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## **Hemolytic Anemia: Part 2**

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*Pediatrics in Review* 1999;20;204

DOI: 10.1542/pir.20-6-204

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# Hemolytic Anemia: Part 2\*

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## OBJECTIVES

Upon completion of this article, readers should be able to:

1. Describe the infections to which children who have sickle cell disease are susceptible.
2. Describe the complications of sickle cell disease.
3. Describe the presentation of thalassemia major.

## Sickle Cell Disease

### DEFINITION

Sickle cell disease is a hemoglobinopathy characterized by the inheritance of two abnormal hemoglobin genes, at least one of which is the sickle hemoglobin gene. The most common types are: hemoglobin SS disease, hemoglobin SC disease, and hemoglobin S-thalassemia. The inheritance of one normal hemoglobin gene (A) in association with hemoglobin S leads to the formation of hemoglobin AS, which also is called sickle trait and is considered a carrier state, not a "disease."

### EPIDEMIOLOGY

The sickle gene is prevalent in West Africa, Central Africa, the Mediterranean, the Middle East, and certain parts of India. It also is present in other parts of the world where black immigrants from Africa comprise a substantial portion of the population. In the United States, the incidence of the sickle gene among African Americans is 8%.

### PATHOLOGY, PATHOPHYSIOLOGY, AND PATHOGENESIS

In the sickle hemoglobin, a mutation in codon 6 of the beta chain leads to replacement of glutamic acid by valine. This hemoglobin undergoes changes precipitated by many factors, with the classic one being deoxygenation. Deoxygenation is

associated with the formation of crystals of less soluble hemoglobin S that align in a unique fashion, leading to the unusual shape of the cell. Other precipitating factors include pH changes and temperature. The rigid cells, in combination with the attendant increase in viscosity, result in sludging and organ infarction.

### CLINICAL PRESENTATIONS

The clinical manifestations of sickle cell disease vary from patient to patient and from region to region, even among those who have apparently similar phenotypes. The variation ranges from a complete lack of symptoms even into adulthood to life-threatening complications beginning in early infancy. Most affected patients, however, have long periods of "wellness" interspersed with recurrent symptomatic episodes. Certain acute events, some of which are rather peculiar to sickle cell disease, frequently may interrupt an otherwise chronic course of the disease. These events, which often are referred to as "crises", will be described in this article as "episodes" because the word "crisis" denotes a situation hopelessly out of control, which is not necessarily the case.

### VASO-OCCLUSIVE EPISODES

These episodes, characterized by tissue infarction and often accompanied by pain, can affect nearly all organs or tissues (except probably the myocardium). The most common sites are the bones, lungs, spleen, liver, penis, and brain. Precipitating events can include infection, stress, dehydration, or changes in tempera-

ture, but precipitants may be unidentifiable.

### PAINFUL BONE EPISODE

This is the most frequent vaso-occlusive episode and results from infarctions of the bone marrow and cortical bone. It may occur early in the first year of life as "dactylitis" that involves the small bones of the hands and feet (hand-foot syndrome), but more commonly it occurs later. No bone in the body is spared, but the spine, ribs, and long bones are affected most frequently.

Clinical features include pain of acute or gradual onset with or without signs of local inflammation. Among systemic features are fever and leukocytosis with neutrophilia mimicking acute osteomyelitis.

Radiographs, bone scans, and gallium scans usually are of no help in differentiating these episodes from osteomyelitis; serial magnetic resonance imaging (MRI) appears to be the most helpful modality. Useful differential features include the fact that long bone infarctions are 50 times more common than osteomyelitis and that multifocal symptoms are uncommon in osteomyelitis. A positive blood culture favors the diagnosis of osteomyelitis; the most common organisms are *Salmonella* sp, *Staphylococcus aureus*, and *Streptococcus pneumoniae*.

### ACUTE CHEST SYNDROME (EPISODE)

Classically this is characterized by an acute episode of chest pain in conjunction with the appearance of a new pulmonary infiltrate. Chest pain may be absent initially or findings on chest radiography may be normal initially. The most common causes are: 1) lung infarction, 2) pneumonia, 3) hypoventilation atelectasis, or 4) a combination of these. It can occur at any age. Features include chest pain, cough, fever, difficulty in breathing, hypoxia, and leukocytosis. Differentiating among the causes is difficult except with the use of a ventilation-perfusion scan and the presence of a positive blood culture.

\*Part 1 of this article appeared in the May 1999 issue.

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**ACUTE ABDOMINAL EPISODE**

Causes of acute abdominal episodes include acute cholecystitis, cholelithiasis, acute intrahepatic sickling, acute splenic infarction, and acute mesenteric/lymph node infarction. If the pain is in the right upper quadrant, the hepatobiliary tree is usually the source. Among the features are fever, chills, right upper quadrant tenderness, enlarged liver, leukocytosis, hyperbilirubinemia, and biochemical evidence of liver injury. Ultrasonography usually identifies the presence of gallstones. Splenic infarctions are associated with left upper quadrant pain and tenderness with "splinting" during inspiration. Mild pleural effusion with pleural rub and segmental lower lobe atelectasis may be accompanying features. The signs and symptoms of mesenteric/lymph node infarction are non-specific. Acute abdominal episodes also may be a presenting feature of lower lobe pneumonia. A surgical abdomen always should be considered in the differential diagnosis.

**STROKE**

This is usually a vaso-occlusive episode resulting from occlusion of the major arteries, such as the internal carotid, the anterior, and the middle cerebral arteries usually at their bifurcation. Occlusion results from repeated progressive intimal fibrosis. It occurs in up to 7% of children and may be silent or overt. The spectrum of clinical features ranges from a decline in intelligence quotient to hemiplegia, speech and visual impairment, seizures, and coma.

Transcranial Doppler is a good predictive screening tool for detecting vasculopathy and altered blood flow, but MRI or magnetic resonance angiography are the best diagnostic tools for detecting stroke.

Treatment includes an initial exchange transfusion followed by regular direct transfusions for an indefinite period to keep levels of hemoglobin S at less than 0.30 Hb fraction (<30%). Untreated strokes are associated with a 20% mortality rate. Following cessation of up to

2 years of transfusions, the recurrence rate for strokes is 70% within 3 years. Rarely, stroke may be from hemorrhage rather than vaso-occlusion; the mortality in these cases is 50%.

**PRIAPISM**

This sustained painful penile erection occurs when drainage of blood out of the corpora cavernosa is impaired because of clogging by sickled cells. It occurs at all ages and is estimated to occur in about 50% of all patients into late adulthood. There are two forms: 1) stuttering, which lasts for fewer than 24 hours per episode and is repetitive, and 2) prolonged, which lasts for more than 24 hours.

The following is a recommended sequential approach to therapy until response is seen: 1) hydration and analgesia for the first 24 hours, 2) direct transfusion for the second 24 hours, 3) exchange transfusion for the third 24 hours, and 4) surgical intervention if there is no evidence of beginning detumescence within a maximum of 48 hours following exchange transfusion. Preferred surgical approaches are corporo-saphenous shunting or corporo-glans shunting. Repeated priapism leads to sexual dysfunction.

*Acute sequestration syndrome in patients who have sickle cell disease results from acute trapping of blood in the spleen. Transfusion invariably is needed for treatment.*

**TRANSIENT RED BLOOD CELL APLASTIC EPISODE**

This transient bone marrow arrest affects primarily red blood cell precursors, but it also can affect white blood cells and platelets to some extent. The causative organism is parvovirus B19. Because the red blood cells in sickle cell disease have a shortened life span (15 to 50 days), the arrest may cause a fall in the hematocrit of up to 0.10 to 0.15 (10% to 15%) per day. The hallmark is severe anemia with reticulocytopenia. During the recovery phase, nucleated red blood cells and reticulocytosis may be present. The virus produces the same clinical syndrome in other hemolytic anemias. Other viral and bacterial infec-

tions may produce the same effect. The aplasia usually lasts 10 to 14 days.

**ACUTE SEQUESTRATION EPISODE**

This is an acute trapping of blood in the spleen and less frequently in the liver caused by impaired egress of blood out of these organs due to clogging by sickled cells. It occurs commonly in preschool-age patients (before autosplenectomy) or in older children who have hemoglobin SC disease or hemoglobin S-beta thalassemia with persistent splenomegaly. The typical clinical picture is anemia of rapid onset possibly with shock and a rapidly enlarging, painful spleen. Precipitating factors are the same as for other acute vaso-occlusive episodes, but infections, particularly upper respiratory tract infections and chest syndrome, have been associated commonly with these episodes. The complete blood count reveals anemia, reticulocytosis, nucleated red blood cells, and thrombocytopenia.

Transfusion invariably is needed for treatment. Educating caregivers about palpation of an enlarged/enlarging spleen and obtaining early medical attention can save lives. The recurrence rate is nearly 50%. Elec-

tive splenectomy following a maximum of two episodes is recommended. Even though sequestration may occur in the liver, the limited ability of this organ to expand results in less severe hematologic and cardiovascular consequences.

**INFECTIONS**

Infections are common among patients who have sickle cell disease because functional asplenia resulting from multiple infarcts leads to impaired production of antibodies and opsonins and the absence of the splenic function of phagocytosis of bacterial organisms. Infections are more frequent and more serious in preschool-age children (15%) and are associated with a 30% mortality rate. Fifty percent of those who have

hemoglobin SS disease are autosplenectomized by 2 years of age and almost 100% are by 7 years of age. The risk of infection is highest with encapsulated organisms such as pneumococci (400 times greater risk), *Haemophilus influenzae* (two to four times increased risk), meningococci, and *Salmonella* sp. Infections with organisms such as *Mycoplasma* sp may present atypically with lobar consolidation. Clinically, infection may present insidiously (eg, *H influenzae*) or as overwhelming sepsis (eg, pneumococcus).

A high index of suspicion and proper use of antibiotics to cover the three most common pathogens can be life-saving. Three cephalosporins provide adequate therapy; the choice is influenced by the patient's clinical condition and by convenience. Ceftriaxone can be used on an outpatient basis once a day in patients who are not ill, cefotaxime has good penetration of the central nervous system, and cefuroxime is available for both intravenous and oral administration. Parents and caregivers should be taught to seek medical help as soon as possible after onset of fever. It is recommended that children be given prophylactic antibiotics (penicillin, erythromycin, or amoxicillin) at least for the first

***It is recommended that children who have sickle cell disease be given prophylactic antibiotics at least for the first 5 years of life.***

5 years of life, starting as early as 3 to 4 months of age. The optimum duration of antibiotic administration remains debatable. The use of 24 valent pneumococcal, *H influenzae*, and meningococcal vaccines also is recommended. Children receiving pneumococcal vaccine at 2 years of age or younger require reimmunization after that age.

#### **LONG-TERM COMPLICATIONS**

Nearly every organ system may be affected by sickle cell disease. Silent strokes may lead to a decrease in intelligence quotient and school performance. Conjunctival vessel tortuosity is common. Blindness may result from retinopathy or central retinal artery occlusion. The presence of any red blood cells with

hemoglobin S in the anterior chamber following trauma may lead quickly to glaucoma. Sensorineural hearing loss may result from damage to the cochlea. Recurrent lung infarctions and pneumonias can lead to chronic lung disease. Resting arterial  $PO_2$  in steady-state may be 65 to 85 mm Hg. There is evidence for increased shunting. Myocardial infarctions are rare because of the rapid transit time of red blood cells in coronary vessels. Left ventricular hypertrophy is common, but right ventricular hypertrophy and cor pulmonale are seen only due to chronic lung disease.

Hyposthenuria leading to enuresis is common. Hematuria that usually is due to papillary necrosis involving the left kidney occurs frequently even in hemoglobin AS (sickle cell trait), but it is more common in hemoglobin SC disease. Gallstones develop in the first decade of life and continue to progress. Repeated infarction leads to fibrosis (sickle cell hepatopathy). Transfusion may lead to hepatitis, and the gall bladder may harbor *Salmonella* sp. Sickle cell facies is characterized by frontal bossing and overgrowth of the maxilla from wide diploic spaces. Codfish vertebrae is a combination of flattened bones with

biconcave deformity. Aseptic necrosis of the femoral head is more common in hemoglobin SC disease.

Increases in both height and weight are affected negatively by sickle cell disease, but the latter is more so. Height catches up during adolescence. This growth delay may be evident as early as 2 years of age. In females, menarche depends on weight as much as on age. Fertility is not affected in females, but males have delayed sexual maturity as well as reduced fertility. Because of recurrent hospital visits and hospitalizations, it is not unusual for patients to fall behind their peers in school work. In addition, the inability to keep up in sports and other activities combined with delayed physical growth and sexual develop-

ment put these patients at a psychological disadvantage.

### **Other Sickle Hemoglobinopathies**

#### **HEMOGLOBIN SC DISEASE**

In this disease, glutamic acid in position 6 of the globin chain is replaced by lysine. The clinical manifestation is primarily chronic hemolytic anemia of lesser severity than seen with sickle cell disease (hemoglobin SS). Persistent painful vaso-occlusive episodes are less frequent. Splenomegaly is not uncommon (60%). The complete blood count reveals increased mean corpuscular hemoglobin concentration, microcytosis, and target cells in addition to anemia and reticulocytosis. The usual complications associated with SS disease are found in SC disease, but hematuria (from papillary necrosis), eye disease, aseptic necrosis of the femoral head, and pregnancy-related complications occur more frequently with hemoglobin SC.

#### **HEMOGLOBIN S THALASSEMIA**

This is usually a severe disease that is characterized by many of the manifestations of thalassemia as well as hemoglobin SS disease.

#### **HEMOGLOBIN SF DISEASE**

This is usually a mild disease.

#### **DIAGNOSIS**

These diseases are diagnosed by hemoglobin electrophoresis. Prenatal diagnosis may be made through chorionic villi biopsy at 8 to 10 weeks' gestation. Electrophoresis may be performed on cord blood in the neonate; ambiguous results require repeat assessment at 3 months of age and examination of family members. In late childhood, electrophoresis may be performed on peripheral blood. Family studies are always desirable.

#### **MANAGEMENT**

Preventive management involves family studies, family counseling, and prenatal diagnosis to reduce propagation of the sickle gene. Appropriate immunizations, penicil-



lin prophylaxis, and avoidance of precipitating factors for acute episodes reduce the incidence of morbidity and mortality.

Education of caregivers about the significance of fever, palpation of the spleen, and early medical intervention for affected patients can help to reduce the severity of complications. Medical interventions include hydration, pain control, exchange transfusion, and chronic transfusion therapy. Interventions at cellular and genetic levels include stimulation of increased hemoglobin F production (hydroxyurea), bone marrow transplant, and gene transfers (this is still experimental).

### PROGNOSIS

Mortality is 2.6% in childhood for those who have hemoglobin SS disease, with the peak incidence of death occurring between ages 1 and 3 years. The most frequent cause of death is infection. For hemoglobin SS disease, the probability of surviving until age 20 is 85%, and for hemoglobin SC disease it is 95%.

## Thalassemia

### DEFINITION

This is a group of hereditary disorders of hemoglobin synthesis that affects the globin chain and is characterized in the more severe deficiencies by mild-to-severe hemolytic anemia. They are classified according to the involved chain as alpha, beta, or delta.

### EPIDEMIOLOGY

The milder forms of thalassemia are among the most frequent genetic defects in humans. Alpha thalassemia is found in people of African descent and in Indochina, Malaysia, and China. Beta thalassemia is found largely in people of African and Mediterranean descent, but it also is widespread in the Far East, the Middle East, and the Asian subcontinent.

### PATHOLOGY, PATHOPHYSIOLOGY, AND PATHOGENESIS

There are four alpha genes. Deficiency of only one gene (silent car-

rier) and deficiency of two genes (alpha thalassemia trait) lead to no symptoms; deficiency of three genes (hemoglobin H disease) and four genes (hemoglobin Bart; hydrops fetalis) leads to disease because of impaired synthesis of alpha globin chains.

There are two beta genes. Deficiency of one leads to essentially no significant hemolysis (beta thalassemia trait/thalassemia minor); deficiency of both genes leads to significant hemolytic anemia (thalassemia major). Thalassemia intermedia is a condition in which the degree of hemolysis is milder even though the patient may have a deficiency of both beta genes. Therefore, thalassemia intermedia is essentially a descriptive term that refers to minimal or no need for transfusions.

***Patients who have thalassemia should receive transfusion therapy accompanied by chelation to reduce iron toxicity with deferoxamine.***

### CLINICAL PRESENTATIONS

#### Hemoglobin H Disease (Alpha Thalassemia)

This hemolytic anemia may present in the neonatal period as severe hypochromic anemia. Later in life the clinical features include anemia with hepatosplenomegaly and jaundice. The hemoglobin level usually is 1.09 to 1.55 mmol/L (7 to 10 g/dL), but it may be lower. Red blood cells show hypochromia, microcytosis, and fragmentation. Hemoglobin electrophoresis reveals increased hemoglobin H (beta<sup>4</sup>) of 0.5 to 0.30 Hb fraction (5% to 30%) and increased hemoglobin Barts (gamma<sup>4</sup>) in the neonatal period. Hemolysis may be precipitated by infections or oxidant drugs such as iron and sulfonamides. Treatment includes administration of folate, avoidance of precipitating drugs, transfusions as needed, and occasionally splenectomy for hypersplenism.

#### Hydrops Fetalis (Alpha Thalassemia)

This is the most severe form of alpha thalassemia. Because it is incompatible with life, affected patients are stillborn or die soon after birth. They are edematous and

have ascites due to heart failure that results from severe anemia. The complete blood count documents hypochromic macrocytes and several nucleated red blood cells. Hemoglobin electrophoresis shows hemoglobin H (beta<sup>4</sup>) and predominantly hemoglobin Barts (gamma<sup>4</sup>).

#### Beta Thalassemia Major

The severity of this anemia results from a combination of ineffective erythropoiesis and shortened survival of the red blood cell in circulation.

The complications of beta thalassemia are those of increased iron absorption (a consequence of ineffective erythropoiesis), hemolytic anemia, and transfusions. Complications of hemolytic anemia include

enlarged bone marrow cavity with thinning of cortex, specific facies, gallstones, and chronic leg ulcers. The complications of iron overload affect all organs of the body, including the heart (arrhythmias, heart failure), liver (cirrhosis), thyroid (hypothyroidism), pancreas (diabetes), and hypothalamic-pituitary axis (delayed growth and sexual maturity).

The aim of transfusion is to maintain the pretransfusion hemoglobin level at 1.55 mmol/L (10 g/dL) or higher; the adequacy of transfusion can be predicted by a nucleated red blood cell count of less than 5 nucleated red blood cells/100 white blood cells. Transfusion is designed to suppress the abnormal activity of the marrow, thereby allowing for normal growth and development. Therefore, it should be initiated as soon as possible (6 months to 1 year of age). After the epiphyses are fused and growth is complete, a lower pretransfusion hemoglobin level of 1.09 to 1.24 mmol/L (7 to 8 g/dL) may be adequate in some patients.

Transfusion therapy should be accompanied by chelation with deferoxamine to reduce iron toxicity. Most institutions prefer to start chelation at 3 to 4 years of age when

there usually is a sufficient amount of chelatable iron to make the risk: benefit ratio and cost effectiveness worthwhile. Chelation at a younger age is technically and socially more challenging, although some centers have embarked on chelation at the time of initiating hypertransfusion. Complications associated with deferoxamine therapy include deafness, color and night blindness, visual field loss, predisposition to *Yersenia* infections, and mucormycosis.

Splenectomy is indicated if:

1) the spleen is enlarged substantially, 2) there is evidence of hypersplenism with or without a massive size leading to pancytopenia, or 3) the requirements exceed 200 mL/kg per year. The success rate of curing thalassemia major by bone marrow transplant is 75% to 80%.

#### **Thalassemia Intermedia**

The definition of thalassemia intermedia is the absence of chronic transfusion support in a patient who has the phenotype of thalassemia major. These patients usually experience normal growth and development and have low hemoglobin levels of 1.09 to 1.24 mmol/L (7 to 8 g/dL) that do not require transfusions.

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#### **PIR QUIZ**

Quiz also available online at [www.pedsinreview.org](http://www.pedsinreview.org).

9. For patients who have hemoglobin SS disease, osteomyelitis is differentiated from painful vaso-occlusive episodes in bone *best* by:
- A. Changes on serial magnetic resonance imaging scans.
  - B. Degree of leukocytosis.
  - C. Early radiographic findings.
  - D. Height of fever.
  - E. Severity of pain.
10. The severe anemia that is produced by parvovirus B19 in many patients who have hemoglobin SS disease reflects *primarily*:
- A. Accentuated intravascular sickling.
  - B. Deficient humoral immunity.
  - C. Dramatic decrease in production of mature red blood cells.
  - D. Impaired cellular immunity.
  - E. Induced hypersplenism.
11. A 2-year-old boy who has hemoglobin SS disease presents with a sudden onset of fever. In your office, his rectal temperature is 39.2°C (102.6°F). Findings on physical examination are otherwise unremarkable. Assuming that close follow-up is assured, the *most* appropriate choice of outpatient therapy is:
- A. Acetaminophen orally.
  - B. Amoxicillin orally.
  - C. Azithromycin orally.
  - D. Cefotaxime intramuscularly.
  - E. Ceftriaxone intramuscularly.
12. Among the following, which is *most* likely to be a long-term complication of hemoglobin SS disease?
- A. Cor pulmonale.
  - B. Gallstones.
  - C. Infertility in females.
  - D. Myocardial infarction.
  - E. Obesity.
13. You are considering the initiation of deferoxamine chelation therapy to limit iron toxicity in a 4-year-old girl who has beta thalassemia major. Among the following findings, which would be *most* likely in a patient who has iron overload?
- A. Cirrhosis.
  - B. Diabetes insipidus.
  - C. Excessively tall stature.
  - D. Hyperthyroidism.
  - E. Precocious puberty.

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