EVIDENCE REPORT

Evidence-Based Management of Sickle Cell Disease

Expert Panel Report, 2014

U.S. Department of Health and Human Services
National Institutes of Health
National Heart, Lung, and Blood Institute

http://www.nhlbi.nih.gov/guidelines

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.

Key Question

KQ15. In people with SCD and ACS, what is the most effective treatment (among transfusion, exchange transfusion, supportive therapy, steroids, and/or antibiotics) to reduce mortality, resolve pain, and prevent clinical deterioration?

Summary of the Evidence

One RCT, 27 observational studies, and 45 case reports described sickle cell-related ACS. The overall quality of evidence was very low for all interventions except the use of opioids.

The single RCT enrolled 38 children and found that dexamethasone compared to placebo decreased the mean hospital stay (from 80 to 47 hours), the need for transfusions (from 47 percent to 9 percent), the number of administered opioid doses (from a mean of 20 to a mean of 2.5), and clinical deterioration (defined as an increase in oxygen requirements and respiratory rate).[254] Participants and investigators were blinded, allocation was concealed, and the study did not report any baseline imbalances. This short-term benefit, however, was not demonstrated to persist when examined by larger observational studies with longer followup. The largest of these studies was done in 2009 and retrospectively evaluated more than 3,000 people (more than 5,000 admissions).[255] After adjustment for propensity scores and hospital case mix, the study demonstrated a significant increase in the length of hospitalization in people who received corticosteroids as part of their ACS management. Other studies showed increased adverse effects related to steroids.

The remaining observational studies described benefits of other therapies for ACS (e.g., supportive treatment including oxygen supplementation, mechanical ventilation, pain management, hydration, antibiotics, and simple or exchange transfusion). The quality of these studies was low due to the noncomparative nature of their design. Studies that evaluated antibiotics did not demonstrate a significant effect on patient-important outcomes. Multiple observational studies evaluated opiates in ACS. In one, nalbuphine hydrochloride reduced the incidence of ACS compared to morphine (12 percent vs. 29 percent) and also reduced hospital stay.[256] In the remaining studies, opiates clearly reduced pain but without other effects on the clinical course of ACS. Transfusion studies in ACS showed conflicting results. In one study, length of hospital stay was similar between simple transfusion and exchange transfusion, and ICU stay was longer in the exchange group (5.6 days vs. 2.6 days).[257] Another study found significant correlation between exchange transfusion and fewer days of hospitalization and oxygen requirement.[258] In these and other transfusion studies, sicker patients were more likely to receive exchange transfusion, which indicates a clear selection bias.

Recommendations

1. Evaluate people with SCD who develop acute onset of lower respiratory tract disease signs and/or symptoms (cough, shortness of breath, tachypnea, retractions, or wheezing) with or without fever for ACS. This should include a chest x ray and measurement of oxygen saturation by pulse oximetry.
   (Consensus–Panel Expertise)
2. Hospitalize people with ACS.
   (Consensus–Panel Expertise)
3. Treat people with SCD who have ACS with an intravenous cephalosporin, an oral macrolide antibiotic, supplemental oxygen (to maintain oxygen saturation of greater than 95 percent), and close monitoring for bronchospasm, acute anemia, and hypoxemia.
   (Strong Recommendation, Low-Quality Evidence)
4. In people with SCA, give simple blood transfusion (10 mL/kg red blood cells) to improve oxygen carrying capacity to people with symptomatic ACS whose hemoglobin concentration is >1.0 g/dL below baseline. If baseline hemoglobin is 9 g/dL or higher, simple blood transfusion may not be required.
   (Weak Recommendation, Low-Quality Evidence)
5. In people with HbSC disease or HbSβ^+-thalassemia with ACS, decisions about transfusion should be made in consultation with an SCD expert.
   (***Strong Recommendation, Low-Quality Evidence***)
6. In all persons with SCD, perform urgent exchange transfusion—with consultation from hematology, critical care, and/or apheresis specialists—when there is rapid progression of ACS as manifested by oxygen saturation below 90 percent despite supplemental oxygen, increasing respiratory distress, progressive pulmonary infiltrates, and/or decline in hemoglobin concentration despite simple transfusion.
   (Strong Recommendation, Low-Quality Evidence)
7. Encourage use of incentive spirometry while awake.
   (***Strong Recommendation, Moderate-Quality Evidence***)

Acute Stroke

Background

Stroke is one of the most common and devastating complications of SCD.[77] In the absence of primary stroke prevention, approximately 10 percent of children with HbSS will have overt strokes. This complication presents as sudden onset of weakness, aphasia, and sometimes seizures or coma and results in adverse motor and cognitive sequelae. Transient ischemic attack often precedes stroke, even in children, but neuroimaging is negative and not predictive of stroke. In the absence of primary stroke prevention, an additional 20 to 35 percent of children with HbSS have silent cerebral infarcts, which can cause cognitive decline and predispose them to additional silent infarcts and to overt strokes.[259]

Overt stroke is generally secondary to stenosis or occlusion of the internal carotid or middle cerebral artery, but events may be precipitated by ACS, parvovirus infection, or other acute anemic events.[77,93] In the absence of secondary prevention measures such as a chronic transfusion program or hematopoietic stem cell transplantation, recurrence rates have been shown to range between 46 and 90 percent in children with SCD.[94] People of all ages with HbSC and HbSβ^+-thalassemia infrequently have overt CNS events.[77]

Primary stroke prevention using regular blood transfusions in children shown to be at high risk of stroke by TCD screening has led to declines in the incidence of stroke in children with SCD.[97] Although high-quality