat culture, particularly in those who did not respond to usual management, should be considered. Culture of pleural fluid may be helpful if thoracentesis was carried out. Culture of endotracheal aspirates also may be helpful if the patient has been intubated. Mycoplasma antibody titers or cold agglutinins titers should be carried out for all patients. Enzyme immunoassay to detect immunoglobulin M against...
Acute chest syndrome ... Al-Dabbous

Table 1 - Investigations for patients with acute chest syndrome.

<table>
<thead>
<tr>
<th>Routine investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete blood counts</td>
</tr>
<tr>
<td>Differential counts</td>
</tr>
<tr>
<td>Peripheral smear study</td>
</tr>
<tr>
<td>Reticulocyte counts</td>
</tr>
<tr>
<td>Lactate dehydrogenase</td>
</tr>
<tr>
<td>Serum bilirubin</td>
</tr>
<tr>
<td>Chest x-ray</td>
</tr>
<tr>
<td>Blood gases</td>
</tr>
<tr>
<td>Cultures (blood, throat and sputum)</td>
</tr>
<tr>
<td>Serology for mycoplasma, chlamydia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Special investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral study</td>
</tr>
<tr>
<td>Fungal study</td>
</tr>
<tr>
<td>Radio-isotope scanning of the lung</td>
</tr>
<tr>
<td>Computerized tomography scanning of the lungs</td>
</tr>
<tr>
<td>Serology for legionellosis</td>
</tr>
</tbody>
</table>

Table 2 - Risk factors for acute chest syndrome.

<table>
<thead>
<tr>
<th>Young age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rib infarction</td>
</tr>
<tr>
<td>Chest, abdominal and back pain</td>
</tr>
<tr>
<td>Severe lower limb’s pain</td>
</tr>
<tr>
<td>Hematocrit, white blood cells, fetal hemoglobin</td>
</tr>
<tr>
<td>Bronchial asthma</td>
</tr>
<tr>
<td>Narcotics</td>
</tr>
<tr>
<td>Over-hydration</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
</tbody>
</table>

Table 3 - Poor prognostic factors.

<table>
<thead>
<tr>
<th>Bronchial asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fall of hemoglobin by 25% or more</td>
</tr>
<tr>
<td>Thrombocytosis</td>
</tr>
<tr>
<td>Pleural effusion</td>
</tr>
</tbody>
</table>

Figure 1 - Yellowish sputum from a patient with acute chest syndrome.

Figure 2 - A patient with moderate attack of acute chest syndrome.

Figure 3 - A patient with severe attack of acute syndrome.
chlamydia pneumonia can be carried out if possible. Serology for legionnaires’ disease may be useful if a patient develops progressive pulmonary infiltrate while on therapy with a penicillin, cefalosporin or aminoglycoside. Viral studies may be useful in severe cases. Fungal cultures of bronchial aspirate may be helpful in a prolonged attack.

**Lung scans.** Radioisotope lung scanning can be carried out (if available). It can show pulmonary infarction, but adds little to the chest x-ray with clear cut consolidation. Early utilization of this scanning may help in the diagnosis of acute reversible pulmonary ischemia, particularly in children, due to the interpretation of pulmonary scans carried out during an acute episode has been found to be difficult in adults with SCD due to the high prevalence of chronic lung changes. It can be carried out on admission and then after a few days.

**Computerized tomography scan of the chest.** Computerized tomography scans of the chest can be carried out for selected patients with ACS, particularly those who had recurrent attacks, to determine the presence and extent of microvascular occlusion, and can help in the timely selection, planning and monitoring of an appropriate treatment regimen.

**Risk factors (Table 2).** Young age. The risk of ACS in sickle cell anemia seems to be related to young age, being highest in children 2-4 years old and lowest in adults.

**Rib infarction.** Rib infarction may cause bone pain, followed by soft tissue reaction, pleuritis, and splinting. The resultant hypoventilation leads to atelectasis and subsequent development of the radiographic changes of the ACS.

**Chest, abdominal and back pain.** Any chest, abdominal or back pain, whether due to painful crises or due to other causes such as postsplenectomy, postcholecystectomy, trauma, may cause hypoventilation and subsequent development of ACS.

**Severe lower limbs infarction.** Severe infarction can occur in the intramedullary cavity of lower limbs during vasoocclusive crisis and generate fat equivalent to that accompanying a major fracture.

**High hemoglobin and white blood cells.** High steady state hemoglobin levels and leukocyte counts are associated with a high ACS incidence. This relationship is unexplained. The association of high hemoglobin levels and ACS may be due to increased blood viscosity. On the other hand, the association of leukocytosis with ACS could reflect the fact that both high leukocytes counts and high ACS rate are more frequent in patients with severe disease.

**Decreased hemoglobin F.** Increased hemoglobin F is a possible protective factor against many complications of SCD, including ACS.

**Bronchial asthma.** Bronchial asthma has been known to precipitate or exaggerate sickle cell crises, including ACS, and can make prognosis of SCD worse.

**Smoking.** Cigarette smoking may increase the risk of ACS.

**Differential diagnosis. Infection versus infarction.** It has been suggested that upper lobe disease, age less than 5 years and positive sputum or blood cultures favor a diagnosis of pneumonia, while a diagnosis of pulmonary infarction is favored by painful bony crisis, lower lobe disease and a clear chest radiograph on presentation in adults, but as mentioned above, the literature clearly support that there are no clinical, laboratory or radiographic features that distinguish pneumonia from pulmonary infarction.

**Pulmonary fat embolism.** Pulmonary fat embolism should be considered in the differential diagnosis when severe painful episodes (bone) occurred before the onset of ACS. Altered mental status in association with ACS strongly suggests that pulmonary fat embolism may be the underlying cause. Lipemia retinalis and petechial lesions in conjunctiva and upper thorax may support the diagnosis. Characteristic laboratory findings in ACS associated with pulmonary fat embolism are: thrombocytopenia, decrease in hemoglobin, increase in nucleated red blood count. Hypocalcemia and hyperuricemia may be found. Lipid droplet found in blood sample obtained by Swan-Ganz catheter, bronchoalveolar fluid, urine and sputum may confirm the diagnosis.

**Acute chest pain.** Other causes of acute chest pain may be considered in the differential diagnosis of ACS. Such causes may include painful crisis of the muscle of the chest wall or painful crisis of chest bones. Severe hypoximia secondary to acute sternal infarction in sickle cell anemia without ACS was reported.

**Management.** The aim of treatment of ACS is to reverse the pulmonary pathology, to correct significant hypoxemia, to relieve the chest pain and to prevent the recurrent attacks.

**Admission.** All patients with ACS should be admitted. In severe cases, intensive care units is required.

**Analgesia.** Analgesia should be administered to patients with ACS, particularly those patients with chest pain. Narcotic analgesia may be required, but large doses of narcotics should be avoided when possible, since they may cause hypoventilation and pulmonary edema.

**Hydration.** Maintenance intravenous fluid should be given. Previous recommendations for aggressive intravenous hydration (1.5-2 times maintenance) have been revised. Excessive hydration especially with hypotonic saline can cause pulmonary edema.

**Oxygen therapy.** Oxygen therapy is indicated for hypoxemia, tachycardia and tachyplea. The use of
supplemental oxygen is warranted when the PaO₂ is less than 60-70 torr. The role of oxygen therapy is to improve arterial hypoxemia caused by a ventilation-perfusion imbalance, to increase oxygen transport to the tissues, and to minimize microvascular occlusion and exaggeration of any underlying pulmonary hypertension. The aim of oxygen therapy is to maintain PaO₂ within normal range. Increasing PaO₂ above normal (100 torr) is not of proven benefit, and may suppress erythropoiesis which may cause rebound elevations of irreversibly sickled cells after discontinuation of oxygen therapy. When patients improve and oxygen therapy is no longer required, supplemental oxygen is preferably tapered to prevent any rebound effects.

**Antibiotics.** Antibiotics should be started empirically in all patients with ACS. These antibiotics should cover organisms commonly causing community acquired pneumonia such as Streptococcus pneumoniae (Strep. pneumoniae) and H. influenzae. Ampicillin may be the drug of choice for mild cases. If the patient does not improve or deteriorates, ampicillin should be substituted by 2nd or 3rd generation of cephalosporin. In moderate to severe cases, the 3rd generation of cephalsporin (Cefuroxime, Ceftriaxone) may be the drug of choice. In very sick patients with life-threatening condition, Vancomycin and extended spectrum of Cephalosporin may be started due to increased frequency of drug-resistant Strep. pneumoniae. Erythromycin can be given in addition to the other antibiotics to cover mycoplasma pneumonia, chlamydia pneumonia and legionella.

**Bronchodilators.** Airway hyperactivity should be assumed to be present, even if the patients is not wheezing, and treatment with bronchodilators should be initiated. It was found that one fifth of the patients who were treated with bronchodilators had clinical improvement.

**Intravenous dexamethasone.** Preliminary results showed that intravenous dexamethasone (0.3mg/kg every 12 hours, for 4 doses) in children with mild to moderately severe ACS significantly reduced the length of hospitalization, the duration of supplemental oxygen therapy, duration of opioid analgesia, need for blood transfusion, occurrence of clinical deterioration, and persistence of fever. Some patients with ACS may deteriorate despite oxygen therapy and partial exchange transfusion. These patients may benefit from mechanical ventilation. Extracorporeal membrane oxygenation. If extracorporeal membrane oxygenation is available, it should be considered for severe ACS when conventional methods of mechanical ventilation fail.

**Nitric oxide.** Nitric oxide may be beneficial in severe cases that have not responded to other treatments. It may cause acute improvement in oxygenation in patients with acute hypoxic respiratory failure.

**Bronchoscopy.** Bronchoscopy can be considered in severe ACS not responding to conventional management.

**Complications.** Complications of ACS can be divided into acute and chronic complications. Acute complications include respiratory failure, pleural effusion, lung abscess and plastic bronchitis. These complications are poor prognostic factors (Table 3). Patients with these complications usually required prolonged treatment and hospitalization and are prone to chronic complications. Progression of pulmonary infilrates, a rapidly falling hemoglobin and worsening hypoxemia may herald the development of acute respiratory failure. Pleural effusion occurs in up to 38%, and can be unilateral or bilateral. Patients may appear acutely ill with fever, non productive cough and chest pain. Infarction is a well-recognized predisposition to pulmonary abscess formation in patients who have other conditions which cause tissue necrosis or vascular stasis. Plastic bronchitis is a rare complication, reported in association with ACS. It is characterized by the formation of branching mucoid bronchial casts. They may become firmly wedged and occlude the tracheobronchial tree at many levels. This possibility can be considered in severe cases not responding to conventional management.
Bronchoscopy may be required. Chronic complications include recurrent ACS, chronic lung disease, pulmonary hypertension, exercise intolerance and pulmonary tuberculosis.11,12,71

**Recurrent acute chest syndrome.** Recurrent ACS may occur in 20-80%.2 Risk factors for recurrent attacks may include cystic fibrosis and bronchial asthma. Treatment may include chronic blood transfusion72 at least for 6 months. Longer periods may be required. Hydroxyurea therapy73,74 and transplantation75,76 reduce the recurrent attacks significantly. Hydroxyurea should be considered for patients who had a severe attack, or two or more mild to moderate attacks of ACS. Transplantation should be considered for patients who had a life threatening condition. It should be performed only in the context of a clinical trial.77

**Prevention.** Patients and their physicians play an important role in the prevention of ACS. Regular follow-up of SCD patients in the sickle cell clinic will provide a good chance for education regarding this complication, vaccination (influenza, H. influenza and pneumococcal vaccines) and penicillin prophylaxis. These measures may play a role in prevention of infection which is an important factor in the etiology of ACS. Behavioral modification of the smoking habit in patients with sickle cell anemia may prevent ACS.76 Careful use of intravenous fluid and opioid analgesia during management of acute painful crisis may also prevent ACS. Use of incentive spirometry during acute painful crisis (particularly acute chest, back and abdominal pain) and postoperatively may play a role in prevention of ACS.77

**References**

Acute chest syndrome ... Al-Dabbous


