platelet and endothelial surfaces. After heparin therapy is stopped, these antibodies remain and trigger thromboembolic complications in many HIT cases. Thus, therapy of HIT is not just stopping heparin treatment. Anticoagulation may not only be needed for the original indication, but for the high risk of thromboembolism due to HIT antibodies. Clinical benefits and platelet recovery were demonstrated in prospective trials of alternative anticoagulants in HIT. Based on these studies, consensus guidelines recommend immediate therapy of HIT to limit thrombin generation, either with one of the direct thrombin inhibitors lepirudin or argatroban, or the factor Xa inhibitor danaparoid, a desulfated heparinoid. Only danaparoid is approved for thrombolytic use in patients with previous HIT. LMWH crossreacts with HIT antibodies and should never be used in HIT. All three alternative agents are not reversible, cause bleeding, and have contraindications and pharmacodynamic quirks that mandate involvement of a clinician familiar with their use. The use of warfarin alone during the acute phase of HIT is discouraged, due to reports of thrombosis from warfarin-mediated protein S depletion in the face of ongoing antibody-mediated thrombin generation. Interestingly, HIT antibodies are transient and HIT antibody generation does not involve an anamnestic response. The platelet factor IV heparin enzyme-linked immunosorbent assay remains positive for an average of 3 months, while the heparin-induced platelet activation assay (serotonin release) remains positive after an average of 50 days. Reflecting this, Lubenow and colleagues found that subjects with prior HIT who were inadvertently reexposed to heparin after 3 months rarely had early HIT develop; their circulating antibodies had cleared. Nonetheless, all HIT patients should have heparin listed as an allergy, and any future heparin therapy can be done only for compelling indications, only when HIT antibodies disappear, and for as briefly as possible. Substitution of alternative anticoagulants may be safer, though their use for cardiac bypass and in renal failure is problematic. Recurrent HIT due to inadvertent readministration of heparin within 3 months of the first HIT event is well documented and preventable.

How do we lessen the punch of HIT? Early diagnosis and immediate cessation of heparin therapy are necessary. Urgent administration of an alternative anticoagulant is recommended. We should rarely stop heparin therapy before day 5 in heparin-naïve patients, as we have learned that HIT is unlikely in that group. Avoiding heparin use in routine catheter flushes should prevent some HIT. Future prevention may involve more widespread use of LMWH or alternative anticoagulants in place of UFH. The higher cost of these agents and the low incidence of HIT from UFH therapy limits the appeal of such a strategy. For now, HIT is here to stay.

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Does Splinting From Thoracic Bone Ischemia and Infarction Contribute to the Acute Chest Syndrome in Sickle Cell Disease?

Research into and treatment of sickle cell disease (SSD) have been the province largely of hematologists and pediatricians. With the realization that
pulmonary complications, both acute and chronic, are major causes of morbidity and mortality in patients with this disorder, pulmonary and critical care specialists who treat adults have begun to focus on this disease as well. Mortality rates for patients with sickle cell anemia have declined, with the median age at death being 42 years for men and 48 years for women. Factors leading to increased survival into adulthood include penicillin prophylaxis, Haemophilus influenzae and Streptococcus pneumoniae vaccinations, widespread use of newborn screening programs for early detection, and improvements in parental education. In the Cooperative Study of Sickle Cell Disease, acute chest syndrome (ACS) was the second most common complication, exceeded only by painful vaso-occlusive crisis (VOC), and was the most common condition at the time of death.

SSD is characterized by microvascular occlusions that result in acute and chronic ischemic damage to the lungs, kidneys, spleen, skeleton, skin, and CNS. Hemoglobin S rapidly polymerizes when deoxygenated due to the single substitution of hydrophobic valine for glutamic acid on the β-globin chain. Conditions that promote sickling are high concentrations of S hemoglobin in the RBCs, hypoxia, slow organ transit times, low pH, and cellular dehydration. The S hemoglobin polymers lead to a distortion of the RBC membrane shape (ie, “sickling”) and to a rigidity that retards transit through the microvasculature. In addition to this mechanical obstruction of the microvasculature, increased adhesion of RBCs to the endothelium occurs as a result of increased levels of circulating inflammatory cytokines; microvascular thrombosis; endothelial damage and cellular interactions among the RBCs, WBCs, and endothelial cells. These mechanical and molecular events all contribute to the obstruction of arterioles and to ischemic damage to tissues.

The major acute pulmonary complication of SSD is ACS, although it has been suggested that asthma and pulmonary thromboembolism also occur with increased frequency. ACS has been defined as the presence of a new pulmonary infiltrate (involving at least one complete lung segment, not atelectasis) with chest pain, a temperature of >38.5°C, tachypnea, wheezing, or cough in a patient with SSD. Multiple pathogenetic mechanisms are thought to lead to this syndrome, including fat emboli from infarcted bone, pulmonary infection, atelectasis from splinting due to thoracic pain during VOC, in situ thrombosis, vascular injury due to cell-cell interactions and inflammatory mediators, and thromboemboli (in some cases).

The National Acute Chest Syndrome Study Group reported on 671 episodes of ACS that were treated in 30 centers. Half of the patients were admitted to the hospital for a reason other than ACS, mostly VOC. Clinical findings of patients with ACS developed in a mean of 2.5 days after hospital admission. A specific cause (eg, pulmonary infection or fat embolism) for the ACS was found in 38% of all episodes and in 70% of episodes with complete data. Pulmonary infection, caused by 27 different organisms, was present in 36% of episodes, with Chlamydia, Mycoplasma, and viruses being the three most common pathogens. Fat emboli, with or without outflow infection, were present in 8.8% of patients, pulmonary infarction was inferred in 16% of patients, and in 46% of patients the cause was unknown. Pleural effusions were present in 36% of patients at the time of diagnosis, and in 55% during the hospitalization. Bilobar involvement was typical. Thirteen percent of patients required mechanical ventilation, 11% had neurologic symptoms, and 9% of those >20 years of age died. Children, in contrast to adults, were more likely to present with fever, cough, and wheeze, with upper and middle lobe opacities present on chest radiographs. Adults had more chest pain, limb pain, and dyspnea, with fever and cough occurring in only about 60% of patients. These differences may reflect differences in the relative frequencies of etiology, with children presenting with ACS due to pulmonary infection and adults more commonly presenting with VOC complicated by subsequent fat emboli and ACS. In this sense, pain is a prodrome of the ACS, indicating the need to monitor for and try to prevent its development in those admitted to the hospital for VOC.

The lung plays an important role as the processing site for protecting the arterial circulation and organs from bombardment by sickled cells containing polymerized hemoglobin S. As oxygen loading takes place in the well-ventilated lung, desickling rapidly occurs. It is thought that when thoracic pain is present in a patient experiencing a VOC, splintering leads to regional hypoventilation, hypoxia, and atelectasis, which can cause intravascular in situ sickling in the pulmonary capillaries, leading to lung infarction. When lung dysfunction develops in a patient with VOC, a vicious cycle develops because of the loss of the lung’s role in desickling. Incentive spirometry and pain control should help to prevent these events.

Bellet and colleagues did a prospective, randomized trial of incentive spirometry in 29 patients with SSDs who were hospitalized with acute chest or back pain above the diaphragm. The incidence of thoracic bone infarction (in the ribs, vertebra, or sternum), documented by nuclear bone scan, was 39.5% (15 of 38 hospitalizations). Patients randomized to incentive spirometry took 10 maximal inspirations every 2 h between 8 AM and 10 PM and while awake during
the night until chest pain subsided. A subsequent chest radiograph showed pulmonary complications (atelectasis or infiltrates) in only 1 of 19 hospitalizations of patients assigned to the spirometry group, compared with 8 of 19 in the nonspirometry group \( (p = 0.019) \). Among those with thoracic bone infarction, no pulmonary complications developed in those assigned to the spirometry group during a total of seven hospitalizations. Complications developed during five of eight hospitalizations in the nonspirometry group \( (p = 0.025) \). The mean hospital length of stay was 6.4 days when a pulmonary complication occurred and 3.6 days when no pulmonary complication developed \( (p = 0.001) \). The duration of hospitalization was not different between the incentive spirometry group and the control group, however. It is important to recognize that the end point that improved was the presence of radiographic opacities \( (i.e., \) the mild end of the spectrum of ACS), not the full-blown ACS as defined by the National Acute Chest Syndrome Study Group.\footnote{12}

Incentive spirometry is now recommended for prophylaxis of ACS in VOC and in the perioperative period.\footnote{2}

In this issue of CHEST (see page 43), Needleman and colleagues at the Children’s Hospital at Montefiore (Bronx, NY) provide data that are supportive of the idea that thoracic pain in a VOC leads to ACS, in part due to shallow breathing. This study used respiratory inductive plethysmography (RIP) to evaluate breathing patterns in 25 patients with SSD who were admitted to the Sickle Cell Center Day Hospital for the treatment of VOC. In comparison to those with pain at other sites, the 10 patients with thoracic cage pain had a lower tidal volume \( (355 \text{ vs } 508 \text{ mL}, \text{ respectively}; p = 0.003) \) and a higher respiratory rate \( (23 \text{ vs } 17 \text{ breaths/min, respectively}; p = 0.03) \). After treatment with opiate medication, these differences became insignificant. This study provides additional support for the concept that a low tidal volume-high respiratory rate pattern of breathing \( (i.e., \) “splinting”) due to thoracic pain in a patient experiencing a VOC leads to regional hypoventilation, atelectasis, alveolar hypoxia, and subsequent intravascular sickling in the lung, which is part of the pathophysiology of ACS. It also suggests that adequate analgesia is an important part of preventing ACS in those with thoracic pain by allowing larger tidal volumes. Aldrich, an investigator in this study, and colleagues\footnote{14} have shown in an animal model that regional hypoxia and/or the resulting vasoconstriction causes the mechanical entrapment of sickle cells, which is reversible with a relief from hypoxia.

There are some inconsistencies in the data that undermine the certainty of the conclusions, although this is likely due to the small study size, an inadequate dose of the opiate, or the use of a suboptimal pain questionnaire. Pain scores and breathing patterns were not significantly changed by opiate administration in the group with chest pain or in the group with pain at other sites, although the baseline differences in tidal volume and respiratory rate between the groups became nonsignificant after pain medication. This weakens the conclusion that the relief of chest pain by opiates leads to a less shallow pattern of breathing. It would be premature to conclude from this study that RIP should be used routinely to monitor breathing patterns in patients with VOC to prevent ACS since this study was not designed to evaluate the impact of RIP on clinical outcomes.

The number of recurrent episodes of ACS, as well as a history of painful VOC with chest pain and aseptic bone necrosis, are the risk factors for sickle cell chronic lung disease.\footnote{15} This chronic condition is characterized by pulmonary vascular bed obliteration, smooth muscle hypertrophy, and parenchymal fibrosis. Chest radiographs show reticular changes. Mixed restrictive and obstructive features are seen with reduced FEV\textsubscript{1}/FVC ratio, total lung capacity, and diffusing capacity. The late stages are characterized by hypoxemia, pulmonary hypertension, and cor pulmonale. This emphasizes the importance of the prevention and treatment of ACS. Rarely, pulmonary hypertension can be due to chronic unresolved large-vessel thromboembolism. Successful pulmonary thromboendarterectomy has been performed in patients with SSD.\footnote{16}

The current treatment for patients with ACS includes treatment aimed at the many factors that may contribute to its pathogenesis. The liberal use of fluids to prevent hemoconcentration, supplemental oxygen to reverse sickling, incentive spirometry, and adequate pain control are central elements of treatment.\footnote{2} Therapy with antibiotics, including a macrolide or quinolone that is active against atypical pneumonia organisms, should be included in a treatment regimen, although it is clinically difficult to determine which patients with ACS have pneumonia.\footnote{4,12} Some investigators have advocated the routine use of bronchoscopy with BAL for the quantification of fat-laden alveolar macrophages to assess for bone marrow/fat emboli, but this procedure is likely to guide therapy only in selected cases, and its routine use is not indicated.\footnote{12,17–19} One study\footnote{20} found a high proportion of pediatric patients to have plastic bronchitis with bronchial casts, which were removed by lavage and suction with the bronchoscope. Bronchodilators are given to the patient when wheezing or airflow obstruction is present, and some investigators recommend its routine use in all pa-
patients.12 The simple transfusion of RBCs that are depleted of leukocytes and matched for Rh, C, E, and Kell antigens results in improved oxygenation with reduced alloimmunization and seems the equal of exchange transfusion.12 This is indicated for most patients with ACS, particularly those with the more severe forms of ACS such as respiratory failure, moderate or severe hypoxemia, or a worsening clinical course.12,19 Therapy with corticosteroids and nitric oxide may be helpful during ACS, and patients with recurrent bouts of VOC or ACS may benefit from hydroxyurea or bone marrow transplantation.2–4,10,21,22

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The Quick and the Dead

The Importance of Rapid Evaluation of Infiltrates in the Immunocompromised Patient

The development of pulmonary infiltrates in an immunocompromised patient remains a difficult diagnostic challenge. The differential diagnosis for pulmonary processes in this population is broad and includes both infectious and noninfectious causes. In addition to bacteria, fungi, viruses, mycobacteria, and protozoa may infect the lung. Similarly, the clinician must consider noninfectious etiologies, such as progression of underlying disease, pulmonary edema, treatment-related toxicity, alveolar hemorrhage, and bronchiolitis obliterans organizing pneumonia. The prognosis for immunosuppressed patients with pulmonary complications is grim, irrespective of the factors leading to the altered immune status. For example, in subjects who require mechanical ventilation (MV) following hematopoietic stem cell transplantation (HSCT), multiple studies1–3 document that mortality rates exceed 50%. Nonetheless, utilization of immunosuppression is expanding, with increasing numbers of both solid-