Serum Biomarkers for Identifying Acute Chest Syndrome Among Patients Who Have Sickle Cell Disease and Present to the Emergency Department

James T. Naprawa, MD*; Bema K. Bonsu, MBChB*; Deborah G. Goodman, RN*; and Mark A. Ranalli, MD‡

ABSTRACT. Objective. To compare the accuracy of biomarkers for identifying acute chest syndrome (ACS) in patients with sickle cell disease presenting to a pediatric emergency department (ED).

Methods. We conducted a 13-month-long (2002–2003) cohort study with nested case-control in patients with sickle cell disease presenting to the pediatric ED with vaso-occlusive crises or fever in which we compared levels of secretory phospholipase A2 (sPLA2), endothelin-1, interleukin-6 (IL-6), and peripheral white blood cell count (WBC) in cases that were complicated by ACS and in control subjects with uncomplicated illnesses. For diagnosis, a test was considered to be accurate when the area under its receiver operator characteristic curve (AUC) was >0.70. Laboratory tests with AUC values ≥0.70 were entered into a binary recursive partitioning model for diagnosis.

Results. For the period of study, samples from 72 visits were obtained from 51 patients who presented with vaso-occlusive crises (range: 1–4 visits per patient; 15 were enrolled more than once). ACS complicated 19 of 72 visits (26%, 95% confidence interval: 17%–38%). At an AUC value of 0.79, only the sPLA2 test was accurate for diagnosing ACS. AUC values for peripheral WBC, endothelin-1, and IL-6 were 0.68, 0.51, and 0.52, respectively. Binary recursive partitioning retained only sPLA2 at a cutoff of 13.7 ng/mL to be accurate for diagnosis. This cutoff had a sensitivity of 74% (14 of 19), a specificity of 87% (46 of 53), a positive likelihood ratio of 5.6, and a negative likelihood ratio of 0.18.

Conclusions. Secretory phospholipase A2 but not endothelin-1, IL-6, or WBC is an accurate test for identifying present or incipient ACS in young patients who present to the ED with sickle cell pain crises. Pediatrics 2005;116:420–425. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-2107; emergency medicine, sickle cell disease.

ABBREVIATIONS. ACS, acute chest syndrome; SCD, sickle cell disease; VOC, vaso-occlusive crises; sPLA2, secretory phospholipase A2; IL, interleukin; ED, emergency department; WBC, white blood cell count; ROC, receiver operator characteristic; AUC, area under the curve; Sao2, oxygen saturation.

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A cut chest syndrome (ACS), a combination of respiratory symptoms and radiographic evidence of new pulmonary infiltrates, is the second leading cause of hospitalization in patients with sickle cell disease (SCD). The success of simple blood transfusions in the treatment of overt ACS is well established and raises the possibility of using such therapy earlier in the course of illness. Symptoms of impending ACS, however, may be subtle, limiting the utility of the clinical examination. In fact, a recent study reported that half of ACS cases were diagnosed after patients had been admitted to the hospital with other complaints (most commonly, vaso-occlusive crises [VOC]).

A strategy of routine chest radiographs in patients who present with VOC may identify early cases of ACS but is undesirable because of the hazards associated with repeated exposure to radiation. Fortunately, other possibilities exist. A promising test is the level of secretory phospholipase A2 (sPLA2). In one small study, elevation of this enzyme predicted impending ACS in children with VOC. No attempts have been made, however, to validate these findings at other sites. Another test is the endothelin-1 level in plasma, which has been shown to rise in VOC but has not been evaluated for predicting ACS. Finally, peripheral blood leukocytes and interleukin (IL) levels increase in many inflammatory conditions and so may have value for detecting ACS. Among ILs, an attractive target for study is IL-6, a pleiotropic proinflammatory protein with many biologic activities that is reported to correlate positively with the number and adhesiveness of neutrophils in SCD.

For now, it is not clear how these biomarkers change in response to ACS. In this study, we addressed this question. Specifically, we validated the accuracy of sPLA2 in a new setting and compared its performance with that of other tests. For ACS detection, we also defined optimal test cutoffs and evaluated a strategy that combines these tests for diagnosis.

METHODS

In this prospective study, we enrolled patients who have SCD (hemoglobin SS, hemoglobin SC, hemoglobin S β-thalassemia) and presented to a pediatric emergency department (ED) with a chief complaint of bone pain, fever, and/or respiratory symptoms from January 2002 to February 2003. Eligible were SCD patients who regularly receive medical care at the hematology clinic of our institution, an academic children’s hospital that, alone, provides specialized health care to children with SCD in central Ohio. Patients were eligible for enrollment at >1 visit during the period of study. Informed consent was obtained from all participants before enrollment in the study.
Blood samples were collected from 52 children who presented to the ED on 81 occasions (1–4 visits per child; 15 enrolled more than once). Samples were collected in the ED except for 1 obtained in the outpatient hematology clinic. Five samples were excluded because they were extraneous samples obtained from hospitalized participants who already had a study specimen collected in the ED. Four additional samples were excluded because they were mislabeled. Mislabeled blood samples were not redrawn, and information for the corresponding visits were excluded from data analysis.

After these 9 visits were removed, 72 visits by 51 patients were retained in the data set for analysis. The median age at retained visits was 12.1 years (interquartile range [IQR]: 6.9–16.6 years; 1 participant at 26.7 years was the only patient who was older than 20 years). Boys constituted 63% (32) of participants. Fever (temperature in triage >38°C) was documented in triage at 10 visits. Arms and legs (30 patients >1 location) were the most common sites of bone pain. Chest radiographs were performed at all visits for fever and at 33 (49%) of 62 visits for VOC at which fever was absent. All visits for fever, and 34 of 62 visits for VOC without fever resulted in admission to the hospital.

ACS complicated 19 (26%) of 72 visits (15 patients). ACS was diagnosed in the ED at 13 visits and within a 7-day interval after such an encounter at 6 visits (during hospitalization at 4 visits and on return to the ED after discharge to home at 2 visits). Table 1 shows demographic and clinical features, as well as results of selected biomarkers at 19 visits that were assigned a diagnosis of ACS. For the remaining 53 visits in 36 patients who did not receive a diagnosis of ACS, ACS was excluded on the basis of the clinical examination without the aid of chest radiographs at 26 (49%) visits. There were no differences in age and gender distributions of patients with and without ACS.

At an AUC value of 0.79 (unchanged after adjusting for intrapatient correlation), only the sPLA2 test exceeded the nominal AUC threshold value of 0.7 (Fig 1). AUC values for other tests were 0.68 for WBC, 0.51 for endothelin-1, and 0.52 for IL-6. The median sPLA2 level among children with ACS was 29.7 ng/mL (IQR: 6.5–53.7 ng/ml). This varied significantly from a median of 5.9 ng/mL (IQR: 1.9–9.2 ng/ml) noted in children without ACS (P = .0002). When entered into the recursive partitioning model, only the sPLA2 test at a level of 13.7 ng/mL was chosen to be optimal for diagnosis with sensitivity of 74% (14 of 19), specificity of 87% (46 of 53), positive likelihood ratio of 5.6, and negative likelihood ratio of 0.18. Peripheral blood WBC, endothelin-1, and IL-6 were not retained for diagnosis after 10-fold cross-validation.

For 53 visits that were not assigned a diagnosis of ACS, pain was the presenting complaint at 49 visits and fever at 4 visits. When pain was the presenting complaint, it was localized to the chest at 13 of 49 visits. Chest radiographs that were performed to
evaluate chest pain at these 13 visits showed no new pulmonary infiltrates. Nine of 13 visits for chest pain resulted in hospitalization for pain management. All were discharged without complications. For the remaining 36 visits with pain localized to other sites, 13 patients were hospitalized for pain management and none developed ACS. Patients of all 4 non-ACS visits for fever had negative chest radiographs in the ED and did not develop ACS on admission or after discharge to home.

Of the 53 visits that were not assigned a diagnosis of ACS, the sPLA2 level was >13.7 ng/mL during 7 visits. The chief complaint in 2 of these visits was chest pain (1 also had a cough). Fever and dyspnea were the chief complaints in a third visit. Fever alone was the chief complaint in a fourth. Each one of these 4 patients had a normal chest radiograph in the ED. The remaining 3 had pain crises alone (no chest pain). None of these patients had a chest radiograph, and none went on to develop overt ACS.

Thirteen of 19 visits that were designated as ACS were established at the initial ED encounter by chest radiographs that revealed a new pulmonary infiltrate. Six (32%) remaining cases in 5 patients (patients 3, 4, 5, 8, and 9; Table 2) were not diagnosed at the initial ED visit but established within 7 days of this encounter—after admission to the hospital or discharge from the ED—and designated occult or

### Table 1. Demographic and Laboratory Findings of 15 Patients With SCD (19 Visits) and ACS Diagnosed at or Within 7 Days of an ED Encounter

<table>
<thead>
<tr>
<th>Patient Identification</th>
<th>Visit No.</th>
<th>Presenting Complaint(s)</th>
<th>Age, Y</th>
<th>Gender</th>
<th>sPLA2, ng/mL</th>
<th>Peripheral WBC, 1000 Cells/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>Abdomen and limb pain, cough</td>
<td>4.1</td>
<td>M</td>
<td>72.35</td>
<td>13.3</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>Fever, cough</td>
<td>2.0</td>
<td>M</td>
<td>71.03</td>
<td>33.7</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>Fever, headache, cough</td>
<td>10.0</td>
<td>M</td>
<td>14.89</td>
<td>15.6</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>Fever, dyspnea</td>
<td>10.9</td>
<td>M</td>
<td>56.52</td>
<td>22.1</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>Fever, left knee pain</td>
<td>11.6</td>
<td>F</td>
<td>56.52</td>
<td>17.8</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>Back, shoulder, and left knee pain</td>
<td>9.9</td>
<td>M</td>
<td>53.39</td>
<td>14.3</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>Chest pain, dyspnea, cough</td>
<td>18.9</td>
<td>M</td>
<td>45.17</td>
<td>24.0</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>Chest, chest pain, back pain, dyspnea</td>
<td>17.0</td>
<td>M</td>
<td>51.42</td>
<td>11.1</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
<td>Chest and arm pain</td>
<td>11.2</td>
<td>M</td>
<td>53.65</td>
<td>17.0</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>Chest and arm pain</td>
<td>11.2</td>
<td>M</td>
<td>31.12</td>
<td>12.9</td>
</tr>
<tr>
<td>11</td>
<td>1</td>
<td>Leg and chest pain</td>
<td>7.1</td>
<td>M</td>
<td>2.44</td>
<td>7.8</td>
</tr>
<tr>
<td>12</td>
<td>2</td>
<td>Chest and back pain</td>
<td>7.1</td>
<td>M</td>
<td>29.74</td>
<td>7.9</td>
</tr>
<tr>
<td>13</td>
<td>1</td>
<td>Chest, back, and extremity pain</td>
<td>15.3</td>
<td>M</td>
<td>22.9</td>
<td>8.7</td>
</tr>
<tr>
<td>14</td>
<td>1</td>
<td>Abdominal pain limb, cough</td>
<td>3.4</td>
<td>M</td>
<td>14.29</td>
<td>22.9</td>
</tr>
<tr>
<td>15</td>
<td>1</td>
<td>Fever, abdominal pain</td>
<td>3.4</td>
<td>F</td>
<td>5.81</td>
<td>23.6</td>
</tr>
<tr>
<td>16</td>
<td>1</td>
<td>Chest and back pain</td>
<td>16.2</td>
<td>M</td>
<td>6.50</td>
<td>23.4</td>
</tr>
<tr>
<td>17</td>
<td>1</td>
<td>Back and leg pain, generalized aches</td>
<td>8.7</td>
<td>F</td>
<td>2.75</td>
<td>17.9</td>
</tr>
<tr>
<td>18</td>
<td>1</td>
<td>Back and extreme pain</td>
<td>15.7</td>
<td>F</td>
<td>2.47</td>
<td>36.5</td>
</tr>
</tbody>
</table>

High sPLA2 levels (>13.7 ng/mL) are in boldface.

**Occult or incipient ACS:** ACS not diagnosed at the ED visit but diagnosed within the 7-day interval after this visit, ie, ¶ during hospitalization or # at a follow-up ED visit.

**Fig 1.** Diagnosing ACS: area under the ROC curve for sPLA2 levels (AUC = 0.79).
incipient ACS. Of these, only patient 3 had a chest radiograph performed at the initial ED encounter. After the ED encounter, 2 were discharged to home and 3 others (at 4 visits) were hospitalized. Five of the 6 cases had elevated sPLA2 levels at the initial ED encounter. Clinical details of these visits are presented below.

Patient 3 presented with headache, cough, and fever to 102.8°F. He was hypoxic in the ED (oxygen saturation by pulse oximetry [SaO₂] was 74% on room air) with diminished breath sounds in the left lung fields. A chest radiograph performed in the ED was normal. A follow-up chest radiograph obtained after hospitalization, 8 hours later, revealed air space disease of both middle lobes, consistent with ACS. His sPLA2 level obtained in the ED was high at 53.65 ng/mL at the initial encounter and again at 31.12 ng/mL at the follow-up visit.

Patient 4 received a diagnosis of ACS on 2 occasions. She presented on the first occasion with knee pain and fever of 103.4°F. She was admitted for pain management and subsequently developed respiratory distress and hypoxia on room air (SaO₂: 82%), prompting a chest radiograph, which showed peribronchial thickening but no obvious infiltrates. On day 2, she developed bibasilar pulmonary infiltrates and pleural effusions and received a transfusion of packed red blood cells. On the second occasion, this patient again presented with left knee pain. She developed a left lower lobe infiltrate on chest radiograph 2 days after admission and received a transfusion. Her sPLA2 level obtained in the ED on both occasions was elevated at 56.52 ng/mL and 21.19 ng/mL, respectively.

Patient 5 was admitted to the hospital with back, shoulder, and knee pain. His sPLA2 level on admission was 53.39 ng/mL. On day 2 of admission, he developed chest and abdominal pain with fevers. Chest radiograph at this time revealed a new left lower lobe infiltrate. Hypoxia (SaO₂: 86%) and worsening anemia on day 3 prompted transfusion of packed red blood cells with rapid improvement in his condition.

Patient 8 was discharged from the ED after presentation with leg and chest pain. No chest radiograph was obtained. His sPLA2 level at the first visit was high at 53.65 ng/mL at the initial encounter and again at 31.12 ng/mL at the follow-up visit.

Last, patient 9 was discharged from the ED after presenting with left leg pain. He was hospitalized for ACS (right upper lobe infiltrate on his chest radiograph). His sPLA2 level was high at 53.65 ng/mL at the initial encounter and again at 31.12 ng/mL at the follow-up visit.

Fifteen children were enrolled on >1 occasion for a total of 36 visits. Nine children (enrolled 22 times) had ACS diagnosed on 1 or more occasions at or within 7 days of an enrollment visit for a total of 13 ACS visits. Of 13 visits classified as ACS, 10 (77%) were associated with high sPLA2 levels. In contrast, all (100%) 9 visits that were not classified as ACS were associated with a low sPLA2 level (Table 2).
are believed to play important roles. Children known, although pulmonary emboli and infection event is 1%–5%). The term, although applied vari-ably by different authors, is generally used to describe the combination of respiratory symptoms (cough, respiratory distress, and chest pain) and new pulmonary infiltrates on chest radiographs in patients with SCD. When present in SCD patients presenting with fever, it is clinically unsuspected in 61% of cases. The cause of most cases of ACS is unknown, although pulmonary emboli and infection are believed to play important roles. Children who develop ACS have longer hospital stays and frequently require admission to the ICU. ACS may also be associated with development of chronic lung disease and early death in patients with SCD. The cost to the health care system in addition to the emotional strain placed on the patients and their families is enormous.

In a recent study, 48% of all patients who had SCD and developed ACS were initially admitted to the hospital with a diagnosis other than ACS. Early identification of these children is desirable, as it would permit aggressive treatment to be instituted. The identification of high-risk patients would also facilitate research into novel therapies that could abort or ameliorate this syndrome. A promising laboratory test that may achieve these goals is sPLA2. This enzyme cleaves phospholipids to generate free fatty acids and lyso-phospholipids such as arachidonic acid. Arachidonic acid, in turn, is a substrate for a number of proinflammatory mediators such as thromboxanes and leukotrienes. sPLA2 is normally present at low levels in plasma. It increases modestly in patients who do not have SCD and have pneumonia but to a comparatively lower level than is found in children who have SCD and ACS. It is also increased in adult respiratory distress syndrome and has been shown to be a potent mediator of lung inflammation in animal models.

In the present study, we show that this enzyme is predictive of ACS in children who present to the ED with VOC or fever. These results confirm findings by Styles et al, in a smaller study, who reported a dramatic increase in the serum levels of this enzyme 2 to 3 days before clinical manifestations of ACS in 4 patients who were admitted to the hospital for VOC. In that study, sPLA2 levels remained low in 3 other SCD patients who were admitted for VOC and did not develop ACS. Our study adds to these findings by providing an optimal cutoff for sPLA2 of 13.7 ng/mL on the basis of binary recursive partitioning. In our study, sPLA2 levels >13.7 ng/mL would have permitted earlier identification of ACS in 5 separate cases that were not recognized clinically or by chest radiograph at the initial encounter (Table 2). One case was a child who was discharged to home and returned within 4 days with ACS. Four additional cases were in 3 children (1 who developed the complication twice) who were admitted for VOC or fever and received a diagnosis of ACS during hospitalization. None of these cases was recognized/established clinically and/or by chest radiograph as ACS at discharge from the ED. Routine ordering of sPLA2 in the ED and serial ordering of the test among hospitalized children with initially normal sPLA2 levels may assist in the early detection of occult or incipient ACS. It is possible that early transfusion of packed red blood cells in children who are identified to be at higher risk for ACS on the basis of high sPLA2 levels may abort progression to or attenuate ACS with the additional long-term benefit of decreasing the incidence of chronic lung disease.

Finally, our findings offer clues for defining the cause of ACS (the elucidation of which has proved to be difficult) and for treating patients. Styles et al proposed that an increase in sPLA2 may indicate a more important role for fat emboli.

### DISCUSSION

ACS is the second leading cause of hospitalization in patients with SCD and accounts for up to 25% of deaths associated with this disease (mortality per event is 1%–5%). The term, although applied vari-ably by different authors, is generally used to describe the combination of respiratory symptoms (cough, respiratory distress, and chest pain) and new pulmonary infiltrates on chest radiographs in patients with SCD. When present in SCD patients presenting with fever, it is clinically unsuspected in 61% of cases. The cause of most cases of ACS is unknown, although pulmonary emboli and infection are believed to play important roles. Children who develop ACS have longer hospital stays and frequently require admission to the ICU. ACS may also be associated with development of chronic lung disease and early death in patients with SCD. The cost to the health care system in addition to the emotional strain placed on the patients and their families is enormous.

In a recent study, 48% of all patients who had SCD and developed ACS were initially admitted to the hospital with a diagnosis other than ACS. Early identification of these children is desirable, as it would permit aggressive treatment to be instituted. The identification of high-risk patients would also facilitate research into novel therapies that could abort or ameliorate this syndrome. A promising laboratory test that may achieve these goals is sPLA2. This enzyme cleaves phospholipids to generate free fatty acids and lyso-phospholipids such as arachidonic acid. Arachidonic acid, in turn, is a substrate for a number of proinflammatory mediators such as thromboxanes and leukotrienes. sPLA2 is normally present at low levels in plasma. It increases modestly in patients who do not have SCD and have pneumonia but to a comparatively lower level than is found in children who have SCD and ACS. It is also increased in adult respiratory distress syndrome and has been shown to be a potent mediator of lung inflammation in animal models.

In the present study, we show that this enzyme is predictive of ACS in children who present to the ED with VOC or fever. These results confirm findings by Styles et al, in a smaller study, who reported a dramatic increase in the serum levels of this enzyme 2 to 3 days before clinical manifestations of ACS in 4 patients who were admitted to the hospital for VOC. In that study, sPLA2 levels remained low in 3 other SCD patients who were admitted for VOC and did not develop ACS. Our study adds to these findings by providing an optimal cutoff for sPLA2 of 13.7 ng/mL on the basis of binary recursive partitioning. In our study, sPLA2 levels >13.7 ng/mL would have permitted earlier identification of ACS in 5 separate cases that were not recognized clinically or by chest radiograph at the initial encounter (Table 2). One case was a child who was discharged to home and returned within 4 days with ACS. Four additional cases were in 3 children (1 who developed the complication twice) who were admitted for VOC or fever and received a diagnosis of ACS during hospitalization. None of these cases was recognized/established clinically and/or by chest radiograph as ACS at discharge from the ED. Routine ordering of sPLA2 in the ED and serial ordering of the test among hospitalized children with initially normal sPLA2 levels may assist in the early detection of occult or incipient ACS. It is possible that early transfusion of packed red blood cells in children who are identified to be at higher risk for ACS on the basis of high sPLA2 levels may abort progression to or attenuate ACS with the additional long-term benefit of decreasing the incidence of chronic lung disease.

Finally, our findings offer clues for defining the cause of ACS (the elucidation of which has proved to be difficult) and for treating patients. Styles et al proposed that an increase in sPLA2 may indicate a more important role for fat emboli.

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### TABLE 3. Laboratory Values of Patients Who Had SCD, Were Enrolled More Than Once, and Had No Visit Coded as ACS

<table>
<thead>
<tr>
<th>Patient Identification*</th>
<th>Chronologic Order of Visits</th>
<th>Interval From First Visit in D</th>
<th>sPLA2 Level, ng/mL‡</th>
<th>WBC Count, 1000 Cells/dL</th>
<th>ACS §</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1.23</td>
<td>5.8</td>
<td>—</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>39</td>
<td>1.44</td>
<td>8.3</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>0</td>
<td>4.59</td>
<td>13.2</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>122</td>
<td>8.01</td>
<td>8.0</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>0</td>
<td>1.78</td>
<td>20.0</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>66</td>
<td>1.88</td>
<td>20.1</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>95</td>
<td>7.50</td>
<td>21.4</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>0</td>
<td>2.01</td>
<td>16.2</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>9</td>
<td>1.18</td>
<td>16.8</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>0</td>
<td>53.64</td>
<td>26.4</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>186</td>
<td>77.83</td>
<td>14.3</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>0</td>
<td>8.19</td>
<td>6.8</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>111</td>
<td>72.10</td>
<td>13.8</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>201</td>
<td>6.28</td>
<td>6.8</td>
<td>—</td>
</tr>
</tbody>
</table>

* Patient identification numbers do not correspond to those in Tables 1 and 2.  
† Visit 1 is assigned an interval = 0 days and used as reference point for successive visits.  
‡ High sPLA2 levels (>13.7 ng/mL) are in boldface.  
§ No ACS is coded as “–.”
marrow of long bones during VOC) as opposed to infection or pulmonary infarction. It is possible that alternative therapies that specifically block the expression of this proinflammatory enzyme may abort progression to ACS in high-risk patients. A drug that has been reported to block the activity of sPLA2 is mepacrine (quinacrine).16,17 Although not tested in children with SCD, animal studies show that this drug attenuates the development of artificially induced acute lung injury.17 Formal investigation of such novel therapies is needed because of the hazards associated with blood transfusions. It does not seem likely that IL-6 and endothelin-1 inhibitors will be beneficial for ACS.

Our study had a number of limitations. Although useful for diagnosis, the sPLA2 assay is not offered widely. In our study, samples were sent to an off-site laboratory. The cost and delay associated with transport of blood specimens limited the utility of the test during the study. The assay, however, is commercially available with a turnaround time of ~3 hours. This makes it a potentially useful test for diagnosis and management. A second limitation is that samples were stored for variable periods of time depending on the time of enrollment. We do not know to what extent storage at low temperatures for varying periods of time may have altered the accuracy of assays; however, we found no relationship between the length of storage and the levels of sPLA2. Future studies are needed to evaluate the performance of sPLA2 levels reported at the point of care and within a time frame that is practical for the management of SCD.

Last, chest radiographs were ordered selectively because of the risk of radiation. This had the side benefit of allowing us to assess the complementary role of tests to the clinical examination in predicting ACS, an assessment that would have been obscured by routine ordering of radiographs. We assumed that cases of ACS that were missed at the initial encounter would progress in severity, necessitating a return visit to the hospital within 7 days of discharge. It is possible, however, that some cases of ACS that were not apparent at the initial visit failed to progress to more overt disease. If so, these cases would be missed by a strategy of selective chest radiographs. This raises the possibility that some participants who had high sPLA2 levels and were not assigned a diagnosis of ACS at the initial encounter may have had or developed clinically occult ACS that resolved spontaneously.

**CONCLUSIONS**

In this new setting, elevation of sPLA2 in serum identified children with ACS. At a value >13.7 ng/mL, this test was associated with an increased risk for ACS. This information may be useful for informing medical decisions, for promoting novel approaches to treatment, and for fostering research of alternative drugs and treatment approaches in high-risk patients.

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**REFERENCES**

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