

## Featured Clinical Topic:

# Summary of the 2014 NHLBI Guidelines to Manage Sickle Cell Disease

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Between 70,000 and 100,000 Americans are affected with sickle cell disease (SCD) and more than 2 million are estimated to have the heterozygous or homozygous sickle cell mutation. In the past few decades, the life span for patients with SCD has increased substantially with the vast majority entering adulthood; however, the overall life span continues to be shorter than the general population.

Patients with sickle cell disease can be afflicted with a multitude of acute and chronic medical issues affecting all major organ systems. Therefore, there is a clear need for evidence-based guidelines to dispense appropriate care to these patients.

Recently, updated guidelines from the National Heart and Lung Blood Institute (NHLBI) were published in an effort to address this need. The document was endorsed by many organizations including the AAP (<http://pediatrics.aappublications.org/content/134/6/e1775.full.pdf+html>) and is available at no cost on the NHLBI website at <http://www.nhlbi.nih.gov/health-pro/guidelines/sickle-cell-disease-guidelines> The executive summary is available at: <http://jama.jamanetwork.com/article.aspx?articleid=1902235>

An Expert Panel, co-Chaired by Drs. George Buchanan and Barbara Yawn, developed this report. Five major topic areas were identified to determine the areas that needed to be addressed. Literature searches were performed to answer the specific questions utilizing the PICOS methodology and GRADE system. The evidence underwent extensive review by the Panel and was subsequently graded on its quality. Evidence-based recommendations were synthesized and graded. If evidence was minimal, absent or inadequate, consensus statements were made based on the adaptations from other sources and/or the panel's expertise.

The five topics covered by the guideline include health maintenance, management of acute and chronic conditions, use of hydroxyurea and blood transfusions in management of SCD. The guidelines are intended to be used by any practitioner who is involved in care of patients with SCD. Here we summarize some of the key recommendations from each of these areas.

### 1. *Health Maintenance for People with Sickle Cell Disease*

- a) Oral penicillin to be given twice daily for all patients with HbSS until 5 years of age. This may be discontinued at 5 years unless the patient had a splenectomy or an invasive pneumococcal infection. Recommendations were made to ensure that patients were adequately immunized against *Streptococcus pneumoniae* including boosters with PPSV23, and immunized against meningococcus.
- b) Annual screening for proteinuria with urinalysis is to begin at 10 years of age. If positive, orthostatic proteinuria should be ruled out before referral to a nephrologist.
- c) No recommendations for or against screening asymptomatic patients for pulmonary hypertension was made.
- d) Routine ECG screening was not recommended in asymptomatic children and adults with SCD.
- e) Adults and children with SCD were to be screened and treated for hypertension.
- f) Screening for sickle cell retinopathy to begin at 10 years of age.
- g) Patients with HbSS or HbSB<sup>0</sup> (not HbSC or HbSB<sup>+</sup>) to be screened annually (from ages 2 to 16 years) with TCD for stroke prevention with actions based on results. Adults were not recommended to be screened with TCD. All asymptomatic patients were not recommended to be screened with MRI or CT.
- h) For pulmonary disease, while routine PFTs were not recommended in asymptomatic patients, screening by history and physical was recommended and evaluation was recommended for those with positive signs and symptoms of pulmonary disease.
- i) Several recommendations regarding reproductive care and contraception were also made.

## 2. *Managing Acute Complications of Sickle Cell Disease*

- a) Extensive recommendations were made regarding the most effective ways to manage vaso-occlusive crises (VOC). This included rapid assessment and treatment of VOC in a manner that is personalized to the patient's needs. The intensity of pain management is to be escalated with the severity of pain symptoms, and with adequate monitoring and reassessment, the doses of opioids can be modified. Incentive spirometry and ambulation should be used to reduce the risk of secondary acute chest syndrome.
- b) Febrile illness should be promptly evaluated and treated. Febrile children should be treated empirically. If not ill, outpatient management with oral antibiotics can be considered, but those who appear sick or have high fevers should be hospitalized. Acute chest syndrome should be ruled out with a chest X-Ray in patients with lower respiratory signs and symptoms.
- c) Priapism should be intervened with 'vigorous' hydration, pain management and urology consultation.
- d) Hepato-biliary complications are to be managed depending on the specific issue. Acute cholecystitis is to be managed with antibiotics and surgical consultation. If cholecystectomy is needed, a laparoscopic approach is preferred and hematology should be consulted for possible pre-operative transfusion. Asymptomatic gallstones should be monitored. Possible acute hepatic or intrahepatic crises are to be treated with hydration and close monitoring and, with a confirmed diagnosis by a hematologist, simple or exchange transfusion is the recommended treatment.
- e) In anemic episodes, the cause of the drop in hemoglobin from baseline should be investigated and CBC and reticulocyte count should be closely monitored. Symptoms of anemia and aplastic anemia should be managed with simple transfusions. Isolation procedures should be in place to prevent transmission of parvovirus B19 to high risk populations.
- f) Acute splenic sequestration should be managed with hydration and a sickle cell expert consultation for safe PRBC transfusion. Elective splenectomy after resolution of the acute episode can also be considered, with expert input.
- g) Acute chest syndrome should be ruled out in SCD patients who present with appropriate signs and symptoms of lower respiratory tract disease. If diagnosed, all patients with ACS should be hospitalized for monitoring and treatment; this should include IV cephalosporin, macrolide, supplemental oxygen if needed, incentive spirometry and simple transfusion. If a patient has worsening clinical course, exchange transfusion should be performed.
- h) SCD patients with neurologic signs and symptoms of an acute stroke should be evaluated urgently with radiologic imaging (non-contrast CT scan followed by MRI and MRA). Exchange transfusion should be performed if diagnosed. Following a stroke, all patients are to be transfused on a monthly basis, and if transfusion is not feasible, hydroxyurea should be started.

## 3. *Managing Chronic Complications of Sickle Cell Disease*

- a) The recommendations of management of chronic pain were mostly consensus-adapted. This includes the determination of the etiology of the pain, using a dedicated practitioner for the patient and an individualized treatment plan.
- b) Avascular necrosis should be ruled out in SCD patients with hip pain. If diagnosed, the pain should be managed with analgesics. Physical therapists and orthopedists with experience in such patients should be involved in the care to provide non-surgical and surgical treatments.
- c) Symptomatic patients suspected of pulmonary hypertension should have echocardiography, followed by right heart catheterization and treatment if the screening echocardiography (when not acutely ill) reveals an elevated TRV.
- d) Management of chronic renal disease (proteinuria, elevation of serum creatinine) in SCD should include consultation with a nephrologist, initiation of ACE inhibitor therapy and renal replacement therapy.

## 4. *Hydroxyurea in the management of SCD*

In this section of the report, the Panel summarized the evidence to demonstrate and firmly establish the safety, tolerability and efficacy of hydroxyurea use in children and adults with SCD. Based on the evidence, several recommendations were made. Adults with HbSS or HbSB0 who have had multiple pain crisis, decreased quality of life from pain or anemia, or those with acute chest syndrome were to be prescribed hydroxyurea. All patients 'regardless of clinical severity' were to be offered hydroxyurea starting at 9 months of age. These were strongly recommended due to the quality of the evidence that supported it. A protocol for implementing the guidelines, including doses and

monitoring parameters are also outlined.

#### 5. *Blood transfusion in the management of SCD*

This section of the guidelines focused on the indications for PRBC transfusions (simple and exchange) in patients with SCD. This included acute and chronic conditions for which transfusions were recommended such as those undergoing procedures with general anesthesia, patients with acute chest syndrome, splenic sequestration, stroke (primary and secondary prevention), vaso-occlusive crisis, etc. Recommendations regarding optimal cross-matching methods (to reduce alloimmunization), goals of transfusion with regards to target hemoglobin and hemoglobin-S levels in acute and chronically transfused patients were also made. A consensus protocol for initiating and monitoring chronically transfused patients was included. Finally, complications from transfusions including alloimmunization, autoimmunization, iron overload, etc. were also discussed and recommendations to manage these complications were outlined.

The current report covers a wide range of issues related to the management of patients with SCD. It is an adequate tool for primary care providers and a good guide to the evidence basis for sickle cell care. Practitioners who are involved in the treatment of these patients will note that the panel made consensus recommendations in some areas of controversy. The report correctly suggests that additional good quality research is needed. There are still many other areas that are not addressed in the guidelines as new information is constantly emerging: 1. When to discuss transplantation with a patient and family and when to refer for consultation with a transplant team, 2. Screening and management of silent cerebral infarcts, 3. Neuro-psychologic function in children and adults, 4. The results of the yet to be published TWITCH (TCD with transfusion in change to hydroxyurea) study and 5. Discussion of pulmonary hypertension guidelines from the American Thoracic Society for asymptomatic adults. Hopefully, these will be covered in the next version of this report.

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