The sickling disorders, sickle cell anemia and its variants, are inherited hemoglobinopathies due to at least one substitution of valine for glutamic acid at position 6 of the beta globin chain. Following deoxygenation of the erythrocyte, hemoglobin (Hb) S undergoes intracellular polymerization with the associated morphologic transformation to the sickled shape. Repeated cycles of Hb S polymerization induce a series of erythrocyte abnormalities, including cytoplasmic and membrane rigidity and cellular dehydration with an increase in intracellular Hb concentration. The circulating erythrocyte population is thus composed of a heterogeneous population of cells, including low-density reticulocytes, very dense discocytes, and irreversibly sickled cells. These dense, poorly deformable cells are ultimately responsible for the elevated whole blood viscosity and microvascular occlusion seen in this disease [1,2]. The clinical features of the disease result from Hb S polymerization and consist of chronic hemolytic anemia, frequent infections, and, most importantly, microvascular obstruction producing acute and chronic ischemia, resulting in organ damage from infarction and fibrosis [3].

Sickle cell anemia is the homozygous form of the disease (Hb SS); it is the most common variant and generally has the most severe clinical manifestations. Other variants are due to the inheritance of compound heterozygous states for Hb S and another Hb that interacts with Hb S and participates in polymer formation, causing disease. Heterozygosity for both Hb S and Hb C results in sickle-C disease, whereas combinations of Hb S with beta0 or beta+ thalassemia are known as sickle-thalassemia. Combinations of Hb S with other variants (eg, D, E, O-Arab) are rare.

Acute pulmonary disease is a common complication of the sickling diseases, with a frequency estimated at several hundred times that of the general population [4], and is the second most common cause of hospital admission in these patients, resulting in considerable morbidity and mortality [5,6]. Nearly half of all patients will have at least one episode, and a subset will have multiple events.
The term “acute chest syndrome” was introduced by Charache and colleagues [7] and reflects the difficulty of establishing a definitive cause for these acute pulmonary episodes, particularly in distinguishing infection from pulmonary infarction by microvascular occlusion. The terminology is potentially misleading, because it includes those cases with a relatively benign course as well as those that develop progressive disease with a picture similar to that of adult respiratory distress syndrome (ARDS). The acute chest syndrome (ACS) in sickle cell disease (SCD) is currently defined as a new infiltrate on chest radiograph associated with one or more symptoms, such as fever, cough, sputum production, tachypnea, dyspnea, or new-onset hypoxia [8]. The illness clinically and radiographically resembles bacterial pneumonia, with fever, leucocytosis, pleuritic chest pain, pleural effusion, and cough with purulent sputum. However, the clinical course in SCD is considerably different from that in hematologically normal individuals. Multiple lobe involvement and recurrent infiltrates are more common in SCD, and the duration of clinical illness and of radiologic clearing of infiltrates is prolonged to 10 to 12 days [5,8–10].

**EPIDEMIOLOGY**

In the seminal reports by Barrett-Connor [4,11], 84 of 169 episodes of ACS had evidence of bacterial infection on culture of blood or sputum. Because there was no difference in the clinical course between culture-positive and culture-negative cases, Barrett-Connor concluded that all cases were most likely due to infection, most commonly to *Streptococcus pneumoniae*. Her conclusion was supported by the known propensity to bacterial infection in SCD and was widely accepted. However, since that time, numerous epidemiologic studies in people with normal Hb type have indicated a changing epidemiology for pneumonia. For example, studies [12] in armed forces personnel indicate that the attack rate of pneumonia in the 1990s (77.6/100,000/year) was one fourth that of the 1970s (307.6/100,000/year). Furthermore, the frequency of *S pneumoniae* has declined substantially while that of *Mycoplasma pneumoniae* and other atypical organisms has increased. Moreover, a definite cause is not established by culture in 65% to 75% of cases. More recent data indicate that viruses, particularly rhinovirus at 45%, account for the majority of events in children, and that infection with *M pneumoniae* at 35% continues to rise in frequency [13]. Moreover, in adult populations, *M pneumoniae* and *Chlamydia pneumoniae* are the leading causes of pulmonary infection outside the hospital setting [14]. In as many as 55% of episodes, no definite causative agent can be identified. Thus, the epidemiology of pneumonia in the general population continues to evolve over time, and the spectrum of pulmonary microbial infection is likely to undergo further changes in both the general and SCD populations.

These secular changes in microbial flora were first demonstrated in SCD by Poncz and colleagues [15], who studied 102 episodes of ACS in 70 patients with careful culture techniques and found that they could document bacterial infection in only 12 episodes. The single most common cause found was *Mycoplasma* (16%), and viral disease at 8% was almost as frequent as the common bacterial
agents. In 66% of the episodes, no cause was established. Nearly identical findings were reported by Sprinkle and colleagues [16] in their study of 100 episodes of ACS in 57 patients. By contrast, in Curacao [17], 43% of sputum cultures were positive in 81 episodes seen in 53 patients. The most common bacterium was *Haemophilus influenzae*, and both *Staphylococcus aureus* and *Klebsiella* were more common than *S pneumoniae*. Other reports have stressed the evolving importance of *C pneumoniae* and *Legionella pneumophilia*. Viral agents causing ACS include influenza, respiratory syncytial virus, cytomegalovirus, parvovirus, adenovirus, and parainfluenza virus.

The publication of data from two large cooperative groups in recent years has provided a clearer picture of ACS and its impact on SCD. The Cooperative Study of Sickle Cell Disease (CSSCD) reported on 1722 episodes of ACS in 939 patients with a new infiltrate on chest radiograph. Data from this study indicate that ACS occurs with an overall incidence of 10.5 per 100 patient-years [5,10], most often as a single episode, but certain patients have multiple episodes. A past history of ACS was associated with earlier mortality than that found in patients who had never had an episode. The disorder is most common in the 2- to 4-year age group, with a peak incidence of 25.3 per 100 patient-years, and gradually declines in incidence with age to 8.8 per 100 patient-years in those more than 20 years old. It is believed that the slower decline of Hb F concentration compared with normals exerts a protective effect in those patients less than 2 years of age. The decline in the incidence of ACS observed in older age groups is believed to be related to at least two factors: (1) excess mortality in the group that had an ACS and (2) fewer viral episodes in adults because of acquired immunity. The incidence of ACS is related to genotype: the frequency in Hb SS is slightly greater than that in Hb S beta° thalassemia, but the frequency is much lower in Hb SC and Hb S beta+ thalassemia. Additional data showed that a lower hematocrit or a higher Hb F was associated with a reduced incidence of ACS, whereas a high white blood cell count was associated with a higher incidence.

The National Acute Chest Syndrome Study Group (NACSSG) [8] employed a more stringent definition of ACS: its inclusion criteria were a new infiltrate plus one or more pulmonary signs or symptoms, such as fever, cough, sputum production, tachypnea, dyspnea, or new-onset hypoxia. Viral culture techniques and acute and convalescent serologies were employed, as well as careful examination of deep sputum cytology for fat-laden macrophages indicative of fat embolism. In this study, there were 671 episodes of ACS in 538 patients. In 48% of the episodes, ACS developed during hospitalization for acute pain or other causes. A definite cause was established in 256 (38%) of these episodes, but incomplete data precluded full assessment in 306 episodes (46%). Of the 27 pathogens identified, the most common infectious agents were *Chlamydia* (7.2%), *Mycoplasma* (6.6%), and viruses (6.4%), particularly respiratory syncytial virus. Pulmonary infarction was diagnosed by exclusion and found in 16.1% of episodes, whereas fat embolism was found in 8.8%. *S pneumoniae* was recovered in only 11 episodes. A variety of bacterial and viral agents were identified in the
remainder of cases. Mechanical ventilation was required in 13% of patients and was associated with extensive lobar involvement, a platelet count of less than 200,000/μL, or a preceding history of cardiac disease. Eighteen deaths occurred (2.7%), primarily as the consequence of pulmonary embolism with bone marrow, fat, or thrombi.

**CLINICAL PRESENTATION**

The clinical characteristics of ACS in both children and adults have been more clearly defined by large clinical studies in recent years. The CSSCD reported on 1722 episodes of ACS in 939 subjects [10], and the NACSSG study [8] described the findings in 671 cases of ACS in 538 subjects (Table 1). Fever of greater than 38.5°C and cough were the most common presenting symptoms and were significantly more common in children than in adolescents or adults. Tachypnea and bronchospasm, particularly in children, were the common physical findings; however, a normal physical examination was found in 35% of the cases, and additional data support the unreliability of the physical examination in the detection of ACS [18]. Chest, rib, and extremity pain were more common in older adolescents and adults. Isolated upper and middle

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Age &lt;10 y*</th>
<th>Age &gt;10 y*</th>
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<tbody>
<tr>
<td></td>
<td>CSSCD n = 483</td>
<td>NACSSG n = 264</td>
</tr>
<tr>
<td>Fever</td>
<td>90</td>
<td>86</td>
</tr>
<tr>
<td>Cough</td>
<td>81</td>
<td>69</td>
</tr>
<tr>
<td>Chest pain</td>
<td>26</td>
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<tr>
<td>Rib pain</td>
<td>NA</td>
<td>14</td>
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<td>Extremity pain</td>
<td>NA</td>
<td>22</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>17</td>
<td>31</td>
</tr>
<tr>
<td>Temperature &gt;39°C</td>
<td>44</td>
<td>86</td>
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<tr>
<td>Respiratory rate &gt;40/min</td>
<td>28</td>
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<tr>
<td>Pulse &gt;140/min</td>
<td>27</td>
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<tr>
<td>ACS not present on admission</td>
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<tr>
<td>Mechanical ventilation</td>
<td>10</td>
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<tr>
<td>Reactive airway disease</td>
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<tr>
<td>Length of stay (d)</td>
<td>9.7</td>
<td>NA</td>
</tr>
<tr>
<td>Mortality</td>
<td>&lt;1</td>
<td>NA</td>
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* The differences between young children and adolescents/adults were significant, at $P \leq 0.006$ or better, for all variables except for length of stay, where $P \leq 0.04$.

lobe involvement were more common in children, with isolated lower lobe disease more common in adults. Pleural effusions were more common in adults. Bacteremia was more common in children aged 2 to 4 years; *S. pneumoniae* was detected in 78% of those children but found in only 25% of adults with bacteremia. Moreover, in nearly half the cases, ACS developed several days after hospitalization for another reason. In both series, the hospital stay was longer for adults than for children. The longer duration of hospital stay in the NACSSG study reflects the enrollment of a more acutely ill population because of more stringent inclusion criteria. These criteria included a new pulmonary infiltrate involving at least one complete lung segment, excluding atelectasis, together with at least one of the following: chest pain, fever greater than 38.5°C, tachypnea, wheezing, or cough. Additional data supporting the greater severity of clinical illness in the NACSSG study were the more frequent use of transfusions and the higher mortality. Mortality in both studies was four- to ninefold greater in adults than in children and was due to respiratory failure, cor pulmonale, hypovolemic shock, or sepsis.

These features of ACS indicate that infection is its most frequent cause in young children. In adults, the strong association with bone pain and less frequent identification of microbial infection suggest that vascular occlusion is the cause of ACS in most cases.

**PATHOPHYSIOLOGY**

The pathophysiology of acute lung injury in the sickling disorders is complex. Microbial infection, in-situ vaso-occlusion, fat embolism from ischemic/necrotic bone marrow, or thromboembolism may initiate this process, and establishing a specific cause is often difficult.

Patients who have SCD have increased susceptibility to infection that is not fully understood but appears related to functional asplenia, decreased opsonic activity in their serum, and a relatively poor antibody response to the polysaccharide component of the bacterial capsule. Splenic hypofunction correlates with the increased susceptibility to infection [19]. Defective activation of the alternate pathway has been demonstrated [20,21] and correlates with a past history of pneumococcal infection [22]. This same defect in alternate pathway activation has been described in sickle-β disease and presumably extends to the other sickle variants; serial studies show that the defect is persistent for at least 1 year [23]. Serotype-specific IgG antibody responses to pneumococcal reimmunization are generally mediocre to poor. This poor response is not surprising, because pneumococcal polysaccharides are T lymphocyte–independent antigens [24] and are not thought to induce immunologic memory in either children or adults [25]. The occurrence of pneumococcal bacteremia is associated with low IgG antibody concentrations to the infecting serotype. The most prevalent pneumococcal serotypes causing disease in this era of prophylactic antibiotics and vaccination include types 6, 14, 18, 19, and 23; these same serotypes were most frequently involved in previously reported “vaccine failures” [26]. Aside from evidence supporting an immune defect related to pneum-
mococcal infections and the phagocytic defect, there is little evidence to suggest that impaired immunity has substantial clinical relevance to the spectrum of the ACS. However, recent evidence for impaired lymphocyte blastogenic response and γ-interferon production in patients with ACS suggests that these immunologic abnormalities may contribute to the clinical severity of acute pulmonary disease in this patient population [27].

Progression of pulmonary disease to an ARDS-like picture is often attributed to vaso-occlusion (reviewed by Chiang and Frenette elsewhere in this issue), in which Hb S–containing cells interact with microvascular endothelium or endothelial matrix. This interaction occurs through a variety of adhesive proteins expressed on the sickle erythrocyte and corresponding molecules on the endothelial cell; these interactions are mediated by plasma ligands, such as thrombospondin and von Willebrand factor (vWF) [28,29]. Adhesogenic molecules on the sickle reticulocyte include the integrin α4β1 (very late activation antigen–4 or VLA-4), CD36, CD47, phosphatidyl serine, basal cell adhesion molecule, Lutheran blood group, and sulfated glycans. Other endothelial cell receptors, such as the integrin αvβ3 and P-selectin, may also play substantial roles. Matrix components participating in adhesion include fibronectin, thrombospondin, vWF, and laminin [28,29]. Hb S polymerization generates reactive oxygen species [30], which activate the transcription factor NF-κB. NF-κB upregulates expression of the adhesion molecule VCAM-1 on endothelium, which facilitates the endothelial adhesion of sickle erythrocytes by means of erythrocyte α4β1 [28,31,32]. VCAM-1 is also upregulated by hypoxia and by inflammatory cytokines such as interleukin-1 and tumor necrosis factor (TNF)–α, both of which are elevated in ACS over the steady-state levels [28].

A growing body of evidence indicates that granulocytes and monocytes play an important role in microvascular occlusion (see Chiang and Frenette elsewhere in this issue). Elevated leukocyte counts in SCD are associated with an increased risk for mortality and with cerebral infarction [6,33]. In addition, leukocyte counts are indicative of overall disease severity [34,35]. Reduction in leukocyte counts on hydroxyurea correlated with the improvement in frequency of both acute painful events and ACS [36]. Several recent reports appear to establish a link between severe vaso-occlusive events and the administration of G-CSF for hematopoietic stem cell mobilization, including apparent induction of an ACS [37–39]. Moreover, intravital microscopy of a transgenic sickle mouse model demonstrated adherence of circulating sickle erythrocytes to granulocytes already adherent to venular endothelium [40]. This interaction increased after administration of TNF-α and resulted in complete vaso-occlusion.

Additional vasoactive components may play a role in the ACS process. Endothelin-1 (ET-1) is a potent vasoconstrictor of the pulmonary vascular bed; its levels are increased with hypoxemia [41]. In patients who have SCD, ET-1 levels are increased during the steady state and rise sharply just before and during ACS [42]. Nitric oxide (NO) is a potent vasodilator that is generated from the amino acid l-arginine by means of NO synthase [43]. When administered by inhalation in low concentration, NO causes selective pulmonary vasodilatation,
improving ventilation/perfusion ratios. Systemic vasodilatation does not occur, because NO is rapidly inactivated by Hb binding. Inhaled NO decreases PAP and PVR in acute lung injury and improves oxygenation in neonates with pulmonary hypertension. L-arginine levels are low in adults with SCD and decrease during acute pain episodes and in ACS, whereas NO metabolites are increased, suggesting accelerated metabolism and possible depletion of NO in these acute illnesses. NO is important in counteracting the upregulation of VCAM-1. It has been shown to reduce cytokine-induced endothelial cell activation by repression of VCAM-1 gene transcription. Furthermore, NO inhibits the adherence of normal and sickle erythrocytes to vascular endothelium and prolongs survival in a transgenic mouse model of SCD exposed to hypoxia. Alterations in the balance between ET-1 vasoconstriction and NO vasodilatation can affect capillary transit time, endothelial cell expression of VCAM-1, and its attendant adherence characteristics, altering intrapulmonary flow and enhancing microvascular obstruction. However, trapping of dense erythrocytes may occur on a mechanical basis in areas of hypoxic lung aside from the mechanisms of cellular adhesion.

Thus, microvascular occlusion in the sickling diseases may occur as the result of a complex series of reactions involving activation of the endothelium by oxygen radicals from the erythrocytes, or it may occur by means of infectious processes that induce the secretion of inflammatory cytokines. Adherence of less-dense sickle erythrocytes or leukocytes to endothelium and adherence of dense sickle erythrocytes to leukocytes follows, leading to partial obstruction of microcirculatory flow. Prolonged transit time allows extensive polymerization of Hb S with its resultant erythrocyte rigidity. Trapping of poorly deformable sickle erythrocytes results in transient or prolonged obstruction of microvascular flow. The subsequent ischemia further induces endothelial activation, leading to a vicious cycle of adherence, trapping, and prolonged ischemia that is responsible for the signs and symptoms of ACS in this disease.

LABORATORY FEATURES

The chest radiographic findings are variable and may include segmental, lobar, or multilobar consolidation. In nearly half the cases, the initial chest radiograph is negative, showing only the characteristic findings of cardiomegaly with redistribution of blood flow to the upper lobes resulting from the chronic anemia. Infiltrates may not appear until 2 or 3 days later. The chest radiograph findings vary by age; children have isolated upper or middle lobe disease significantly more often than adults, whereas adults have lower lobe or multilobe disease more often. Pleural effusions are seen in more than half the episodes and are more common in adults. The chest radiograph underestimates the degree of pulmonary involvement, as has been shown by simultaneous high-resolution CT scan or perfusion scintigraphy. Thin-section (3-mm) CT scans have shown consolidation, hypoperfusion, a paucity of arterioles and venules, and areas of ground-glass attenuation in areas both involved and uninvolved on plain radiograph. Perfusion lung scans have
also shown defects in areas that were normal on radiograph [56,57]. These imaging findings are consistent with vascular occlusion of large vessels as an important component of ACS.

Typically, the Hb declines by 0.7 g/dL, and the white blood cells increase by 70% on average [5,8,10]. Bacteremia is more common in children, with *S pneumoniae* and *H influenzae* found most often. Sputum and blood cultures are insensitive means of detecting bacterial pneumonia and most likely underestimate its frequency. There is a growing trend toward the use of bronchoscopy to obtain high quality material for culture. In one study, bacterial disease was detected by bronchoalveolar lavage in 20% of adult cases [58], a substantially higher frequency than that reported in the multi-institutional group studies, despite an aggressive approach to obtaining deep sputum for culture. Bronchoscopy has been extremely successful in detecting lipid-laden macrophages for the diagnosis of fat embolism [59,60]. Bronchoscopy has the additional advantage of detecting plastic bronchitis, a complication with branching bronchial cast formation that can produce worsening hypoxemia from ventilation/perfusion mismatch [61]. Plastic bronchitis was detected in 21 of 29 episodes of ACS (72%) in one study where bronchoscopy was performed in patients with worsening lung consolidation and progressive hypoxemia [61]; it was associated with improvement in chest radiograph findings after the procedure. This high frequency of plastic bronchitis may not be representative of all cases of ACS, because the procedure tends to be performed in the most seriously ill group of patients [59,61].

Secretory phospholipase A₂ (sPLA₂) is a potent inflammatory mediator that has been implicated in the pathophysiology of multiple conditions, including sepsis, multiorgan failure, arthritis, and ARDS [62–64]. sPLA₂ hydrolyzes phospholipids to produce free fatty acids and lysophospholipids, both of which cause acute lung injury. Additional inflammatory hydrolysis products, such as leukotrienes, thromboxanes, and prostaglandins, are produced when arachadonic acid is the fatty acid product of sPLA₂ [62]. sPLA₂ is modestly elevated in sickle cell patients at baseline and increases dramatically with ACS; the degree of elevation correlates with measures of the severity of the lung injury, such as A-a gradient [65,66]. Because nearly half of ACS episodes occur in patients presenting with acute pain and because sPLA₂ rises 24 to 48 hours before the onset of ACS in preliminary studies [65,66], sPLA₂ in combination with fever may have predictive value for the development of ACS in patients presenting with pain. It may indicate the fat embolism syndrome, in which free fatty acids and eicosanoids may be generated from the fat particles lodged in the pulmonary circulation.

Measurement of oxygen saturation in Hb S disorders is confounded by the lower oxygen affinity of Hb S (Fig. 1) [67,68] and by elevations of carboxyhemoglobin and methemoglobin consequent to the hemolytic anemia. The oxygen saturation as assessed by automated blood gas analyzers calculates the saturation from the measured PaO₂ against a standard oxygen dissociation curve for Hb A; consequently, this method overestimates the saturation for samples containing
Hb S [68]. Co-oximetry uses multiple wavelengths to distinguish oxyhemoglobin from deoxyhemoglobin, carboxyhemoglobin, and methemoglobin and is the most accurate method [69,70]. Pulse oximetry measurements may overestimate the oxygen saturation by including methemoglobin and carboxyhemoglobin, which are often slightly increased in Hb S disorders; pulse oximetry is further affected by conditions that reduce the pulse amplitude, such as hypotension, hypothermia, and vasoconstriction [70]. In one study comparing the three methods, the co-oximetry and pulse oximetry showed near agreement (pulse oximetry only 2% greater than co-oximetry), but the calculated saturation overestimated the co-oximetry measurement by nearly 7% on average [68]. A subsequent study confirmed that pulse oximetry overestimates co-oximetry by only 1.1% [71].

**DIAGNOSIS**

The causes of ACS are multiple (Box 1) and include disorders directly or indirectly related to the sickling process as well as causes distinct from sickling. Chlamydia, Mycoplasma, and viral infections are now the infectious agents most commonly identified [8,15,16]. Chlamydia was found more commonly in adolescents and adults, whereas Mycoplasma and viral infections were more common in young children. Sputum and blood culture should be performed, despite the historically low yield, so as to identify bacterial agents when present. Cultures positive for nonrespiratory pathogens must be carefully interpreted [72]. Negative cultures are often explained by problems in contamination, collection, storage, or handling or by prior antibiotic administration [73,74]. Serologic studies for Mycoplasma, Chlamydia, and parvovirus are helpful in the diagnosis of these infections. Nasopharyngeal samples for viral cultures should
be included, especially in children, where viral disease is increasingly recognized [13]. Recent data indicate that fiber optic bronchoscopy and bronchoalveolar lavage (BAL) provide higher-quality specimens for culture and microscopic examination and a higher yield, thus improving confidence in a negative result [58–60].

However, all studies stress that, as in the general population [14], most ACS episodes in this patient population cannot be proved to be of infectious origin, and noninfectious causes must be sought carefully. Vichinsky and colleagues [75] published a study in which 12 of 27 episodes of ACS had evidence of fat embolism as the cause; subsequent reports indicate an even higher prevalence of fat embolism in ACS [59,60]. Data from the NACSSG indicate that fat embolism,
at 8.8%, was the most common diagnosis established and was found more often in adults [8]. Fat and bone marrow elements within the circulation, released from necrotic marrow sites of ischemic vaso-occlusion, can produce embolic phenomena involving the lungs and other tissues. The spectrum of disease in fat embolism varies widely, from isolated pulmonary fat embolism to a fulminant multiorgan failure syndrome with high fever, severe tachypnea, hypoxemia, bilateral alveolar infiltrates, tachycardia, neurologic changes, thrombocytopenia, worsening anemia, and altered renal or liver function [76,77]. Laboratory findings in the fat embolism syndrome include a dramatic rise in LDH, uric acid, and nucleated red blood cells and a decline in serum Ca++. Serum lipase and sPLA2 increase. None of these biochemical tests are specific for the diagnosis, so that clinical suspicion remains its mainstay. Examination of deep sputum or BAL specimens for fat-laden macrophages [59,60] is useful in the diagnosis of the fat embolism syndrome, as is examination for trunkal petechiae and lipemia retinalis; fat globules may be found in the blood and urine. Severe bone pain and relative thrombocytopenia may provide clues to this diagnosis in sickle cell patients.

Vascular occlusion by sickle cells and pulmonary infarction appear to be important causes of ACS, as suggested by the lack of positive bacterial or viral cultures in carefully studied patients and by the data indicating that antibiotic therapy produces no faster resolution than treatment with supportive care alone [7,8,10,72]. The results from the Multi-Institutional Study of Hydroxyurea in SCD, which indicate a significant reduction in ACS in those patients who are on hydroxyurea, further suggest that a substantial number of ACS episodes are secondary to vascular obstruction [36]. Hence our focus on infection as the most prevalent cause may have been misplaced.

Fibrin thromboembolism appears to occur at a rate similar to that in the general population [78], but distinguishing thromboemboli from sickle cell vaso-occlusion by chest tomography or scintigraphy is extremely difficult; recent data indicate nearly identical findings with these modalities [55,57]. Evidence for concomitant venous thrombosis, comparison of current lung scintigraphy with baseline data or angiography may be helpful in establishing a diagnosis [79]. In those cases of ACS where pulmonary angiography has been performed, the findings were most consistent with vascular occlusion [80]. Exchange transfusion before angiography is recommended to prevent vaso-occlusion due to sickling induced by hyperosmolar contrast media [81].

Hypoventilation can lead to regional pulmonary hypoxia and initiate the sequence of events that leads to adhesion-related vascular occlusion. The recognition that splinting due to the pain of rib infarction was frequently associated with atelectasis and evolved into ACS led to the use of incentive spirometry for prevention [82,83]. More recently, it was found that patients receiving oral sustained-release morphine for pain control during a vaso-occlusive crisis (VOC) developed an ACS at a rate threefold that of patients randomized to continuous-intravenous morphine [84]. The difference was attributed to an area under the curve for sustained-release morphine that was two- to threefold greater.
than that for intravenous morphine and was associated with a significant
decrease in SaO₂ for those on oral morphine, related to hypoventilation.

**MANAGEMENT**

In the absence of a specific causative diagnosis, treatment of ACS is primarily
supportive and can be approached from three general directions: prophylaxis,
standard management, and treatment of evolving respiratory failure. Prophy-
lactic penicillin and the use of the pneumococcal and *H influenza* vaccines may
have had a role in the changing epidemiology of ACS in SCD. Although specific
studies of vaccine impact on the frequency of pneumococcal pneumonia have
not been reported, the reduced frequency of this organism in the ACS, as
reported in recent studies, may be extrapolated from vaccine use and from the
effect of prophylactic penicillin on the frequency of pneumococcal sepsis [85,86].
The HiB vaccine may have had a similar effect on the previously reported
high frequency of pulmonary infection with this organism in SCD. Parvovirus
B19 infection has been associated with a particularly severe form of ACS, so
vaccination for this virus, as well as influenza and respiratory syncytial virus,
should be considered, depending on future availability [87]. Treatment with
hydroxyurea reduces the incidence of ACS by approximately 40% and is
indicated for those who have had two or more episodes of ACS, independent
of its indication for recurrent VOC [36]. Because of the relationship between
ACS and premature mortality, prevention of ACS and its associated complica-
tions with hydroxyurea is a possible factor in the reduction of mortality recently
reported for hydroxyurea-treated patients [88].

In an episode of ACS, the immediate goals of therapy are prevention of
alveolar collapse, maintenance of gas exchange, and prevention of further
pulmonary injury leading to a progressive downhill course. Serial determination
of arterial blood gases can be quite useful in assessing progress. Charache and
colleagues [7] first noted that an increase in arterial oxygen tension is the first
sign of improvement, before a change in chest radiograph, and that a PaO₂ of
less than 75 mm Hg (approximately equal to an SaO₂ of 85% to 90% [see Fig. 1])
is associated with a poor prognosis.

The chest radiograph lags behind the physiologic changes by a substantial
margin and is not as useful for prognostication, although Davies and colleagues
[72] noted that the duration of fever and degree of tachycardia were related to
the extent of chest radiograph involvement. However, Charache and colleagues
[7] did not find a difference in PaO₂ among patients with more extensive
radiographic changes. The arterial blood gas data should be carefully interpreted
relative to the fraction of inspired oxygen required to achieve adequate oxy-
genation [89] and in view of the reduced oxygen affinity of Hb S (see Fig. 1) [67].
SaO₂ should be maintained with supplemental oxygen at 92% or greater,
because the effect of moderate arterial desaturation on the microvascular rheol-
ogy of sickle erythrocyte is adversely affected by partial polymerization
of intracellular Hb S [90,91], with its attendant risk for pulmonary trapping
of poorly deformable erythrocyte [52,53]. In patients who have partial nasal obstruction, oxygen by mask may provide superior efficacy over delivery by nasal cannula.

Serial chest radiographs are needed to assess the extent and course of the pulmonary changes. However, serial arterial blood gas determinations on an FiO2 of 0.21 provide a clearer picture of ongoing pulmonary function, because the chest radiograph often lags behind physiologic events. Arterial blood gas measurements may be replaced by continuous pulse oximetry monitoring, especially when there have been simultaneous determinations in the patient to establish the correlation between the two. Oxygen saturation or the alveolar-arterial oxygen gradient, rather than oxygen tension, provide more relevant information [92]. Careful attention to clinical parameters—vital signs, respiratory effort, and overall status—is the key ingredient in overall assessment.

Antibiotics are generally administered, although the studies of Charache [7] and Davies [72] and their colleagues indicate that antibiotic treatment may not shorten the clinical course. The choice of antibiotic coverage must be made on clinical grounds, considering the well-described secular changes in microbial flora as well as geographic effects on the microbial spectrum [8,12,17]. In view of recent epidemiologic studies, the current recommendation is to use a third- or fourth-generation cephalosporin and a macrolide [8], but the decision should be guided by knowledge of local bacterial patterns and by the results of sputum smear analysis and should be modified as culture results become available. Alternative regimens include a quinolone or a macrolide plus a betalactam. Progression of disease should prompt a reassessment of antibiotic coverage because of the occasional gram-negative organism and the high frequency of viral agents.

Pain management often requires narcotic analgesia, which can produce respiratory depression with its attendant risk of hypoxia and its potential for acceleration of pulmonary vaso-occlusion [84]. Pleuritic chest pain is a particular problem, because splinting reduces ventilation and may predispose to atelectasis. Intercostal nerve block with a long-acting local anesthetic, such as bupivacaine, can alleviate chest wall pain and splinting and has the additional advantage of reducing the amount of systemic analgesia needed to control pain and lessening the consequent risks of respiratory depression, hypoxia and atelectasis. A nerve block may provide relief for 18 to 24 hours and can be repeated as needed to control symptoms [67].

Limiting intravenous fluid administration to a rate of 1.5 to 2.0 times maintenance is the standard practice, because overly aggressive hydration, as well as opioid administration, can lead to pulmonary edema and cause ACS [16,93]. It appears unlikely that fluid overload alone could be a common cause of ACS, given the large numbers of patients treated with this modality, unless those affected had a subtle underlying cardiopulmonary pathologic condition that was unmasked by high-volume saline administration. Because the objective is rehydration of erythrocytes [91], a hypotonic infusion, such as half-normal saline (0.25 normal for children) with or without dextrose, is preferred over normal
saline, which might be responsible for the reported cases of pulmonary edema [16,93].

Incentive spirometry (maximum of 10 inspirations every 2 hours while awake) has been shown significantly to reduce the development of atelectasis and the risk for ACS and should be instituted for all hospitalizations for pain as well as for those with ACS [94]. The high frequency of reactive airway disease with wheezing reported in SCD supports the universal use of bronchodilators as an important adjunctive therapy [8,10,95,96]. Mechanical ventilation is indicated, as for other causes of progressive respiratory insufficiency. Both high-frequency ventilation and extracorporeal membrane oxygenation have been successfully employed in severe cases of respiratory failure in ACS [97–101].

The role of transfusion support is not clearly defined, although there are sporadic case reports of rapid reversal of chest radiograph findings and symptoms immediately posttransfusion [72,102,103]. At least two broad indications for transfusion clearly appear to exist. Simple transfusion of one or two units may be given to raise the Hb level whenever there is a need for an increase in oxygen-carrying capacity. The therapeutic objectives are to make the patient more comfortable and to reduce the cardiac workload; the indications include moderately severe anemia, high cardiac output, tachycardia, and easy fatigability. Whenever the clinical situation indicates impending respiratory failure such that mechanical ventilation might be required, exchange transfusion should be considered on an urgent basis. Exchange transfusion should be used early, at the first hint of difficulty, rather than later, when the situation may no longer be reversible. Exchange transfusion may produce rapid resolution of ACS, which justifies its early use and suggests that vascular occlusion is readily reversible, at least in the early stages [72,102,103]. This rapid improvement after transfusion is further evidence for microvascular occlusion as a part of ACS, but it could also indicate another reversible lung disease, such as fat embolism.

The indications for exchange transfusion in ACS have not been fully defined, but extrapolation from the pneumonia severity index identifies poor prognostic factors that are applicable to SCD (Box 2) [104]. The pneumonia severity index has not yet been applied to ACS but has features that are intuitively attractive. In clinical practice, transfusions are recommended whenever there is evidence of worsening pulmonary function, as evidenced by a progressive decrease in SaO₂, a decrease in PaO₂, an increase in A-aO₂ gradient, worsening infiltrates on chest radiograph, or increasing tachycardia or work of breathing. In addition to these indications, exchange transfusion may have a specific therapeutic action in the fat embolism syndrome, where normal red cells may bind the free fatty acids, preventing further pulmonary damage. Finally, exchange should be considered whenever there is general clinical evidence of a declining course or when indicators of poor prognosis are present. Exchange transfusion dilutes the proportion of sickle cells, improves the blood rheology and flow, reduces the risk of further organ damage from either intrapulmonary or peripheral sickle vaso-occlusion, and improves oxygenation (see the article by Wanko and Telen elsewhere in this issue for further exploration of this topic) [8]. The objective of
transfusion in these situations is life saving, because progressive worsening of clinical status is associated with high mortality.

Transfusion carries two risks that are particularly relevant to the sickle cell patient: alloimmunization and acute hyperviscosity. Alloimmunization data from the preoperative transfusion study indicate a 10% rate of new alloantibody formation from a transfusion intervention [105]. Subsequent transfusion therapy has an increased risk for delayed hemolytic transfusion reaction [106]; such reactions are extremely difficult to treat, because further transfusion is usually ineffective in maintaining the hematocrit. An extended phenotype match can reduce the incidence of alloimmunization [107,108] and should include Rh, C, E, and Kell antigens at a minimum [108] (see the article by Johnson elsewhere in this issue for further exploration of this topic). The hyperviscosity syndrome may occur with mixtures of A and S cells at near-normal hematocrits [109,110].

The syndrome is characterized by hypertension and altered mental status or seizure activity. Screening donor units for sickle cell trait and maintaining the posttransfusion hematocrit at levels less than 35% may prevent this syndrome. It is widely believed that a posttransfusion level of Hb S of less than 10% is therapeutically superior to one of 20% or 30%. Data in support of this con-

### Box 2: Clinical features that imply poor prognosis and are potential indications for exchange transfusion in the acute chest syndrome

**Physical Examination Findings**
- Altered mental status and other acute neurologic findings
- Persistent tachycardia >125/min
- Persistent respiratory rate >30/min or increased work of breathing (nasal flaring, use of accessory muscles, sternal retractions)
- Temperature >40°C
- Hypotension compared with baseline

**Laboratory and Radiographic Findings**
- Arterial pH <7.35
- Arterial oxygen saturation persistently <88%, despite aggressive ventilatory support
- Serial decline in pulse oximetry or increasing A-a gradient
- Hemoglobin concentration falling by 2 g/dL or more
- Platelet count <200,000/μL
- Evidence for multiorgan failure
- Pleural effusion
- Progression to multilobe infiltrates

(Data from Refs. [8,67,104].)
tention are lacking. However, the hypothesis is intuitively attractive. The simplest method of monitoring the posttransfusion Hb S level is to determine the percentage of sickled cells in a meta-bisulfite preparation. Alternatively, Hb S can be measured by one of the common column chromatography methods.

Recurrent episodes of ACS may lead to sickle cell chronic lung disease, characterized by diffuse interstitial fibrosis on chest radiograph, abnormal pulmonary function tests, symptomatic hypoxia, pulmonary hypertension, and sudden death [111–113]. The further association of recurrent ACS with premature mortality in the CSSCD [5] provides justification for aggressive secondary prevention approaches in patients with recurrent episodes, including hydroxyurea, chronic transfusion therapy, and stem cell transplantation [114].

FUTURE DIRECTIONS

Despite the recent advances in our understanding of the pathophysiology and epidemiology of ACS, there are still needs for better methods of distinguishing vaso-occlusion from fibrin or fat embolism, for rapid diagnostic tests to identify microbial infection positively, for adjunctive therapies that would affect prognosis, and for identification of factors that influence prognosis and might predict which patients will recover with supportive care alone and which will progress to pulmonary failure. Documentation of the clinical utility of sPLA₂ for ACS and its relationship to the fat embolism syndrome would be useful as an early marker for the ACS and, perhaps, for clinical severity. Potential therapies for sPLA₂ inhibition are under development, and clinical trials examining the predictive capability of sPLA₂ are under way [115].

In a recent study, dexamethasone, 0.3 mg/kg, was administered to patients who had ACS at 12-hour intervals for four doses and produced significant reductions in the treated group versus placebo with respect to duration of fever, analgesic use, supplemental oxygen therapy, transfusion requirements, and hospital stay (reduced by 40%) [116]. The beneficial effect was attributed to inhibition of sPLA₂ and inhibition of inflammation; however, this steroid also prevents cytokine induction of VCAM-1 on endothelial cells and could ameliorate the course of ACS by this mechanism as well [117]. Prolonged infusion (240 mg/d for 7 days) of glucocorticoid has been reported in studies of community-acquired pneumonia in the general population; beneficial effects on chest radiograph, oxygenation, indices of inflammation, length of hospital stay, and mortality have been shown [118]. In addition, beneficial effects of high-dose steroid in the fat embolism syndrome have been reported in small controlled trials in trauma patients [119,120] and could have produced benefit in sickle ACS, where fat embolism is common, owing to inhibition of inflammation. These results indicate the need for further studies of the efficacy of steroid use in ACS.

A beneficial effect of nitric oxide (NO) has been reported in small numbers of patients who had ACS, where inhaled NO at 80 ppm for 47 to 92 hours rapidly improved A-a gradient, reduced PAP and PVR, and was believed to have accelerated recovery [121–123]. Inhaled NO could benefit patients who have
ACS by pulmonary vascular dilation, reducing pulmonary vascular resistance and improving intrapulmonary blood flow. Further studies are needed to define the therapeutic utility and potential for methemoglobin toxicity of this agent, but its use has the potential to reduce the need for more aggressive therapies and to improve prognosis.

Purified polaxamer 188 is a nonionic surfactant that reduces blood viscosity and inhibits erythrocyte adhesion to endothelium [124]. A recent clinical trial of this agent showed a modest effect on the duration of VOC [125]. The results of the polaxamer 188 study suggest that blocking sickle cell adhesion to endothelium may be beneficial for vascular occlusive events in SCD, such as ACS. A further step in this process is the development of a recombinant P-selectin glycoprotein ligand that binds to P-selectin and, to a lesser degree, to E- and L-selectin [126]. Recent studies using monoclonal antibodies and knock-out mice have shown that P-selectin mediates the initial interaction of sickle erythrocytes and leukocytes with activated endothelial cells [127,128]. Thus, blockade of P-selectin using this fusion protein could provide clinical benefit in ACS by inhibiting the adhesion of leukocytes and sickle erythrocytes to pulmonary endothelium in the vaso-occlusive process. Additional agents that inhibit other adhesogenic proteins involved in the vaso-occlusive process, such as the integrin \( \alpha \nu \beta_3 \) and VLA-4, are also under study [129–131].

**SUMMARY**

The recent large clinical studies of ACS have improved our understanding of the pathophysiology and epidemiology of ACS. However, there are still needs for better methods of distinguishing vaso-occlusion from fibrin or fat embolism, for rapid diagnostic tests to make positive identifications of microbial infection, for adjunctive therapies that would affect prognosis, and for identification of factors that influence prognosis. The difference in clinical course and severity between children and adults supports the results of current studies indicating multiple causes for ACS. Infectious causes are more common in children, as suggested by the shorter and milder course, seasonal variation, upper lobe disease, and higher rate of bacteremia. In adults, severe bone pain and lower lobe or multilobe disease point to vascular occlusion as the common cause of ACS, much as Barrett-Connor indicated in her initial reports [4,11]. The mainstay of successful treatment remains high-quality supportive care. Consultation with pulmonary, infectious disease, and intensive care specialists is a necessary part of management. Fluid management, oxygenation, bronchodilators, and incentive spirometry are essential elements of supportive care management. The judicious use of transfusion therapy has a major role in preventing mortality in the absence of a specific therapy that consistently improves the clinical course.

**References**


