A: In sickle-cell disease, an autosomal recessive genetic mutation changes the properties of hemoglobin and alters the shape of the red blood cells (RBCs) that carry it. Normally, RBCs are plump and round and move easily throughout the blood vessels, delivering oxygen and nutrients to the cells. In sickle-cell disease, the shape of RBCs is distorted; instead of spherical, RBCs are half-moon or sickle shaped.

Sickle-cell disease is one of the most common genetic disorders in the United States; it’s present in 1 in 600 African-Americans (about 80,000 individuals), the most commonly affected ethnic subgroup. For an individual to have sickle-cell disease, he must inherit the mutated gene from both parents. The carrier state, which occurs in individuals who inherit the gene from only one parent, is usually asymptomatic, although hematuria and sickle complications can occur under conditions of severe physical stress like dehydration, temperature extremes, infection, or drastic pressure changes. In the United States, 8% of African-Americans carry the sickle gene; this translates to about 2 million individuals.

The clinical manifestations of sickle-cell disease are thought to result from increased blood viscosity and changes in RBC deformability, fragility, and adherence to vascular walls. The coagulation system also plays a role because markers of increased platelet activation are found in patients with sickle-cell disease. RBC dehydration and deoxygenation add to the cells’ deformation, further increasing blood viscosity and capillary plugging. The result is a disruption of blood flow, causing vascular occlusion, hemorrhages, infarctions, hemolytic anemia, and possibly tissue death. Years ago, people with sickle-cell disease commonly died in their teens. With improved treatment, greater use of immunizations, and earlier detection, more patients with sickle-cell disease are now living longer, well into adulthood.

Q: What is sickle-cell disease? How does it affect individuals who have it?

A: An RBC affected by sickle-cell disease has a lifespan of only about 10 to 20 days, compared with the normal 120 days. This premature death results in hemolytic anemia, and bone marrow proliferates as the body tries to maintain an adequate level of RBCs. Hemolytic anemia also affects liver function, which is evidenced by increased indirect (unconjugated) bilirubin and lactate dehydrogenase levels.

Intense pain in the extremities, back, chest, and abdomen is a common symptom of sickle-cell disease. It may be caused by the inflammatory response to bone marrow and muscle necrosis, ischemia, or infarction secondary to blood flow obstruction and sludging. Chronic hypoperfusion and hypoxia can also damage end organs like the brain, lungs, liver, spleen, kidneys, bones, and eyes. Pain severity has been reported to range from mild, transient attacks lasting no more than 5 minutes, to debilitating pain lasting days or weeks that requires hospitalization and may recur. Cumulative ischemic
tissue damage and fibrosis can lead to chronic pain. The frequency of pain crises varies with the individual and depends to some extent on hemoglobin phenotype, physical condition, comorbidities, and psychological or social variables.

Clinical manifestations can be divided into three classifications: vaso-occlusive, hematologic, and infectious. Let’s look at each type in more detail.

**Vaso-occlusive crises** arise from sickled RBCs interfering with microcirculation, which leads to ischemia and damage to the structure where the blood supply is cut off. Bones, abdominal organs, lungs, and the vessels supplying the brain are all vulnerable. Ischemic pain is the most frequent complaint and most common characteristic of sickle-cell disease.

Complications include liver and kidney failure, functional asplenia, transient ischemic attacks, cerebral infarction/hemorrhage, skin ulcers, retinal hemorrhage, and priapism.

**Hematologic crises** are characterized by a rapid worsening of anemia due to splenic sequestration, in which sickled RBCs become trapped inside of the spleen, or aplasia, in which the bone marrow stops producing RBCs.

Splenic sequestration is second only to infections as a cause of death in infants with sickle-cell disease. The hemoglobin level rapidly falls and the spleen becomes enlarged. Patients are generally admitted to the intensive care unit for aggressive blood transfusions; in some cases, an emergency splenectomy may be needed. Hepatic sequestration (sickled RBCs trapped in the liver) may occur later in life with similar signs and symptoms, including a rapidly enlarging liver and a falling hematocrit. The treatment consists of aggressive simple blood transfusion or RBC exchange transfusion.

In an aplastic crisis, the bone marrow slows or stops RBC production. Signs and symptoms include falling hemoglobin and hematocrit levels, a drop in the reticulocyte count, weakness, pallor, dyspnea, and dizziness. Treatment for aplastic crisis includes immediate hospitalization and blood transfusions to support the hemoglobin level.

Sources of the aplastic event, such as Parvovirus infection or folate deficiency, should be investigated and treated.

**Infectious crises** are characteristic of and common in patients with sickle-cell disease. Functional asplenia interferes with the immune system’s ability to combat dangerous infectious agents. The best treatment is prevention through vaccination and prophylactic antibiotics.

Bacterial infection is one of the main causes of morbidity and mortality in patients with sickle-cell disease. Fever or fever with pain is the most common presentation. Children under age 3 years are at greatest risk for fatal sepsis caused by *Streptococcus pneumoniae*. Because spleen function is markedly decreased or absent in sickle-cell disease, patients are at high risk for infection with encapsulated organisms, like *S. pneumoniae*, *Haemophilus influenzae*, salmonella, meningococcus, and others. Serious infections, such as meningitis, pneumonia, sepsis, and osteomyelitis, must be aggressively excluded and treated empirically early to prevent morbidity and mortality.

**Battle strategy** highlights some of the most
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<th>Battle strategy</th>
<th>Diagnostic tests</th>
<th>Differential diagnosis</th>
<th>Treatment options</th>
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<tr>
<td><strong>Hand-foot syndrome (dactylitis); swollen hands and feet</strong></td>
<td>• Hemoglobin  • Electrophoresis</td>
<td>• Sickle-cell disease</td>
<td>• Fluids  • Pain management</td>
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<tr>
<td><strong>Chills, fever</strong></td>
<td>• Complete blood count (CBC)  • White blood cell (WBC) differential (check for elevated bands and total WBC count), blood cultures  • Chest X-ray</td>
<td>• Sepsis  • Pneumonia  • Osteomyelitis</td>
<td>• Treat empirically with antibiotics until cultures are known  • Prevent infections with immunization and prophylactic penicillin up to age 6</td>
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<td><strong>Headache</strong></td>
<td>• Computed tomography (CT) scan  • Magnetic resonance imaging (MRI)  • Magnetic resonance angiography (MRA)  • Lumbar puncture</td>
<td>• Stroke  • Aneurysm  • Meningitis</td>
<td>• Treat etiology</td>
</tr>
<tr>
<td><strong>Chest pain, dyspnea, cough</strong></td>
<td>• Chest X-ray  • Arterial blood gas analysis</td>
<td>• Chest syndrome  • Pneumonia</td>
<td>• Treat empirically with antibiotics and transfusion</td>
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<td><strong>Abdominal pain and swelling</strong></td>
<td>• Ultrasound or CT scan  • CBC  • Chemistry profile</td>
<td>• Splenic or hepatic sequestration  • Gallstones</td>
<td>• Transfusion for sequestration  • Surgery for sequestration</td>
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<td><strong>New weakness, paresthesias, difficulty talking</strong></td>
<td>• CT scan  • MRI  • MRA</td>
<td>• Stroke</td>
<td>• Transfuse acutely  • Chronic transfusion program for prevention</td>
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<tr>
<td><strong>Pain in extremities, low back</strong></td>
<td>• CBC  • Reticulocyte count  • Chemistry profile  • Urinalysis</td>
<td>• Pain crisis</td>
<td>• Oral or I.V. hydration  • Pain management  • Hydroxyurea may prevent crisis</td>
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<td><strong>Weakness, lethargy, pallor (aplastic crisis)</strong></td>
<td>• CBC  • Reticulocyte count</td>
<td>• Aplastic crisis, bleeding, hyperhemolysis</td>
<td>• Transfusion support until bone marrow responds</td>
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<tr>
<td><strong>Acute decline after routine pain crisis with multiple organ system failure evidenced by kidney and liver failure, acute respiratory distress syndrome, disseminated intravascular coagulation</strong></td>
<td>• CBC  • Reticulocyte count  • Chemistry profile  • Urinalysis  • Chest X-ray  • PTT and aPTT</td>
<td>• Multiorgan system failure</td>
<td>• Transfusion and support for failing organ systems</td>
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<tr>
<td><strong>Jaundice</strong></td>
<td>• CBC  • Reticulocyte count  • Chemistry profile  • Hepatitis screen  • Consider gallbladder ultrasound</td>
<td>• Increased hemolysis  • Hepatitis  • Bile duct obstruction</td>
<td>• Treat etiology  • Administer folate, 1 mg daily, due to red blood cell production demands</td>
</tr>
<tr>
<td><strong>More frequent emergency department visits for pain</strong></td>
<td>• Assess psychosocial aspects</td>
<td>• Inadequate pain management  • Infection  • Increased anemia</td>
<td>• Pain management  • Consider hydroxyurea therapy to prevent pain</td>
</tr>
<tr>
<td><strong>Focal bone pain</strong></td>
<td>• CBC  • X-ray of focal pain  • Consider bone scan or MRI of focal pain</td>
<td>• Bone infarction  • Osteomyelitis  • Avascular necrosis (AVN; if pain is in the hip or shoulder)</td>
<td>• For bone infarction or AVN, long-acting nonsteroidal anti-inflammatory drugs and decreased weight bearing</td>
</tr>
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common signs and symptoms, diagnostic tests, and treatment options for sickle-cell disease.

**Q:** How is sickle-cell disease managed?  
**A:** In general, management of acute events should include a thorough history, physical exam, lab workup, and X-rays. Precipitating causes like infection, dehydration, hypoxia, and exposure to temperature extremes should be identified and corrected.

General treatment measures include I.V. hydration with hypotonic fluids (dextrose 5% water or 0.45% sodium chloride), analgesia, and oxygen (if the patient is dyspneic or hypoxic).

If the patient shows evidence of stroke, myocardial infarction, multiple organ system failure, or sequestration of RBCs in the spleen or liver, phenotypically matched, sickle-negative, leukocyte-depleted packed RBCs are the blood product of choice. A posttransfusion hematocrit of 36% or less is recommended; higher values are thought to cause hyperviscosity, a potentially dangerous complication.

Managing acute episodes of sickle-cell disease requires adequately controlling pain, excluding correctable precipitating causes, detecting life-threatening complications, and diagnosing causes of pain unrelated to sickle-cell complications. Pain scores using a standard pain rating scale should be measured before medication and several times after to document treatment progress. Pain therapy requires choosing agents that are safe and provide rapid analgesia. Pain medication should be administered on a fixed time schedule at intervals that equal the period of adequate analgesia. This will maintain a steady serum drug level, which will improve pain control, minimize complications, and decrease anxiety. The oral route is safest for pain medications, but the intravenous route is the fastest. A patient-controlled analgesia pump that provides a constant, low-dose infusion of morphine with defined rescue doses offers excellent pain treatment.

Adverse effects of opioid analgesics include itching from histamine release, respiratory depression, nausea, vomiting, hypotension, constipation, increased bladder tone, urinary retention, and decreased seizure threshold. Synthetic agonist-antagonist agents such as buprenorphine (Buprenex) and nalbuphine (Nubain) are alternative choices for some patients, but they can cause withdrawal symptoms similar to use of naloxone (Narcan) in patients with frequent opioid usage.

Frequency of pain events may be minimized by keeping the patient well hydrated, avoiding temperature extremes, preventing infections, and maintaining a healthy lifestyle. It’s been shown that daily administration of hydroxyurea can cut the number of pain events in half; it boosts the production of hemoglobin F, which reduces the severity of sickle-cell disease by suppressing the formation of hemoglobin S polymers, and it’s been shown to improve life expectancy.

Oxygen should be administered if the patient has an underlying pulmonary problem and hypoxia is documented by arterial blood gases or pulse oximetry. Low oxygen saturation in symptomatic patients must be investigated with arterial blood gases, chest X-rays, and pulmonary testing.

Bone marrow transplant is curative, but it has a 10% mortality rate. Further limiting its usefulness is a scarcity of human leukocyte antigen (HLA) matched donors.

One of the newer treatment options under investigation is the use of nitric oxide, which acts as a vasodilator. It slows and can even reverse sickling of the RBCs. The oral antifungal clotrimazole is undergoing clinical trials to determine if it can reduce sickling and maintain RBC hydration by preventing potassium loss. The combination of clotrimazole and hydroxyurea may reduce the severity of anemia and decrease hemolysis. Also under investigation is the surfactant poloxamer 188 (Flocon, RheothRx), which coats sickled RBCs, thus allowing them to move more freely over each other and through vessels. This improved blood flow helps restore oxygen delivery to hypoxic tissue.
Q: What’s “acute chest syndrome” in patients with sickle-cell disease?
A: Acute chest syndrome is defined as the appearance of a new pulmonary infiltrate on the chest X-ray, accompanied by fever and multiple respiratory symptoms, including cough, tachypnea, wheezing (especially in children), and chest pain in a patient with sickle-cell disease. The etiology of acute chest syndrome is infection in about a third of cases; fat embolism from bone marrow necrosis is the cause of about 10% of cases; and the rest are idiopathic.

Patients with acute chest syndrome should be treated with transfusion, empiric antibiotics, incentive spirometry and chest therapy, supplemental oxygen (for a drop in oxygen saturation), analgesia, and fluid management. Studies are under way to see if inhaled nitric oxide can safely benefit patients with acute chest syndrome.

Q: What are the benefits of infant screening and genetic counseling?
A: According to the National Institutes of Health, neonatal screening should be requested for all infants. Any infant not screened at birth should be screened for hemoglobin abnormalities prior to age 2 months.

Why is early screening important? For one thing, children with sickle-cell disease should get all recommended immunizations, including pneumococcal-conjugated vaccine, influenza vaccine, and meningococcal vaccine.

Secondly, children with sickle-cell disease require routine oral penicillin prophylactically to prevent pneumococcal infection. Administration is started as early as age 2 months and is stopped at approximately age 5 years. (Erythromycin is used for patients with penicillin allergy.)

As for genetic counseling, individuals of childbearing potential who carry the sickle-cell trait should be aware that they can pass the trait to their offspring. A couple in which both partners have the trait has a 25% chance of producing offspring with full-blown sickle-cell disease in each pregnancy.

Learn more about it


