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. 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

studies have been done on primary stroke prevention in children, few studies have examined secondary stroke prevention.

Adults with HbSS also have a high risk of both ischemic and hemorrhagic stroke. The latter is usually sudden and is accompanied by severe headache and loss of consciousness. The mortality rate is high. Limited data suggest that TCD is not predictive of stroke risk in adults. This section of the guidelines addresses the management of acute stroke and the prevention of stroke recurrence (i.e., secondary prevention).

Key Question

KQ16. In people with SCD presenting with acute stroke, what is the most effective treatment strategy (transfusion, thrombolytics, hydroxyurea, or other therapies) to reduce mortality, preserve neurological function, and reduce recurrence rates?

Summary of the Evidence

The systematic review of the literature did not identify comparative studies that evaluated different management strategies to reduce mortality or improve neurologic outcomes of acute stroke in people with SCD. Therefore, the panel based their initial management recommendations on the principles of stroke management in patients without SCD and on their clinical expertise and provided consensus statements.

The systematic review identified seven observational studies[260-266] that reported primarily on the effect of transfusion on preventing recurrent stroke (secondary stroke prevention). Two studies[262,263] reported on the outcomes of stopping chronic transfusion therapy in children who have had prior stroke. There were a total of 20 patients in these studies, and 12 had recurrent central nervous system (CNS) events after discontinuing transfusions. Hulbert et al.[266] conducted a small retrospective study in 52 children presenting within 24 hours of stroke onset and demonstrated that recurrent stroke occurred in 57 percent (8 of 14) of patients treated with simple transfusion, compared with 21 percent (8 of 38) of those treated with exchange transfusion. The study by Russell et al.[261] included 35 children with SCD. Without transfusion, arterial changes documented by arteriography progressed in all four patients who had disease of multiple arteries. After transfusion, vessel changes stabilized. Two of the observational studies reported on long-term outcomes of chronic transfusion. One study followed 60 subjects for a median duration of 36 months, and recurrent strokes were documented in 8 subjects.[265] The other study[264] followed 111 patients and found 1.9 events per 100 patient-years, despite long-term transfusions, thus concluding that the risk of recurrent stroke is decreased but not eliminated by regular blood transfusion therapy. The final study[260] looked at changing the pretransfusion goal of maintaining an HbS of <30 percent to a goal of 50 percent. The median duration of followup was 84 months, and none of the 15 patients studied had a recurrent cerebral infarction during 1,023 patient-months in which the target pretransfusion HbS was 50 percent. These preliminary single-institution findings were then tested in the prospective Stroke With Transfusions Changing to Hydroxyurea (SWiTCH) multicenter phase 3 clinical trial. Children with previous stroke and iron overload were randomized to receive either continued transfusions with iron chelation (standard arm) or hydroxyurea with phlebotomy (alternative arm). The SWiTCH trial had a noninferiority design,[g] with a composite primary end point consisting of recurrent stroke and liver iron concentration.[267] At interim data analysis, there were seven (7/67) strokes on the alternative arm and none (0/66) on the standard arm; this was still within the noninferiority stroke margin, but equivalent liver iron

[g] A noninferiority trial is a classification of RCT. This type of trial aims to determine whether a new treatment is no less effective than a reference treatment using statistical significance.

content between treatment arms, indicating futility for the composite study end point. Accordingly, the study was closed, and the authors concluded that transfusions and chelation remain a better way to manage children with SCA, stroke, and iron overload.[268]

In addition to the use of transfusion for secondary stroke prevention, the systematic review identified three small observational studies that evaluated the role of hydroxyurea.[94,269,270] The studies enrolled a total of 56 children with a history of stroke who were treated with hydroxyurea. The largest of these studies[270] included 35 children with prior stroke who were discontinued from chronic transfusion therapy. Children were followed on average 42 months with an average hydroxyurea dose of 26.7 mg/kg/d. The stroke recurrence rate for the whole cohort was 5.7 events/100 patient-years, but for children who overlapped transfusion therapy with hydroxyurea treatment, the event rate was 3.6/100 patient-years. The two smaller studies[94,269] showed similar results that were consistent with reduction of stroke recurrence associated with using hydroxyurea. The quality of this evidence was low due to imprecision (small sample size) and the uncontrolled nature of the studies.

Recommendations

1. In people with SCD who present with severe headache, altered level of consciousness, seizures, speech problems, and/or paralysis, evaluate for acute stroke by seeking neurologic consultation and performing an urgent head computerized tomography (CT) scan followed by magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) if available.
   (Consensus–Panel Expertise)
2. In consultation with a sickle cell expert, perform exchange transfusion in people with SCD who develop acute stroke confirmed by neuroimaging.
   (Consensus–Panel Expertise)
3. Initiate prompt evaluation, including neurologic consultation and neuroimaging studies, in people with SCD who have mild, subtle, or recent history of signs or symptoms consistent with transient ischemic attack.
   (Consensus–Panel Expertise)
4. In children and adults who have had a stroke, initiate a program of monthly simple or exchange transfusions.
   (***Moderate Strength, Low-Quality Evidence***)
5. In children and adults who have had a stroke, if it is not possible to implement a transfusion program, initiate hydroxyurea therapy.
   (***Moderate Strength, Low-Quality Evidence***)

Multisystem Organ Failure

Background

Multisystem organ failure (MSOF) is a severe and life-threatening complication usually associated with a VOC and characterized by failure of the lungs, liver, and/or kidneys.[163] MSOF may occur after several days of hospitalization and treatment for a severe VOC, often when pain is beginning to improve. In most cases, patients do not have a history of chronic organ failure. Deterioration is rapid and unexpected. It is usually associated with fever, a rapid decline in hemoglobin concentration and platelet count, and nonfocal encephalopathy. Acute respiratory failure is usually associated with development of ACS. Hepatic failure is associated with marked elevations in total and direct bilirubin, liver enzymes, and blood coagulation screening tests. Acute renal failure is associated with a rapid elevation of serum creatinine, with or without the presence of oliguria and hyperkalemia. Rapid diagnosis and treatment of MSOF is necessary to prevent death.