EVIDENCE REPORT

Evidence-Based Management of Sickle Cell Disease

Expert Panel Report, 2014

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gastrointestinal hemorrhage, can also occasionally be responsible for a rapid decline in hemoglobin concentration. Slow but progressive reduction in hemoglobin values should raise concern about renal failure in the older child or adult with SCD.

Summary of the Evidence

An adequate systematic review of the literature with fair sensitivity and specificity for all studies indexed by SCD terms and the symptom of acute anemia was not feasible. A large and nonspecific return of studies with significant heterogeneity, high miss rate, and low-quality evidence (lack of comparative studies) was anticipated. No systematic evidence review was conducted, and the panel used a consensus process to develop a proposed strategy for triaging and promptly managing acute anemia.

Recommendations

1. During all acute illnesses in people with SCD, obtain a CBC and reticulocyte count, repeat daily in all hospitalized patients, and compare the results with the patient's prior measurements.
   (***Consensus–Panel Expertise***)
2. Assess people with SCD whose hemoglobin concentration is 2 g/dL or more below their baseline (or less than 6 g/dL when the baseline is unknown) for acute splenic sequestration, an aplastic episode, a delayed hemolytic transfusion reaction, ACS, and infection.
   (***Consensus–Panel Expertise***)
3. Use simple transfusion in people with SCD and acute anemia whose symptoms are due to anemia.
   (***Consensus–Panel Expertise***)
4. Perform a CBC and reticulocyte count promptly and again 7 to 10 days later in siblings and others with SCD who are exposed to a person with an aplastic episode.
   (***Consensus–Panel Expertise***)
5. Manage aplastic events with immediate red blood cell transfusion aimed at restoring the hemoglobin to a safe (not necessarily baseline) value. Isolation of hospitalized patients (droplet precautions) is required to prevent spread of the parvovirus B19 to pregnant women and others with SCD or compromised immunity.
   (***Consensus–Panel Expertise***)

Splenic Sequestration

Background

Splenic sequestration is defined as sudden enlargement of the spleen and reduction in hemoglobin concentration by at least 2 g/dL below the baseline value. It is a major cause of acute anemia. During splenic sequestration, the reticulocyte count and circulating nucleated red blood cells are usually elevated, and the platelet count is generally decreased because both red cells and platelets are trapped in the spleen. Sequestration usually develops without warning or known cause. It may occur as early as several months of age,[239] although it is more typical in children between the ages of 1 and 4 years old. Parents may note an enlarging mass in the left upper quadrant. Involution and autoinfarction of the spleen usually occurs by age 5, so sequestration events are less common in older children and adults with HbSS. In people with HbSS, the lifetime prevalence of acute splenic sequestration has been reported to be between 7 percent and 30 percent. In people with HbSC and HbSβ^+-thalassemia, splenic sequestration often occurs later in childhood or even during the adult years. Splenic sequestration in older patients is often accompanied by severe pain from splenic infarction, which can be documented by imaging studies.[240]

Some people with SCD have a chronically enlarged spleen and may develop hypersplenism. This presents as a reduction in the white blood cell and platelet counts in addition to acute anemia. Such people are particularly prone to develop acute sequestration events.[239]

In infants with HbSS, splenic sequestration may present acutely with severe anemia and hypovolemic shock. In older people, it may occur more insidiously. Although usual care for splenic sequestration consists of blood transfusion aimed at partial correction of the anemia, excessive transfusion (to hemoglobin values over 8 g/dL) should be avoided, as the sequestered erythrocytes in the enlarged spleen typically reenter the circulation several days later. The result could be hyperviscosity due to an excessively high hemoglobin concentration.

People with splenic sequestration must be monitored for recurrences. Thus, parents and patients are instructed to monitor splenic size and immediately report any marked increase above baseline. People with recurrent sequestration or a single life-threatening acute sequestration event most commonly have a splenectomy. Most people with chronic splenic sequestration accompanied by local pain and hypersplenism are also managed with splenectomy. Splenectomy for splenic sequestration does not further increase the risk of death or bacteremia[241] since most patients are already functionally asplenic. Regularly scheduled transfusions aimed at avoiding the need for subsequent splenectomy have not been proven to be beneficial.[242]

Key Question

KQ14. In people with SCD with acute anemia and splenic sequestration or hypersplenism, what are the most effective strategies to reduce mortality, correct anemia, and prevent recurrence?

Summary of the Evidence

No RCTs were found that evaluated the treatment of splenic complications in SCD. Twenty observational studies (involving more than 950 people) and 39 case reports described various splenic complications in SCD. Reported complications in these observational studies included: splenic sequestration (*n*=16), hypersplenism (*n=3*), splenic abscess (*n=2*), and functional asplenia/splenic auto infarction (*n=2*). Overall benefits were reported for transfusion and splenectomy; however, since 75 percent of the studies had no comparative arm, the general quality of the evidence was considered low.

Only four studies, all involving children, had a comparative design.[242-245] The first compared an intensive transfusion program (to achieve an HbS concentration <20 percent) to a conventional transfusion program in children with prior stroke.[243] It reported the finding of normal or increased splenic size and improved function in the population receiving intensive transfusion, while all people receiving fewer transfusions had decreased splenic function (functional asplenia). A second study assessed three options for treating splenic sequestration: prompt splenectomy, a short-term transfusion program, or observation. Short-term transfusion was equivalent to observation and therefore of limited benefit in preventing recurrent splenic sequestration.[242] The third comparative study did not report group-specific outcomes but rather overall mortality rates.[244] The final comparative study included people with SCD with various splenic complications (splenic sequestration, hypersplenism) and compared outcomes in people who received splenectomy and those who did not.[245] The remaining studies described splenectomy (*n*=13), transfusion (*n*=3), an age-dependent approach (*n*=1),[246] and hydroxyurea (*n*=1).[247] The splenectomy studies reported favorable outcomes following the surgery. Infection rates after splenectomy did not increase. Transfusion was reported to be effective in treating acute splenic sequestration.[248,249]

Recommendations
1. In people with hypovolemia due to severe acute splenic sequestration, immediately provide IV fluid resuscitation. (***Strong Recommendation, Low-Quality Evidence***)
2. In consultation with a sickle cell expert, transfuse people who have acute splenic sequestration and severe anemia to raise the hemoglobin to a stable level, while avoiding over-transfusion. ***(Strong Recommendation, Low Quality Evidence)***
3. In consultation with a sickle cell expert, address the performance and timing of splenectomy in people with recurrent acute splenic sequestration or symptomatic hypersplenism. (***Moderate Recommendation, Low-Quality Evidence***)

Acute Chest Syndrome

Background

ACS is one of the most common and serious acute complications of SCD.[250-252] It is the second most frequent reason for hospitalization in children and adults with SCD and the most common cause of death. Clinically, ACS resembles pneumonia and can develop suddenly or insidiously, during hospitalization for a VOC, or after a surgical procedure, especially one involving the abdomen. ACS occurs with increased frequency in people with asthma or prior ACS events. The clinical, laboratory, and radiographic features of ACS—as well as its management and outcome—were comprehensively assessed in a landmark study performed by the National Acute Chest Syndrome Study Group.[251]

A person with ACS typically has sudden onset of signs and symptoms of lower respiratory tract disease (e.g., some combination of cough, shortness of breath, retractions, rales, etc.) and a new pulmonary infiltrate on chest radiograph. In the early stages of ACS, the clinical manifestations can be subtle. Children usually have fever and upper or middle lobe involvement, whereas adults are often afebrile and present with multilobe disease. The most common well-defined etiology is infection (e.g., viral, bacterial, chlamydia, or *Mycoplasma*), but the complication may also result from bone marrow fat embolism, intrapulmonary aggregates of sickled cells, atelectasis, or pulmonary edema. In many cases, the specific cause or inciting factor is not apparent. There are no distinctive laboratory features of ACS, although the hemoglobin concentration often declines sharply below the patient's baseline value. In brief, what would be considered pneumonia in a person without SCD usually fulfills the criteria for ACS.

People with ACS generally improve within several days but some develop rapid respiratory failure and/or involvement of other organs such as the brain, kidneys, and liver. This latter complication is known as "multisystem organ failure (MSOF)" (see page 50). Treatment of ACS may include broad spectrum antibiotics, supplemental oxygen, bronchodilators, and blood transfusions. Markers of an impending severe course of ACS are multilobe disease, increased work of breathing, inability to maintain oxygen saturation above 95 percent even with supplemental oxygen, and pleural effusions. Exchange transfusion is often necessary in such circumstances. The therapeutic role of corticosteroids and other anti-inflammatory agents is uncertain and requires further study.[253] Repeated episodes of ACS occur in many patients and can contribute to development of chronic lung disease.

ACS during a hospital admission for an acute VOC may be prevented by incentive spirometry every 2–4 hours while awake.