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REVIEW

Acute chest syndrome of sickle cell disease: genetics, risk factors, prognosis, and management

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ABSTRACT

Introduction: Sickle cell disease, one of the world's most prevalent Mendelian disorders, is a chronic hemolytic anemia punctuated by acute vasoocclusive events. Both hemolysis and vasoocclusion lead to irreversible organ damage and failure. Among the many sub-phenotypes of sickle cell disease is the acute chest syndrome (ACS) characterized by combinations of chest pain, cough, dyspnea, fever, abnormal lung examination, leukocytosis, hypoxia, and new radiographic opacities. ACS is a major cause of morbidity and mortality.

Area covered: We briefly review the diagnosis, epidemiology, etiology, and current treatments for ACS and focus on understanding and estimating the risks for developing this complication, how prognosis and outcomes might be improved, and the genetic elements that might impact the risk of ACS.

Expert opinion: The clinical heterogeneity of ACS has hindered our understanding of risk stratification. Lacking controlled clinical trials, most treatment is based on expert opinion. Fetal hemoglobin levels and coexistent α-thalassemia affect the incidence of ACS; other genetic associations are tenuous. Transfusions, whose use not innocuous, should be targeted to the severity and likelihood of ACS progression. Stable, non-hypoxic patients with favorable hematologic and radiographic findings usually do not need transfusion; severe progressive ACS is best managed with exchange transfusion.

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Hydroxyurea; fetal hemoglobin; SNPs; fat embolism; oxygen saturation; lung; transfusion

1. Introduction

In 1979, Sam Charache, a leading hematologist at Johns Hopkins coined the term 'acute chest syndrome' (ACS) to describe the pneumonia-like events, which were common in sickle cell disease (SCD) [1]. ACS is the second most common reason for hospitalization in SCD and is one of the top causes of mortality. Chest pain, dyspnea, cough, fever, an abnormal lung exam, particularly with wheezing, leukocytosis, hypoxia and a new infiltrate involving at least a segment of a lobe on chest radiography are its key diagnostic components. All are not required for diagnosis or be present simultaneously.

2. Epidemiology

ACS often develops 1–3 days after a hospitalization, which is usually for an acute painful episode (sometimes referred to as a vasoocclusive event or VOE). In 3,751 patients observed prospectively for at least 2 years in the Cooperative Study of Sickle Cell Disease (CSSCD), the incidence of ACS was inversely related to age. Children aged 2–4 years with the HbS-only phenotype (HbS homozygosity or HbS-β^0 thalassemia) had an incidence of 25/100 while the incidence in adults was 9/100 patient years [2]. Additional CSSCD studies highlighted the differences in ACS in pediatric and adult age groups. Children aged 2–4 years presented with fever and cough, a negative physical exam, and rarely had pain; adults often complained of dyspnea, chills, and severe pain. Upper lobe disease was more common in children; multilobar and lower lobe disease more often affected adults. Severe hypoxia occurred in 18% of adults. Bacteremia was present in 14% of infants and 1.8% of patients aged >10 years. Adults were hospitalized an average of 9 days, children for 5.4 days. Adults were 4 times more likely to die than children [3]. These studies, and many other cited below, predate the introduction of hydroxyurea and newer pharmacologic approaches to preventive treatment and management. They largely reflect ACS outside of Africa, India, and the Middle East where SCD is most common. In the Multi-institutional Study of Hydroxyurea (MSH), which lead to the FDA approval of hydroxyurea for SCD, after 9 years of follow-up patients who developed ACS at any point had 32% mortality compared with 18% in participants who avoided this complication [4]. Interestingly, in the CSSCD, the cause of nearly half of 617 ACS cases was not established despite a stringent prespecified diagnostic protocol that included viral cultures, bronchoscopy with bronchoalveolar lavage and sputum collection to detect fat emboli and infection [5].

3. Etiology

3.1. Infection

Pulmonary infections have been linked to ACS, particularly in children. However, the frequency of isolated organisms varies greatly among study populations. In one study, about 30% of

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Article highlights

- Acute chest syndrome can be caused by infarction and thromboembolism. Severity ranges from very mild to fatal.
- Predicting severity is difficult, but radiographic and laboratory studies with careful assessment of the trajectory of oxygen saturation are helpful
- Treatment, predicated on severity includes transfusion, antibiotics and cooperation among hematologists, pulmonologists, and at times, critical care specialists.
- HbF levels and the coexistent α-thalassemia affect the incidence of acute chest syndrome. Genetic variants that are directly related to the incidence of acute chest syndrome have been difficult to replicate.

ACS episodes were caused by infectious agents with a nearly equal distribution among *Chlamydia pneumoniae, Mycoplasma pneumoniae*, viruses, bacteria and mixed infection. Twenty-seven different pathogens were detected. A pulmonary infarct, diagnosed by exclusion of infection or fat embolism, was presumed present in 16% of patients [5,6]. In a study of 101 hospitalized children with a median age of 3.2 years who were screened for respiratory pathogens, 33 had *Rhinovirus*, 14 *Adenovirus*, 13 *Respiratory syncytial virus* and 11 *Parainfluenza virus. Mycoplasma pneumoniae* was detected in only one. Twenty-three of these children developed ACS. When they were compared with matched SCD patients without ACS there was no statistical association between viral detection and ACS [7]. Of 37 patients, aged 25–75 years with ACS who were admitted to an intensive care unit, 37% had an infectious etiology with *Staphylococcus aureus* isolated in 8 and a respiratory virus in 6 cases. Influenza viruses, particularly H1N1, might trigger ACS and provide a rationale for the importance of the annual influenza vaccines to mitigate this risk [5]. SARS-CoV-2 vaccination with timely boosters is strongly recommended as ACS has been associated with Covid-19 [8]. Among 36 patients admitted to the ICU with ACS *Staphylococcus aureus* was found in 8 and a respiratory virus in 6 [9]. Serologic evidence of *Mycoplasma pneumoniae* infection was present in 9% of 598 ACS cases and was associated with severe disease, with multilobar infiltrates and pleural effusions. Fat emboli were present 5 of 25 patients when adequate testing could be completed. Six percent required mechanical ventilation and 86% of patients were transfused [10]. Recent Parvovirus B19 infection was found in 24% of cases of pulmonary fat embolism [11].

3.2. Fat embolization

Severe, rapidly progressive ACS with high morbidity and mortality is often triggered by embolization of necrotic fatty bone marrow. In most instances, the presumption of fat emboli is made by clinical and hematologic characteristics rather than the diagnostic feature of fat laden pulmonary macrophages whose detection requires capture of these cells by bronchoscopy and bronchoalveolar lavage. Bone marrow infarction in sickle cell disease is likely to occur often, be patchy and remain asymptomatic. At times, the infarcted area becomes large with severe bone pain – often the worst the patient has ever experienced – in the pelvis and back. When the barrier between the hematopoietic compartment and the venous circulation is breeched, infarcted marrow can embolize to the lungs. Infarcted fatty marrow can traverse the lungs entering the arterial circulation where it can trigger an acute inflammatory response leading to multi-organ failure [12]. In 27 patients with ACS, 12 had fat embolism diagnosed by quantitative evaluation of pulmonary macrophages for intracellular fat. Compared with ACS patients without fat emboli, the affected patients were more likely to have bone pain, neurologic symptoms, longer hospitalization, >2 g/dL decrease in hemoglobin, thrombocytopenia and increased numbers of circulating nucleated red cells. In recent reviews of this syndrome, rapid progression to multi-organ failure with renal, hepatic and central nervous system disease was more common in adults than children with ACS; 6% of adults died. The development of thrombocytopenia (in contrast to the typically observed thrombocytosis in 'steady-state' SCD) was the sole predictor of rapid progression with an odds ratio of 4.82 (95% CI 1.2–19.4) [13–15]. Seizures, silent cerebral infarcts, cerebral hemorrhage, and reversible posterior leukoencephalopathy syndrome developed in five children where the severity of ACS necessitated intubation and erythrocytopheresis [16].

3.3. Dysregulated Inflammation and thrombosis

Pathophysiologically, ACS resembles other forms of acute lung injury. In transgenic sickle mouse models, histology reveals diffuse alveolar damage and there are elevated markers of inflammation both in the circulation and within bronchoalveolar lavage fluid from patients with ACS [17]. None of these inflammatory biomarkers are specific for ACS limiting their utility as potential therapeutic targets.

3.4. Asthma

Asthma can be an important modulator of ACS, particularly in children and adolescents. Physician-diagnosed asthma occurs in approximately 25% of children with SCD, but it is much less common in adults [18]. Many more children and adolescents exhibit isolated recurrent wheezing, lower airway obstruction, or airway hyper-reactivity without meeting diagnostic criteria for asthma [19–26]. Childhood asthma is associated with more frequent VOEs, earlier onset of ACS, recurrent ACS, and mortality [18,27,28]. Additionally, a history of ACS may predispose patients to a diagnosis of asthma [18]. Wheezing and other physiologic evidence of reactive airways disease such as airflow obstruction on spirometry can occur during ACS and this can contribute to the observed hypoxia, particularly in children and adolescents.

4. Treatment

4.1. Prophylaxis with hydroxyurea and transfusion

To prevent ACS (and other disease complications) most patients with the HbS-only phenotype should be started on hydroxyurea beginning, if possible, at 9–12 months of age [29–31]. Multiple retrospective and prospective studies demonstrated that hydroxyurea reduced the incidence of

ACS [32–35]. More recently, a phase 1–2 open-label trial of maximally tolerated dose hydroxyurea in 606 children with sickle cell disease aged 1–10 years was completed in four clinical trial sites in sub-Saharan Africa. There was a decreased rate of vasoocclusive pain and ACS although the rate of ACS was quite low and the results did not reach significance [36]. While there are real word studies in low resource settings suggesting the benefits of low (9–10 mg/kg/day) or intermittent-dose hydroxyurea in preventing ACS, a randomized, double-blind trial of 187 children in sub-Saharan Africa compared hydroxyurea at a fixed dose (approximately 20 mg/kg/day) with dose escalation (approximately 30 mg/kg/day) found a reduction in cases of ACS in the dose escalation group (incidence rate ratio, 0.27; 95% CI, 0.11 to 0.56) [37]. Together, these studies suggest that hydroxyurea is effective in ACS prevention, particularly when used at maximally tolerated doses.

Chronic transfusion therapy is often used in the pediatric SCD population for stroke prevention in patients with an elevated transcranial Doppler velocity by ultrasound. During the STOP (Stroke Prevention Trial in Sickle Cell Anemia) trial, 130 children with sickle-cell anemia or sickle β^0-thalassemia were randomized to chronic transfusion or usual care. Those in the chronic transfusion group had a reduction in episodes of ACS (2.2 vs 15.7 events per 100 patient-years, $P = .0001$) over 19.6 ± 6.5 months of follow-up [33]. There may be a role for chronic transfusion in ACS prevention in both children and adults, particularly those who are intolerant of hydroxyurea [29,38].

ACS is a common postoperative complication in SCD. When simple transfusion to a hemoglobin level of ~10 g/dL was compared with exchange transfusion or repeated transfusions to reduce HbS levels to about 30% of total hemoglobin, there was a 10% rate of postoperative ACS in both study arms. The simple transfusion group had half the rate of transfusion-related complications as the more aggressive transfusion group that was exposed to more units of blood [39]. A randomized trial of no preoperative transfusion ($n = 33$) compared with simple transfusion ($n = 34$) was stopped early because nine patients in the group that was not transfused developed ACS compared with one patient in the transfusion group [40]. Based on these studies, prophylactic preoperative simple transfusion with a goal hemoglobin level of ~10 g/dL is indicated for most common surgeries, particularly those requiring general anesthesia, in the HbS-only phenotypes of SCD. We recognize that this option may not be available in lower resource settings. However, we would advocate for transfusion to increase hemoglobin as close to 10 g/dL much as possible prior to surgery. Studies of pre-operative risk stratification should be undertaken to determine those most in need for transfusion. Expert opinion would support the use of transfusion for surgeries requiring prolonged general anesthesia or with anticipated blood loss of greater than 100 mL.

Some of the newly approved SCD treatments might also prevent ACS. A Phase 3 study of L-glutamine compared with placebo in 230 subjects (156 completed the trial), led to a reduction in the frequency of ACS from 23.1% to 8.6% after 48 weeks ($p = 0.003$) [41]. The monoclonal P-selectin antibody crizanlizumab was FDA approved after its Phase 2 study showed a reduction in the frequency of VOE from 2.98 to 1.63/year with high-dose crizanlizumab after 52 weeks of treatment ($p = 0.01$). While there was no difference in the rate of ACS observed, the overall frequency of events was low [42]. The frequent occurrence of ACS during acute painful episodes suggests that crizanlizumab might decrease its incidence.

Multi-modal strategies in patient care have a role in preventing ACS after hospitalization for VOE. Provider education, individualized patient care plans focused on assessing and treating hypoxemia, limiting atelectasis via early ambulation and use of incentive spirometry, treatment of acute asthma if present and judicious use of opioids was studied in 173 pediatric SCD hospitalized for VOE. There was a 50% reduction in ACS (12%, [21 of 173] vs. 25% [39 of 159]) compared with pre-protocol results ($p = 0.003$) [43].

4.2. Treatment of acute events

In the nearly total absence of controlled clinical trials, ACS management is guided by expert opinion that should be predicated on the risk for respiratory failure [44–47]. Howard and her associates provided 23 recommendations for management [48]. Especially noteworthy were the possible etiologic roles of volume overload that is typically due to diastolic dysfunction of the left ventricle and opioid-induced hypoventilation. Also noted were the poor prognosis associated with worsening hypoxia, thrombocytopenia and increasing anemia. A treatment pathway that included the use of higher levels of care such as the intensive care unit was beneficial. Little has changed since this and other reviews (Table 1). Incentive spirometry is recommended for all patients admitted to the hospital, especially those with ACS even though not all studies confirm its prophylactic efficacy [49,50]. Rib infarction, reported in up to 40% of ACS cases, can produce splinting with hypoventilation and atelectasis, hence the benefits of incentive spirometry [49,51]. Atelectasis may produce localized hypoxia in the setting of ventilation perfusion mismatch that can propagate the acute lung injury of ACS.

4.3. Transfusion

The benefits of transfusion therapy for treatment of ACS have been understood for greater than 30 years [53]. In the absence of controlled clinical trials, which are likely to be impossible to complete, the use of blood transfusion in ACS is guided by expert opinion. Transfusions are at times likely to be lifesaving. Conversely, at times, transfusions are likely to be unnecessary. The minimally affected patient, without hypoxia, with a small segmental infiltrate and little change from 'steady-state' blood counts is not likely to need transfusion. This scenario is often observed in pediatric patients and sometimes in adults. Patients with progressive hypoxemia, multilobar disease, progressive anemia, thrombocytopenia and leukocytosis will likely benefit from rapidly instituted exchange transfusion. Between the clinical extremes of 'benign' and severe ACS, the choice of whether to use simple or 'top-up' transfusion or exchange transfusions is informed by clinical experience, appraisal of a patient's clinical and laboratory findings and the rapidity

Table 1. Treatment of ACS by risk category.

Risk category	Mild	Moderate	Severe
	Need for <50% FiO_2 supplementation; single segment of a lobe affected; no thrombocytopenia, WBC <15,000, Fall in hemoglobin <1 g/dL; low grade fever T < 101 F	Need for 50–80% FiO_2, 1 lobe involved; no thrombocytopenia, WBC 15–20,000; Decrease in Hb > 1 g/dl, T > 102 F	Need for FiO_2 >80%, high flow oxygen, noninvasive ventilation, invasive ventilation, ≥ 2 lobes involved; absolute or relative thrombocytopenia, decrease in hemoglobin ≥2 g/dL; WBC > 20,000, T > 102 F
Admission	Inpatient floor	Higher level of care – stepdown unit or ICU	ICU
Incentive spirometry	Yes	Yes	Yes
Arterial blood gases	No	Yes	Yes
Transfusion	None or simple (top-up)	Simple or exchange	Exchange if possible
Antibiotics	Yes	Yes	Yes
Bronchodilators	Possible	Possible	Possible
Chronic hydroxyurea	yes	yes	Yes
Opioids	Avoid when possible	Use sparingly if needed	Use sparingly if needed

Because of the possibility of rapid progression, all adults with ACS should be admitted to the hospital and placed on telemetry for at least 72 hrs. Some mildly affected children can be treated as outpatients. Hydration should use half-normal saline solutions. Overhydration can exacerbate diastolic congestive heart failure and cause pulmonary edema. More detailed treatment guidelines can be found in Refs [52,57.

with which compatible available blood can be obtained. For mildly hypoxic patients with minor changes in blood counts, simple transfusion will usually suffice; if the patient has HbSC disease and a packed cell volume more than 30, exchange transfusion might be the prudent choice to avoid hyperviscosity. When alloantibodies make transfusion difficult, simple transfusion might be the first choice; history of delayed hemolytic transfusion reaction and the presence of uncharacterized antibodies makes the choice of any transfusion method challenging.

5. The genetics of SCD and ACS

5.1. Effects of SCD genotypes, coincident α-thalassemia and β-globin gene haplotype

The phenotype of sickle cell disease is caused by several common and many rare genotypes. The most common genotype is homozygosity for the HbS gene; second most common is compound heterozygosity for HbS and HbC genes, or HbSC disease. HbS-β thalassemia or compound heterozygosity for HbS and either a β^{0-} or β^{+}-thalassemia gene make up the third common genotype. ACS occurs in all genotypes of sickle cell disease. Its incidence in HbSC disease and HbS-β^{+} thalassemia (5 and 4/100 patient-years, respectively) is less than in sickle cell anemia and HbS-β^{0} thalassemia (13 and 9/100 patient-yea rs, respectively) [2]. Paradoxically, despite this reduced incidence, severe cases of ACS associated with multiorgan failure and necrotic fat emboli appear more common in the so-called 'milder' genotypes of HbSC disease and HbS-β^{+} thalassemia. Perhaps this is a result of increased blood viscosity due to a higher hemoglobin concentration and packed cell volume [13]. Minimally symptomatic or asymptomatic patients with HbSC disease can present to the ED with an ultimately fatal ACS as the first disease manifestation. In 3 young men with HbSC disease, severe ACS with 1 fatality was caused by necrotic fat emboli associated with Parvovirus B19 infection [54].

α-Thalassemia, present in ~30% of HbS homozygotes, modulates sickle cell anemia by reducing the intracellular concentration of HbS, decreasing HbS polymer-induced cellular damage and ameliorating hemolysis. With less hemolysis hemoglobin concentration increases. In children, coincident α-thalassemia was associated with a lower incidence of ACS (20/100 patient-years vs. 27/100 patient-years in sickle cell anemia without α-thalassemia). These same patients had higher incidence of acute painful episodes (43/100 patient-years vs. 28/100 patient-years in sickle cell anemia) [55,56]. However, in another study of 1284 patients aged <2 to >20 years, α-thalassemia was not associated with ACS [2].

The incidence of ACS is inversely related to the fetal hemoglobin (HbF) level. Bantu (CAR), Benin, Cameroon, Senegal and Arab-Indian haplotypes of the *HBB* gene cluster are associated with the HbS gene. These haplotypes reflect regions in Africa, the Middle East, and India with the highest HbS gene density and are loosely associated with overall severity of disease through their characteristic HbF levels [52]. The association of haplotype and HbF is likely to be mediated by a binding site for an uncharacterized HbF repressor that is −158 base pairs upstream of the *HBG2* gene transcription start site [52]. In 820 children, haplotype was associated with HbF and rate of hospitalization for ACS but not VOE [58]. Children with the Bantu haplotype-equivalent had the lowest HbF and highest rate of ACS hospitalization. Senegal haplotype-equivalent children had the highest HbF and lowest ACS hospitalization rate. Benin haplotype-equivalent patients were intermediate. Adults with the Arab-Indian haplotype of sickle cell anemia or HbS-β^{0} thalassemia, which have an average HbF of 16%, had a 47% prevalence of ACS [59]. Children with HbS-β^{0} thalassemia and 22% HbF had 3 episodes of ACS/100 patient-years compared with 14/100 patient-years in sickle cell anemia with 10% HbF even though their total hemoglobin level was 1 g/dL higher [60].

In addition to regulation by elements linked to the haplotype of the HbS gene, HbF levels are regulated by *BCL11A* and *MYB*, whose products are repressors of HbF gene expression [52]. Single-nucleotide polymorphisms (SNPs) in *BCL11A* and *MYB* have been associated with the incidence of VOE. With the observed increase in HbF levels and decreased incidence of

VOE, it is likely that variants of *BCL11A* and *MYB* will also reduce the incidence of ACS, although this has not been directly tested [61].

5.2. Genetic association studies and ACS

Besides the studies of HbF-associated genetic modulation or α-thalassemia, candidate gene or genome-wide association studies (GWAS) studies of ACS rarely return replicable results. A sharply defined phenotype is a prerequisite for genetic association studies making the multifactorial etiology of ACS inimical to the precision required. Genetic association studies of the ACS phenotype, while numerous have unfortunately not provided new mechanistic, therapeutic, or prognostic insights.

Combined *P*-values from a discovery and replication cohort of 1514 patients from the CSSCD and 2 smaller replication cohorts revealed that the SNP rs614893, located in an intergenic area between *COMMD7* and *DNMT3B* on chromosome 20, was associated with ACS in the discovery cohort but not in the other smaller replication cohorts where the association between ACS and rs6141893 only trended in the right direction. ACS was defined differently in the three cohorts studied and the mean ages of patients in the cohorts were very different. *COMMD7* encoding an adaptor protein that interacts with subunits of the nuclear factor (NF)-κB complex is highly expressed in the lung [62].

In an unreplicated candidate gene-based study of *HMOX1* promoter polymorphisms affecting gene expression, children with shorter alleles had lower rates of hospitalization for ACS after adjusting for sex, age, history of asthma, percentage of HbF and α-thalassemia [63].

ATT intronic repeat polymorphisms of *NOS1* were associated with exhaled nitric oxide levels in 13 children with ACS. In 86 children [64] *NOS1* AAT repeats were associated with the risk of ACS in patients without physician-diagnosed asthma [65]. *NOS1* SNPs were not associated with ACS in the studies of Galarneau [62]. In another unreplicated study, the T786C SNP in *NOS3* was associated with ACS only in females [66]. In contrast, *NOS3* C786 alleles were associated with a decreased risk of ACS in 157 children [67]. In this same study, the *ET1* T8003 allele was associated with an increased ACS incidence. A SNP in *VEGFA*, rs3025020 (−583 T) was associated with low VEGF serum levels and an increased risk of ACS in 351 children with a history of ACS and 261 without ACS [68]. Null genotypes of the antioxidant enzymes *GSTM1* and *GSTT1* null were associated with an increased risk of ACS (and other disease complications) in 278 sickle cell anemia patients [69].

Candidate gene association studies of multiple sickle cell disease sub-phenotypes including ACS found several genes of the TGF-β (transforming growth factor-β)/Smad/BMP (bone morphogenetic protein) pathway, associated with ACS and other sub-phenotypes [70,71]. This very complex pathway affects many processes felt to have roles in the pathophysiology of sickle cell disease. GWAS have failed to replicate the results of candidate gene-based studies. To meet GWAS evidence of statistical significance thousands of subjects are required when the contribution of a genetic variant to a phenotype is small, as it is likely to be in ACS, and the trait being studied is polygenic. ACS presents a very difficult phenotype to analyze genetically and sufficiently large studies that might be able to confidently detect these genetic associations have not been done.

6. Predicting ACS and markers of ACS severity

Who will develop ACS and how severe will it be are questions of prognostic and therapeutic importance. Of 247 sickle vasoocclusive events that led to hospitalization of patients aged 27.7 ± 7.3 years, 18% developed ACS. A predictive score that included decreased reticulocyte counts and increased leukocyte counts plus spine and pelvic pain had a 98.8% negative-predictive value but only a 39.5% positive-predictive value for incident ACS [72]. A retrospective analysis of less than half this number of patients who were compared with 20 controls without ACS found, as expected, many differences between the groups. Fever, reduced oxygen saturation, low hemoglobin concentration, and leukocytosis were predictors of ACS [73]. In children younger than 4 years of age, wheezing and positive skin tests for allergens were predictive of future ACS [18]. Nevertheless, despite the high incidence of airway hyper-responsiveness in sickle cell disease, when measured by methacholine challenge, hyper-responsiveness alone was not predictive of ACS or vasoocclusive pain episodes [74].

6.1. Current diagnostic approaches

Few recent advances have changed the approach to diagnosis and treatment of ACS. Management is heavily based on expert opinion. Frequently, ACS occurs 1–3 days after hospital admission for VOE, but it can occur independent of an acute painful episode. A high degree of suspicion is paramount in making this diagnosis early and appropriately risk stratifying patients insofar as possible.

ACS presents some diagnostic challenges as numerous coexisting conditions can trigger or perpetuate lung injury. These include (1) acute asthma exacerbations, particularly in children and adolescents; (2) acute pulmonary thromboses/thromboembolism; (3) acute congestive heart failure, typically due to diastolic dysfunction of the left ventricle; (4) atelectasis and alveolar hypoventilation in the setting of pain related reduced inspiratory effort/chest wall splinting and the respiratory suppressive effects of the intravenous opioids used to treat VOEs. When making the diagnosis of ACS, one must consider these possibilities in conjunction with respiratory infections.

6.2. Diagnostic testing

In addition to history and physical examination and the usual vital signs, assessment of oxygenation via pulse oximetry and/or arterial blood gas sampling is essential, particularly in adults. All patients with a clinical suspicion for ACS should have complete blood counts, reticulocyte count, renal and liver function testing and, depending on the clinical status, blood type and hold or crossmatch for possible transfusion. Blood cultures and other microbiologic workup for viral and atypical organisms can help

guide the choice of antimicrobials that are nearly always given even in the absence of proven bacterial infection [52]. In adult patients, brain natriuretic peptide or N-terminal-pro brain natriuretic peptide levels are increased in both acute congestive heart failure and pulmonary embolism. Chest radiography is key to the diagnosis. The new infiltrate must involve at least one segment of a lobe to be diagnostic. Sometimes, radiologic evidence of atelectasis and linear scarring will be present; this is not consistent with a diagnosis of ACS yet might be responsible for some or all the observed hypoxia.

Point-of-care lung ultrasonography has gained interest in the diagnostic management of a wide spectrum of pulmonary conditions due to its lack of radiation exposure, portability, and ease of use. Point-of-care lung ultrasonography was performed on 191 SCD patients with a mean age of 8 years; 17% of patients were diagnosed with ACS. Accuracy of point-of-care lung ultrasonography to detect ACS was 92%, with a sensitivity of 88%, and specificity of 93% compared with chest radiography [75]. Computed tomography (CT) pulmonary angiograms are often used diagnostically in ACS. They should be considered in patients for whom the degree of hypoxia is not explained by chest radiography, or for those where there is suspicion for acute pulmonary embolism. Bronchoscopy and ventilation/perfusion scanning in the diagnosis of ACS is generally not helpful [52].

6.3. Secretory phospholipase A_2

Secretory phospholipase A_2 ($sPLA_2$) cleaves free fatty acids that can circulate with fat embolism. One study of 21 admissions for an acute painful event found increased $sPLA_2$ in 6 cases who subsequently developed ACS [76]. $sPLA_2$ levels were highest in ACS compared with patients who had pneumonia but did not have SCD and SCD patients without ACS. The levels of $sPLA_2$ correlated with severity of ACS [77]. Fifteen patients with ACS and elevated $sPLA_2$ were randomized to receive either a single transfusion or standard care. Five of eight standard care patients developed ACS compared with none of the seven transfused patients. While the *P*-value of these differences was 0.026 the confidence interval of 1, 557 was extremely wide [78]. A multicenter study of 43 patients suggested an 80% reliability of $sPLA_2$ to predict ACS [79]. $sPLA_2$ remains a research biomarker with little utility for diagnosis and management in the clinical setting as its measurement is not available in most hospital laboratories. Whether it is reflective of some specific pathophysiology of ACS or is it just another marker of inflammation is unsettled.

6.4. Determining ACS risk and severity

Severe chest, spine or pelvic pain, magnitude of fever and oxygen saturation coupled with reticulocyte, leukocyte, and platelet counts provide a guide to whether a patient with an acute VOE has or is likely to develop ACS. Impending severe ACS due to fat embolization is suggested by reticulocytopenia, leukocyte counts >20,000/dL, LDH levels >1500 IU, more than few nucleated red cells in the blood and thrombocytopenia $<150 \times 10^9$/L. Additional risk factors for severe ACS most likely to requiring mechanical ventilation include multilobar disease on chest radiography and a history of pulmonary hypertension or cardiac dysfunction [12,80,81].

Stratification of ACS severity is based upon clinical features associated with risk for clinical deterioration and death. One important factor is the degree of respiratory compromise as assessed by the degree of hypoxia. The optimal target oxygen saturation in SCD is unclear, but expert opinion is that an oxygen saturation <95% is abnormal. In adults, an initial oxygen saturation or partial pressure of oxygen on arterial blood gas sampling may be helpful initially but perhaps the trajectory of hypoxia is most essential to the assessment. Additional factors to consider in assessing the severity of ACS are the presence of chronic end-organ failure prior to the event and the development of acute organ failures during the event. Acute and chronic organ dysfunction, particularly of the heart, lungs, brain, and kidneys, are common in SCD and their presence may increase mortality risk in ACS [82–84]. Most notably, this is observed in patients with co-existent pulmonary hypertension [85]. Pulmonary hypertension diagnosed by right heart catheterization occurs in 6–10% of adults with the HbS-only phenotype. During ACS, an acute rise in pulmonary artery systolic pressure can occur leading to acute right-sided congestive heart failure and increased mortality risk [85]. The National Acute Chest Syndrome study group found that the presence of an acute neurologic event, present in 11% of patients was associated with a 46% risk of acute respiratory failure [5]. Acute kidney or hepatic injury, coagulopathy, and/or shock all can occur and each of these could increase ACS severity.

7. Long-term impact of ACS on pulmonary function

The impact of ACS on subsequent chest radiography and pulmonary function can be quite variable. Scarring and fibrotic changes of the lungs can be observed radiographically, particularly on chest tomography scanning [6]. Recurrent ACS has been associated with reduced lung function in young adults and children [86–88]. Pulmonary function testing data were reviewed in 310 CSSCD HbS homozygotes, aged 20–67 years that included 210 with a history of prior ACS. Ninety percent of subjects had abnormal pulmonary function with restrictive disease and an abnormal diffusion capacity predominating. There was no difference observed in these patterns in those with a history of ACS, but there was a trend toward lower total lung capacity and hemoglobin-adjusted diffusing capacity compared with 89 individuals without ACS [89].

8. Expert opinion

Except for point-of-care lung ultrasonography few recent advances have informed the diagnosis and treatment of ACS. Most treatment is based on expert opinion rather than controlled clinical trials. We recommend that all patients hospitalized with acute painful episodes be monitored with continuous pulse oximetry for the first 72 hours of admission. It is within this period that most new episodes of ACS following an acute VOE will occur. One means for stratifying ACS severity, particularly in adults, is by the amount of required oxygen supplementation/

ventilatory support. In adults, mild disease is consistent with a need for 50% or less fraction of inspired oxygen (FiO_2) supplementation; moderate disease requires a need for 50–80% FiO_2 and severe disease requires >80% FiO_2 or the need for noninvasive or invasive ventilation. Early monitoring might also help prevent sudden cardiac death during this fraught interval. Recommendations for treatment based on the severity of ACS are summarized in Table 1.

The gold standard for measuring blood oxygen content is an arterial blood gas with co-oximetry that measures carboxyhemoglobin and methemoglobin. Widespread implementation of pulse oximetry provided clinicians with a noninvasive assessment, which is cost-effective and easy to use. However, the accuracy of pulse oximetry in patients with SCD, particularly during VOE and/or severe anemia, has been questioned due to rightward shifts of the oxyhemoglobin dissociation curve and variant hemoglobins, which absorb light at the two wavelengths analyzed by pulse oximetry thereby confounding this measurement. However, sequential readings in the same patient are clinically reliable and should be used [90]. There is controversy concerning the appropriate normal oxygen saturation range in SCD. The adaptive rightward shift of the oxyhemoglobin dissociation curve in the setting of severe anemia suggests that oxygen saturation targets appropriate for the general population may not be applicable in SCD [91]. Many clinicians target an oxygen saturation of >92–94% in patients with SCD, but there is scanty literature to support this practice. Using supplemental O_2 in patients who are not hypoxic is unlikely to be helpful, and some very small studies suggest prolonged continuous O_2 supplementation can affect erythropoiesis [92].

In our practice, adult patients hospitalized with a VOE and/or ACS are treated with incentive spirometry and venous thromboembolism prophylaxis. Patients diagnosed with ACS are often placed in an environment where they can receive a higher level of care such as an intermediate or intensive care unit. Intravenous fluids should be used judiciously (1–1.5 mL/kg ideal body weight per hour) to prevent development of acute diastolic congestive heart failure. Diastolic dysfunction is common in SCD and often can be subclinical until an excess of fluids from transfusions and intravenous hydration occurs [93]. While an infectious agent is uncommonly identified in ACS, many favor the empiric use of antibiotics to cover the atypical organisms including *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* and encapsulated bacteria including *Streptococcus pneumoniae* and *Haemophilus influenzae*. Transfusions, whose use not innocuous, should be targeted to the severity and likelihood of progression of ACS [52,57]. Factors that support the use of transfusion therapy include severity of anemia, presence of thrombocytopenia, and organ failure. Stable, non-hypoxic patients with favorable hematologic and radiographic findings need not be transfused; severe progressive disease is best managed with exchange transfusion.

The severity of ACS ranges from mild and self-limited, particularly in children under the age of 5 years, to multiorgan system failure and death that is more common in adults. This lack of uniformity makes the development of an ACS risk and severity stratification algorithm a priority for clinical care and clinical trials.

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