SICKLE E DISEASE (Hb SE Disease)

Hemoglobinopathy screening in Utah identifies infants with sickle cell disease as well as other hemoglobin disorders. Isoelectric Focusing (IEF), a screening process, separates, identifies, and quantifies each type of hemoglobin present in a sample. At birth there is normally more fetal hemoglobin (Hb F) than adult hemoglobin (Hb A) and is reported as FA. Infants with sickle cell hemoglobin E disease (Hb SE) have one hemoglobin S (Hb S) and one hemoglobin E (Hb E) with no Hb A and is reported as FSE. Abnormal IEF screens are validated by Hb fractionation using High Performance Liquid Chromatography (HPLC), which shows the hemoglobin pattern with somewhat more accuracy.

Genetics and Heredity
Normal hemoglobin (Hb A) consists of 2 α-globin chains and 2 β-globin chains. Both Hb S and Hb E are inherited autosomal recessive variations of the β-globin chain. The normal β-globin chain has a glutamic acid in the β-6 position (codon), located on the short arm of chromosome 11. The formation of Hb S occurs from substitution of valine for glutamic acid (glu→val). Hb E generally results from substitution of lysine for glutamic acid at β-26 (glu→lys). Sickle cell hemoglobin E disease results when an infant has inherited one copy of the Hb S variant gene from one parent and one copy of the Hb E variant gene from the other parent. There is a 25 percent chance of inheritance of compound heterozygous Hb SE disease with each pregnancy.

Pathophysiology
The coinheritance of Hb S and Hb E (Hb SE), may result in a clinically significant sickling disorder similar to that of sickle cell disease (homozygous Hb SS). This is in contrast to the benign nature of the homozygous form (Hb EE) disease, which is usually clinically silent. Hb SE is accompanied by vaso-occlusion and hemolysis, producing moderately severe anemia and pain episodes, although usually milder than with sickle cell anemia (Hb SS). Hb SE disease exhibits much of the combined symptomatology seen in both Hb S and Hb E diseases independently:
♣ Hb SS cells sickle as a result of deoxygenation, dehydration, acidosis, stress and temperature changes.
♣ Hb E interacts with the sickle hemoglobin erythrocyte membrane, causing vaso-occlusion, premature RBC breakdown and decreased erythrocyte survival rate.
♣ Hb E disease may manifest target red blood cells, microcytosis, hypochromia, decreased hemoglobin concentration and reduced oxygen affinity.
♣ Predictive of disease severity, a high Hb F level is linked with milder disease by inhibiting Hb sickling and hemolysis.
♣ Hb SE disease may be symptomatically milder that Hb SC disease, even though it has a higher concentration of Hb S.

Complications that make sickle cell disease (Hb SS) renown are also associated with hemoglobin SE disease (Hb SE). Hemolysis shortens the average life span of RBCs from 120 days to approximately 30 days and is associated with reticulocytosis, pulmonary arterial hypertension, chronic anemia and gallstones. RBCs break down easily in the circulation and are rapidly removed by the spleen leading to hemolytic anemia. Functional asplenia occurs as a result of repeated infarction. Vascular occlusion is associated with tissue ischemia, stroke, acute chest syndrome (chest pain, fever, dyspnea, hypoxia), joint necroses (especially head of femur and humerus), pain crises, acute and chronic organ dysfunction/failure, retinal hemorrhages, and increased risk of infection. These manifestations are potentially life threatening.
**Prevalence**

The gene mutations for Hb S and Hb E are present in all racial and ethnic groups affecting males and females equally. Hb S is more prevalent in people of African, Caribbean, Southeast Asian, Central and South American descent and in much less frequency in Mediterranean and Middle Eastern people. Hb E is one of the most common mutations. It is very high among persons from Southeast Asia, especially Cambodia, Laos and Thailand, whose borders are considered the “Hb E Triangle”. Hb E is also found in Vietnam, Malyasia, northeastern India, Bangladesh, Pakistan, Nepal and Sri Lanka. Both Hb S and E hemoglobin traits have evolved as “positive” genetic mutations in areas where malaria is endemic as a response to the selective pressure of malaria (impairing malaria growth and development).

**Sickle E Disease and Alpha Thalassemia**

Sickle cell-E disease (Hb SE) can occur in combination with alpha thalassemia (BARTS). While Hb SE reflects variations of the β-globin chains structure (quality), alpha thalassemia is characterized by a decrease in the rate of α-globin chain production (quantity). Deletions of one or both of the α-globin genes on chromosome 16 (αα/αα) may occur in association with Hb SE (FSEBARTS) because α-globin genes are located on a different chromosome from β-globin genes. The disease severity is related to the severity of Hb SE and to the number of α-globin gene deletions and resultant degree of anemia. It is thought that the co-inheritance of an alpha thalassemia trait in patients with sickle cell disease is of some advantage in modifying the severity of the condition.

**Essential Steps**

1. Inform the family of confirmed sickle cell hemoglobin E disease (Hb SE); explain the possible complications and required interventions.
2. Educate parents and care givers regarding signs and symptoms, risks of infection, and preventive measures such as administering antibiotic prophylaxis, maintaining hydration, avoiding temperature extremes, physical exhaustion, and extremely high altitudes without supplemental oxygen.
3. Advise parents to have their child immediately evaluated with a fever of ≥ 38.5° C (≥ 101° F), significant respiratory symptoms and chest pain.
4. Initiate penicillin prophylaxis.
5. Ensure all childhood vaccines are administered in accordance with schedules approved by the Advisory Committee on Immunization Practices, the American Academy of Pediatrics, and the American Academy of Family Physicians. Additional vaccinations should be considered due to the high risk of infection in children with Hb SE.
6. Consult with a pediatric hematologist regarding patient evaluation and disease management, and current therapies for vascular occlusion, hemolysis and infections.
7. Consider family referral to a genetic counselor.

**Pediatric Hematology**

Primary Children’s Medical Center  
Department of Hematology  
100 North Mario Capecchi Drive  
Salt Lake City, Utah 84113

(801) 662-4700
### Sickle Cell Hemoglobin E Disease (Hb SE)

**Guidelines for Health Care Providers**

<table>
<thead>
<tr>
<th>Complications</th>
<th>Manifestations</th>
<th>Comments</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>Vascular occlusion</td>
<td>Episodic pain</td>
<td>Swelling of hands and feet (may be the first manifestation of disease in infants)</td>
<td>If mild: oral fluids, over-the-counter pain medication (acetaminophen and ibuprofen), heating pads</td>
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<td></td>
<td>Dactylitis (hand-foot syndrome)</td>
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<td></td>
<td>Acute chest syndrome (ACS)</td>
<td>With chest pain, fever, dyspnea, and hypoxia</td>
<td>If severe: hospitalization with intravenous analgesia, fluids and antibiotics, blood transfusions, oxygen therapy, spirometry, bronchodilators, hematology consult</td>
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<tr>
<td></td>
<td>Pulmonary hypertension</td>
<td>Occlusion of the pulmonary microcirculation</td>
<td>Exchange transfusions, oxygen, hydroxyuria, inhaled nitrous oxide, hematology consult</td>
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<tr>
<td>Stroke</td>
<td>Occlusion of the pulmonary microcirculation</td>
<td></td>
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<tr>
<td>Vision problems</td>
<td>Recurrent, may be severe</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>(Retinitis proliferans)</td>
<td></td>
<td></td>
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<tr>
<td>Episodic priapism</td>
<td>Recurrent, may be severe</td>
<td></td>
<td>Hydration and analgesia. Aspiration and irrigation by a urologist for severe episodes (&gt; 2-4 hours)</td>
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<tr>
<td>Hemolysis</td>
<td>Chronic anemia</td>
<td>Shortened life span of sickled RBCs</td>
<td>Monitor hematocrit, reticulocyte count, cardiovascular status. Blood transfusions as needed</td>
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<td></td>
<td>Splenic sequestration with abdominal pain, nausea, vomiting (may lead to shock, death)</td>
<td>Enlarging spleen (common between 6 months to 3 years of age) and later in patients with Hb SE disease, SC, SD or Sickle Beta-thalassemia, who usually maintain an enlarged spleen</td>
<td>Monitor spleen for enlargement Hospitalization, intravenous fluids Emergency transfusion for cardiovascular instability Hematology consult May require splenectomy with severe and multiple episodes</td>
</tr>
<tr>
<td>Aplastic crisis</td>
<td>Exacerbation of baseline anemia with decreased reticulocyte count (&lt;1%)</td>
<td></td>
<td>Hospitalization, with possible splenectomy Monitor hematocrit, reticulocyte count, cardiovascular status, and spleen for enlargement. Blood transfusions Hematology consult</td>
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<tr>
<td>Recurrent infections</td>
<td>Septicemia, pneumonia, meningitis, osteomyelitis</td>
<td>Microorganisms: <em>Haemophilus influenzae type b</em>, <em>Streptococcus pneumoniae</em>, <em>Neisseria meningitidis</em>, <em>Pneumococcus pneumoniae</em>, <em>Staphylococcus aureus</em> and <em>Salmonella</em></td>
<td>Broad spectrum antibiotic therapy Hematology consult Hospitalization with intravenous fluids, oxygen therapy, blood transfusions, parenteral analgesia</td>
</tr>
</tbody>
</table>

**Other Therapies:** Hydroxyurea, a chemotherapy agent, induces Hb F production (which in combination with Hb SE) prevents Hb S sickling. It lowers white blood cell (WBC) and reticulocyte counts, and increases patient survival. Nitric oxide, by inhalation, dilates pulmonary blood vessels especially in the presence of pulmonary hypertension. Bone marrow transplant from a compatible donor may cure sickle cell disease in patients with severe manifestations such as repeated strokes where the advantage out weights the risk of transplant. Therapies under investigation include stem cell transplant and gene therapies.