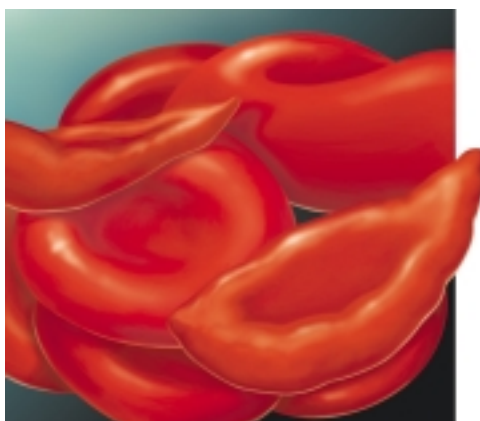


# Sickle Cell Disorders: Evaluation, Treatment, and Natural History

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**S**ickle cell disease (SCD) is a group of genetic disorders most commonly seen in people of African descent. These are among the most frequently seen genetic disorders in the United States, and they carry significant morbidity and are potentially fatal. Symptomatic patients experience painful crises and may have renal failure, heart failure, infections, and other complications.



A significant population of the United States is affected by sickle cell disorders. Of African Americans, 7.8% carry the hemoglobin S trait, 2.3% carry the hemoglobin C trait, and 0.8% carry the  $\beta$ -thalassemia trait.<sup>1</sup> Consequently, 1 out of 650 African Americans is at risk of severe sequelae from sickle cell anemia, 1/1100 from hemoglobin SC disease, and 1/3200 from hemoglobin S- $\beta$  thalassemia. However, SCD is not strictly confined to those of African descent—the hemoglobin S gene is found in as many as 25% of emigrants from parts of Greece, Saudi Arabia, and India.<sup>2</sup>

In addition to its impact on patient health, SCD is important economically. In 1996, sickle cell disorder accounted for 75,000 hospitalizations in the United States, each averaging 6 days in length and \$6300 in cost, totaling \$475 million for acute care alone.<sup>3</sup> Regular follow-up care may augment a patient's ability to lead a productive life and reduce acute care costs; however, long-term care may be costly as well (eg, \$3000/year for hydroxyurea therapy and \$100,000 to \$200,000 for bone marrow transplant).<sup>4</sup> The lost work potential of persons with SCD is also immense.

Because of the substantial impact of this common disease on society and the individual, it is important for the medical community to thoroughly understand

SCD. This article reviews the natural cycle of the painful crisis, as well as its precipitants and proposed pathophysiology. Evaluation and treatment of patients with complications of sickle cell disorder are discussed.

## NOMENCLATURE

Small differences in nomenclature may signify a large difference in patient outcome. The term *sickle cell disorder* encompasses all states in which a sickle gene is inherited. This group includes

all patients with a positive sickle preparation smear; the patient may or may not be symptomatic. *Sickle cell disease* is any type of sickle cell disorder in which significant morbidity, such as organ failure or vaso-occlusive pain crisis (VPC), results from the sickling of red blood cells. The term *sickle cell anemia* is usually reserved specifically for patients who are homozygous for hemoglobin S (hemoglobin SS).

## GENETIC BASIS OF SICKLE CELL DISEASE

Sickle cell disorder was first noted to affect erythrocytes in 1911, when James Herrick and a medical student of African descent discovered sickle-shaped erythrocytes while examining the student's blood. Linus Pauling further categorized the disorder by noting an abnormal hemoglobin electrophoretic pattern, designated hemoglobin S, and declaring it a molecular disease.

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**Table 1.** Frequency of Vaso-Occlusive Pain Crisis (VPC) in Patients with Sickle Cell Disease

Pain Rate	Disorder			
	Sickle Cell Anemia ( $\beta^S/\beta^S$ )	Hemoglobin S/ $\beta^0$ Thalassemia	Hemoglobin SC Disease	Hemoglobin S/ $\beta^+$ Thalassemia
0	39%	29%	54%	50%
0 < r < 1	40%	37%	37%	42%
1 < r < 3	16%	26%	7%	6%
3 < r < 6	4%	8%	2%	2%
6 < r	1%	0%	0%	0%

r = number of episodes of pain per patient-year. Data from Platt OS, Thorington BD, Brambilla DJ, et al: Pain in sickle cell disease: rates and risk factors. *N Engl J Med* 1991;325:11-16.

**Table 2.** Life Expectancy of Persons with Sickle Cell Disorders

Gender	Disorder		
	Sickle Cell Trait ( $\beta^A/\beta^S$ )	Sickle Cell Anemia ( $\beta^S/\beta^S$ )	Hemoglobin SC disease
Male	normal	42 y	60 y
Female	normal	48 y	68 y

Data from Platt OS, Brambilla DJ, Rosse WF, et al: Mortality in sickle cell disease: life expectancy and risk factors for early death. *N Engl J Med* 1994;330:1639-1644.

The hemoglobin S aberration stems from a mutation of chromosome 11 in codon 6 of the hemoglobin  $\beta$  chain gene, causing a valine amino acid to be substituted for glutamic acid. A person inherits one  $\beta$  chain gene from each parent in a mendelian autosomal recessive fashion. Persons with sickle cell trait (one  $\beta^S$  gene, one normal  $\beta$  gene [ $\beta^A$ ]) are mostly asymptomatic<sup>1,5</sup> except for occasional hematuria, isosthenuria (inability to form concentrated urine), or, very rarely, VPC occurring under conditions of extreme low oxygen (eg, in submarines or high altitude<sup>6</sup>).

Several genotypes produce sickle cell disease; each is characterized by the presence of one  $\beta^S$  gene and one of the following genes: another  $\beta^S$  (homozygous disease), a hemoglobin C gene, a gene for  $\beta^+$  or  $\beta^0$  thalassemia, or a hemoglobin D or hemoglobin E gene (these last two are of low prevalence).

Genotype affects the course of disease<sup>5,7,8</sup> (Tables 1 and 2). Sickle cell trait carries a normal life expectancy and is rarely symptomatic. Patients with hemoglobin SC disease (hemoglobin S/hemoglobin C genotype) and hemoglobin S- $\beta^+$  thalassemia experience relatively

infrequent episodes of VPC compared with patients with sickle cell anemia or hemoglobin S- $\beta^0$  thalassemia. Sickle cell anemia reduces life expectancy by more than 20 years, whereas people with hemoglobin SC disease regularly reach the seventh and eighth decades of life. After studying a cohort of 3764 patients, Platt et al<sup>8</sup> documented the most common circumstances of death in adults (Table 3) and found 8 statistically significant risk factors for early death (Table 4). Infection, particularly pneumococcal sepsis, is the leading cause of death in children.<sup>8,9</sup>

Hemoglobin F was first noted to mitigate SCD in Bedouin Arabs and tribes from central India who naturally have a high hemoglobin F level and mild disease.<sup>10</sup> A glutamine residue at  $\gamma 87$  of the hemoglobin F molecule prevents cross-bridging of the hemoglobin S  $\beta$  chains.<sup>10</sup> The effect of hemoglobin F is incremental—a small increase in hemoglobin F will produce a small decrease in pain rate.<sup>7</sup> Without intervention, hemoglobin F levels are relatively constant throughout life (although normally high during the first few months of life), and people with lower levels are likely to die earlier.<sup>8</sup> These observations encouraged the development of hydroxyurea therapy, which raises levels of hemoglobin F and decreases morbidity<sup>11</sup> (and hopefully mortality).

A multitude of genetic contributions other than the  $\beta$ -globin allele affect SCD severity.<sup>12</sup> Vascular tone control (linked to nitric oxide production), von Willebrand factor expression,  $\alpha$  thalassemia, X-linked factor (which affects hemoglobin F concentration), and intrerythrocyte volume regulatory controls may alter SCD manifestations. These characteristics are determined by “associated alleles” located next to the  $\beta$ -globin allele. These associated alleles, by genetic linkage, are responsible for the 5 different haplotypes (ie, Benin,

(continued on page 21)

(from page 18)

**Table 3.** Causes of Death in Adults with Sickle Cell Disease

Circumstance of Death	Percent of Deaths
Acute pain episode	21.5
Circumstance not known	17.7
Renal failure	10.5
Stroke	9.6
Perioperative	6.7
Trauma	6.7
Infection	6.2
Congestive heart failure	5.2
Acute chest syndrome	4.3

Data from Platt OS, Brambilla DJ, Rosse WF, et al: Mortality in sickle cell disease: life expectancy and risk factors for early death. *N Engl J Med* 1994;330:1639-1644.

Bantu, Cameroon, Indian, and Senegal) that account for some of the variation among sickle cell anemia patients. Genetic linkage is a process whereby a group of alleles are tightly clustered on a chromosome; consequently, they maintain their association during meiosis crossing over. Genetic factors on chromosome 11 but not linked to the  $\beta$  gene and genetic factors located on other chromosomes may also affect the course of SCD.

#### CLINICAL MANIFESTATIONS OF SICKLE CELL DISEASE Manifestations Relative to Age

The manifestations of SCD are age dependent.<sup>2,9</sup> For sickle cell anemia, the first symptoms usually occur after 10-12 weeks of life as a colic-like syndrome of irritability after a feeding. Poorly compensated hemolytic anemia, significant reticulocytosis, and sickling are noted in peripheral blood smears at initial presentation.

Splenic involvement in sickle cell anemia relates to age as follows: by 5 to 6 months, splenomegaly is present; from the age of 9 months to 4 years, sequestration crises are common; from the age of 5 to 8 years, splenic involution and resolution of splenic sequestration occurs. Persistent adenopathy, including tonsillar and mediastinal, is present for the first 5 years of life, but is uncommon thereafter.<sup>9</sup>

In people with SCD, more total years of growth eventually compensates for diminished height and weight as children, and adults with SCD are of equal size compared with the general population. Puberty is delayed approximately 2.5 years in persons with SCD. Infectious complications, such as parvovirus aplastic crisis and sepsis from encapsulated organisms (eg,

**Table 4.** Statistically Significant Risk Factors for Early Death in Patients with Sickle Cell Anemia

Acute chest syndrome (fever, chest pain, pulmonary infiltrate)
Renal failure (creatinine 20% above baseline and creatinine clearance < 100 mL/min)
Seizures (major/minor motor, not associated with strokes)
Pain episode (> 1/y)
Acute anemic episode (hemoglobin concentration 30% below baseline in absence of bleeding)
Leukocyte count > $15.1 \times 10^3/\text{mm}^3$
Hemoglobin F < 8.6%
Hemoglobin concentration < 7.1 g/dL

Adapted with permission from Platt OS, Brambilla DJ, Rosse WF, et al: Mortality in sickle cell disease: life expectancy and risk factors for early death. *N Engl J Med* 1994;330:1643.

pneumococci), occur more frequently in youth, as opposed to chronic pain states and organ failure, which occur more frequently in adults. VPC frequency gradually increases from birth to 30 years, and gradually decreases thereafter.<sup>7</sup> Maternal mortality, usually due to frequent VPC episodes or acute chest syndrome, is 1% in women with SCD.<sup>13</sup>

#### Vaso-Occlusive Pain Crisis

Episodes of VPC are common and are perhaps the most noted feature of SCD. VPC is defined as the occurrence of pain in the extremities, back, abdomen, chest, or head that lasts 2 or more hours and cannot be explained except by the presence of SCD.<sup>7</sup> Bone is the usual site of vaso-occlusion during pain crisis, and ischemia may be visualized by magnetic resonance imaging if vaso-occlusion leads to aseptic necrosis.

There is a typical circadian pattern to the occurrence of VPC, with bimodal peaks at 2 PM and 9 PM (with approximately 10% of cases occurring at each peak) and a trough at 5 AM (approximately 1% of cases).<sup>14</sup> Well-known precipitants of VPC include cold weather, relative high hemoglobin concentration, dehydration, infection, exercise, dampness, poor diet, hypoxia, acidosis, emotional stress, and fatigue. Platt et al<sup>7</sup> showed that people older than 20 years with 0 to 3 VPC episodes/year have 1.8 deaths/100 patient-years, whereas those with more than 3 episodes/year had 3.7 deaths/100 patient-years. In patients younger than 20 years, however, there was no association between VPC frequency and mortality.

Four distinct VPC phases<sup>15</sup> may be elucidated by a thorough history. A *prodromal phase* of extremity

numbness, aches, and paresthesias is described by 58% of patients 1 day before pain onset.<sup>15</sup> During this phase, increased numbers of irreversibly sickled cells (ISCs) and dense cells, and decreased erythrocyte deformability (relative to the individual's steady state values), have been reported.<sup>15</sup> The *initial phase* (also called first, evolving, or infarctive phase) is characterized by the onset of pain with fever, anorexia, and anxiety. This phase is characterized by a relative increase in dense cells, ISCs, and erythrocyte distribution width and a decrease in platelet count. The *established phase* (second, inflammatory, or post-infarctive phase) lasts an average of 4 or 5 days in adults. This phase is characterized by severe, persistent pain. Inflammatory signs and symptoms may be prominent, including fever, leukocytosis, swelling, arthralgias, and joint effusions. Bone infarction typically occurs during the established phase. Laboratory evaluation yields an increased C-reactive protein and lactate dehydrogenase along with reticulocytosis and a low concentration of hemoglobin compared with steady state values. Finally, in the *resolving phase* (last, healing, recovery, or post-crisis phase) the pain gradually decreases over 1 or 2 days and the number of dense cells, ISCs, and the degree of erythrocyte deformability return to steady state values. A subsequent rebound increase in reticulocytes, viscosity, fibrinogen, platelets, and vascular cell adhesion molecule 1 (VCAM-1) may be the cause of the 20% rate of recurrent crises that occur within 1 week of the resolving crisis.<sup>16</sup>

#### **Priapism and Sequestration**

Priapism and sequestration are the other two most common acute pain states in patients with SCD. Priapism is classically defined as a prolonged and painful penile erection without concurrent sexual desire.<sup>5</sup> Repeated episodes of priapism lead to impotence, and subsequent episodes of priapism may be characterized by a painful, but not fully erect, penis.

Sequestration denotes trapping of erythrocytes within an encapsulated organ (commonly the spleen or liver), producing intense pain as the engorged organ strains against a taut capsule. Sequestration may result in critically low hemoglobin concentrations and organ rupture, and is occasionally fatal. Splenic sequestration is rare in patients older than 5 years.

#### **Anemia**

In addition to pain states, anemia is also a hallmark of SCD. Hemoglobin concentrations are typically 6 to 9 mg/dL in adults with SCD because the lifespan of erythrocytes is only 10 to 12 days, compared to the

norm of 120 days.<sup>2</sup> Compensatory mechanisms include an increased cardiac output and a right-shifted oxygen dissociation curve, producing a high level of oxygen delivery for the hemoglobin concentration. Because of these compensatory mechanisms, certain clinical symptoms and signs of anemia (eg, dyspnea on exertion, fatigue, mucosal pallor, cardiomegaly) are often not prominent during the SCD steady state.

The chronic hemolytic destruction of ISCs produces physical examination findings of jaundice (usually first noted as scleral and sublingual icterus) and changes secondary to hyperplastic marrow (ie, tower skull, hepatomegaly secondary to extramedullary hematopoiesis). Aplastic anemic crises occur more frequently in children with a parvovirus infection, which is characterized by mild fever, dyspnea on exertion, anorexia, and pallor. Recovery from aplastic crisis typically requires a week, but the patient may need to be transfused with packed erythrocytes until marrow recovery; a single transfusion of 2 units of packed erythrocytes is usually sufficient to support a patient through a VPC.

#### **Stroke**

Central nervous system events can be particularly catastrophic in patients with SCD.<sup>2</sup> Strokes occur at a median age of 6 years, and affect 8% of sickle cell anemia patients by the age of 14 years. Eighty percent of stroke cases present with total occlusion of 1 of the major cerebral vessels, causing hemiplegia; unfortunately, there is a 50% to 70% chance of recurrence in these patients within 3 years. Stroke may cause death or decreased potential for social interaction or meaningful advancement in schoolwork or employment. Patients with recurrent strokes may be candidates for high-risk treatments such as recurrent transfusions or bone marrow transplant.

#### **Organ Damage**

Organ damage is progressive throughout the course of the disease. It may be either slow, steady, and irreversible, or marked by acute deficits, some of which may be reversible. Spleen damage is universal in patients with SCD. Antibody formation, opsonization, and alternate complement pathway activation are all decreased by splenic hypofunction, which occurs early in childhood. Recurrent and irreversible small infarcts cause auto-splenectomy and predispose the individual to infections with encapsulated organisms (eg, pneumococci, meningococci, salmonella). The risk for pneumococcal sepsis is particularly important in children—80% of cases occur in patients younger than 3 years.<sup>17</sup>

In addition to infection, other pulmonary calamities include the acute chest syndrome and respiratory failure caused by marrow emboli from aseptic necrosis. Acute chest syndrome is defined as the finding of new pulmonary infiltrates in addition to chest pain, a temperature greater than 38.5°C, tachypnea, wheezing, or cough. Fat emboli cause up to 8.8% of cases of acute chest syndrome.<sup>18</sup> Infections, including community-acquired pneumonia, also frequently cause acute chest syndrome.

Because adults with SCD are hyposplenic, senescent erythrocytes are destroyed in the liver. The liver may be the site of sequestration crises, infarcts leading to postnecrotic cirrhosis, and damage secondary to hemochromatosis. Because of increased erythrocyte turnover, cholelithiasis is widespread in patients with SCD, with an 80% prevalence at age 35 years,<sup>5</sup> increasing the risk of infection, colic, and pancreatitis.

Starting in the first decade of life, the entire kidney is affected in patients with SCD and can lead to loin pain, hematuria, focal interstitial nephritis, tubular dysfunction, nephrotic syndrome, and papillary necrosis. Twenty-five percent of adults with SCD have proteinuria due to hyperfiltration and glomerulopathy.<sup>17</sup> Isosthenuria, which is tubular dysfunction resulting in urine tonicity equaling that of plasma regardless of fluid status, is very common both in persons with SCD and those with the sickle cell trait. This inability to concentrate urine leads to high volume output, nocturia, and a lack of response to antidiuretic hormone when oral intake of fluid decreases. Isosthenuria exacerbates dehydration, a factor that encourages sickling.

#### **Other Chronic Manifestations**

Both acute and chronic pain occurs in bones, joints, and extremities. Chronic damage causes osteosclerosis and osteoarthritis, which are frequently visible radiographically. Skeletal malformations occur as a result of bone infarction at a growing epiphyseal plate; this is common in digits, but fortunately is uncommon in the long bones.

Leg ulcers are produced by minor trauma, stasis, pressure, and sickling in the small skin vessels. Ulcers typically occur at the lower lateral shin. They are more common in the tropics<sup>4</sup> and among lower socioeconomic classes.<sup>2</sup>

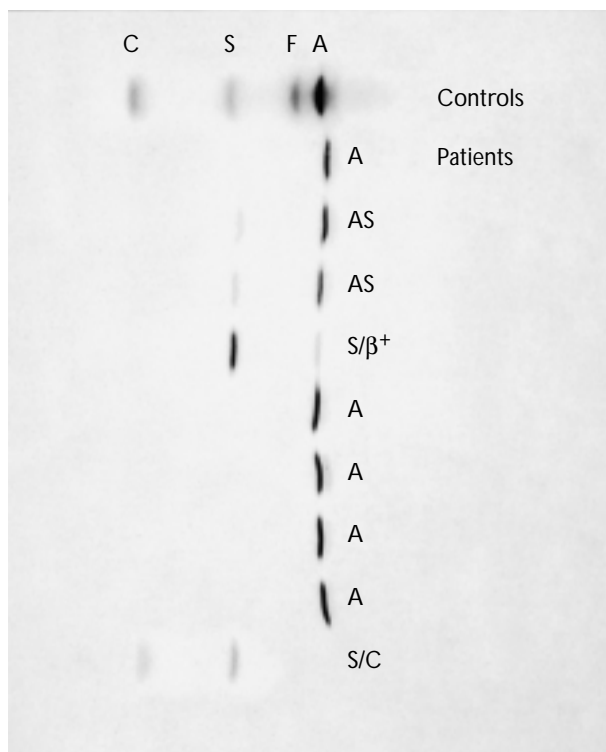
#### **PATHOPHYSIOLOGY OF SICKLE CELL DISEASE**

The mechanisms by which abnormal hemoglobin produces the profound, systemic, and severe effects of SCD are complex.<sup>10,19,20</sup> Young, "sticky" erythrocytes containing hemoglobin S adhere to the postcapillary

venule, narrowing its lumen. This decreases velocity of blood flow and increases erythrocyte transit time. Subsequently, hemoglobin S becomes deoxygenated as the stagnant blood unloads more oxygen to surrounding tissues. Deoxyhemoglobin S is much less soluble than the oxygenated variety, and a hydrophobic interaction between hemoglobin S  $\beta$  chains precipitates a double-stranded, ropelike polymer that causes erythrocyte sickling and rigidity. ISCs become wedged and occlude the small vessels, producing ischemia and eventually necrosis in the affected vascular territory, initiating an inflammatory response and neuropeptide release. The latter two factors produce pain, which is a potent stimulator of the sympathetic nervous system. Classic norepinephrine-mediated tachycardia, tachypnea, and relative hypertension may be noted. The high sympathetic activity also produces vasoconstriction, further decreasing distal blood flow and renewing the sickling cycle.

As described by Bunn,<sup>10</sup> erythrocytes in patients with SCD are more adherent to the endothelium than in normal subjects, and the degree of adherence is associated with disease severity. The erythrocyte  $\alpha_4\beta_1$  integrin complex interacts with endothelial VCAM-1 and fibronectin. Additionally, erythrocyte CD36 and sulfated glycans interact with endothelial CD36. Of note, endothelial factors VCAM-1 and fibronectin are up-regulated by infectious or inflammatory processes via tumor necrosis factor- $\alpha$ ; similarly, the CD36 interactions are mediated by von Willebrand factor and thrombospondin from activated platelets. These interactions explain infection as a cause of increased frequency of VPC.

The rate and extent of  $\beta^S$  polymer formation depends primarily on the degree of erythrocyte oxygenation, the concentration of intraerythrocyte hemoglobin, and the concentration of hemoglobin F.<sup>10</sup> Physical chemistry dictates that higher concentrations of solutes promote precipitation; therefore, as the erythrocyte becomes dehydrated, the high intraerythrocyte hemoglobin concentration encourages  $\beta^S$ - $\beta^S$  polymerization. The potassium-chloride and calcium-potassium erythrocyte ion channels are particularly important.<sup>10</sup> Hemoglobin S and C mutations both lead to increased potassium-chloride cotransport, resulting in the formation of target cells, erythrocyte dehydration, increased intraerythrocyte hemoglobin, and promotion of  $\beta^S$  polymerization. The  $Ca^{++}$ -activated  $K^+$  efflux (Gardos) channel also produces dehydration/polymerization, particularly when activated by the acidotic environment in stagnant capillary beds.



**Figure 1.** Hemoglobin isofocusing of several patients with and without sickle cell disorder. Patients with sickle cell trait (AS), hemoglobin SC disease (S/C), and hemoglobin S- $\beta^+$  thalassemia (S/ $\beta^+$ ) are compared to patients with normal hemoglobin (A).

### Pathophysiology of Vaso-Occlusive Pain Crisis

Questions still remain about the pathophysiology of VPC. The pain is frequently bilateral and symmetrical. Also, a given patient may have stereotypical sites of VPC recurrence; for example, a patient may always have low back pain only. Erythrocyte characteristics alone do not explain these patterns, because the blood changes should produce the same manifestations throughout the body. Local influences, such as trauma, differences in the regional vasculature due to previous VPC episodes, or region-specific expression of endothelial factors, could explain such patterns. These pain patterns are clinical support of the importance of non-erythrocyte factors in SCD.

### EVALUATION OF ADULT PATIENTS IN VASO-OCCLUSIVE PAIN CRISIS

Patient history and physical examination are the most important aspects of SCD evaluation; however, select laboratory tests are essential for specific diagnosis, prognosis, and for assessing the presence of concur-

rent diseases. The chart of any patient with SCD should include a hemoglobin electrophoresis confirming the diagnosis. Disease processes in addition to VPC should be evaluated on their own merit.

### Patient History

Important historical points to elicit during VPC include whether the current episode is similar to prior episodes; if it differs from the patient's usual pattern, an additional process may be occurring. Prodromal symptoms and other signs may group the patient into 1 of the 4 VPC phases and predict the time course of the current crisis. Searching for a precipitant (eg, dehydration, excessive exercise, cold exposure) may reveal the necessity and opportunity for patient counseling to reduce future events as well as to guide therapy.

Use of a written pain scale at each evaluation is essential for documenting VPC severity, gauging progress over time, and estimating treatment adequacy. Inquiries regarding the success of past interventions involve the patient in the disease management process, thereby augmenting the patient-physician relationship, and may expedite the development and implementation of a reasonable treatment plan.

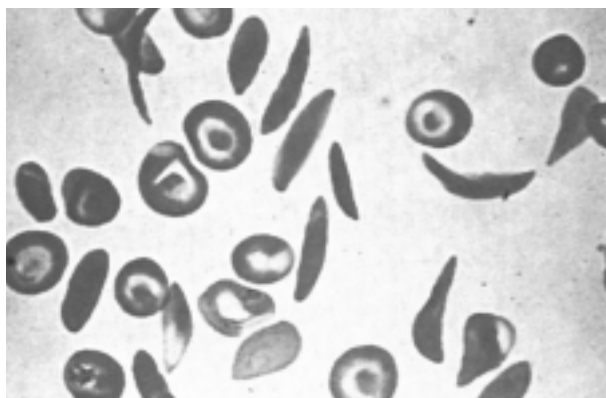
### Physical Examination

In the physical examination, signs of chronic organ damage should be sought. Also, the patient should be evaluated for signs of infection, as these predispose to VPC. Other common findings include icterus, tortuous scleral vessels, cardiomegaly, flow murmur, hepatosplenomegaly (age-dependent), presence of a short digit, osteoarthritis, leg ulcers, and joint effusions. Volume depletion should be ruled out by searching for dry mucous membranes, longitudinal tongue furrows, skin tenting, orthostatic hypotension, and by comparison to previous body weights, if available.

### Laboratory Evaluation

Laboratory analysis should be tailored to the specific patient and guided by whether the patient has other active medical issues in addition to VPC and whether documentation of hemoglobin S is available. Electrophoresis or isofocusing (**Figure 1**) is important in new patients because it provides prognostic information (pertaining to VPC frequency and life expectancy), supports genetic counseling, and can rule out Munchausen syndrome or malingering.<sup>21</sup>

In patients with frequent VPC episodes whose veins are difficult to access because of many blood draws, a fingerstick may be used to obtain capillary blood for a complete blood count (CBC) and smear.



**Figure 2.** Peripheral smear showing target cells and irreversibly sickled cells.

A CBC and peripheral blood smear (**Figure 2**) are inexpensive and simple procedures that should be included in every patient evaluation. The hemoglobin concentration and leukocyte count, as well as the amount of hemoglobin F are important prognostic factors (Table 4). A reticulocyte count is used to determine whether the patient is having an anaplastic crisis. Cytologic features characteristic of blood smears of patients with SCD are shown in **Table 5**.

If a patient's blood smear does not contain any ISCs, diagnosis of SCD is not confirmed. A sickle preparation (adding sodium metabisulfite to the sample to deoxygenate the blood and produce sickle cells) may be used to guide treatment until results of hemoglobin electrophoresis or isofocusing are available. It is important to note that the presence of ISCs on the peripheral smear or sickle preparation does not differentiate between SCD and sickle trait.

#### Other Diagnostic Testing

Ander and Vallee<sup>22</sup> evaluated the usefulness of empiric chest radiographs and urinalysis/culture in VPC evaluation. In 98 encounters, they found a routine chest radiograph confirmatory only in patients who already were diagnosed with pneumonia based on the presence of more than 4 of the following clinical findings: fever, chills, cough, sputum, dyspnea, chest pain, hemoptysis, abnormal pulmonary examination, and temperature greater than 37.8°C. Therefore, if no clinical suspicion of pneumonia was present, the chest radiograph did not change management.

In contrast, a urinalysis and culture was diagnostic in two thirds of patients with asymptomatic bacteriuria (which may have served as a VPC precipitant) and did change treatment. Consequently, routine urinalysis and culture but not chest radiograph appears justified. On

**Table 5.** Cytologic Features of Peripheral Blood Smears in Sickle Cell Disease

Feature	Description
Irreversibly sickled cells (ISCs)	Crescent-shaped erythrocyte with no central pallor; pathognomonic
Target cells	Erythrocytes with central brown hemoglobin surrounded by a ring of pallor and an outside ring of brown hemoglobin; higher numbers of target cells in hemoglobin SC disease
Dense cells	Small erythrocytes with dense cytoplasm; may be irregular in shape with no central pallor
Basophilic stippling	Punctate speckling of the erythrocyte cytoplasm occurs with basophilic staining
Pappenheimer bodies	Visible erythrocyte phagosomes
Reticulocytosis	> 1% of circulating erythrocytes are reticulocytes (young erythrocytes); frequently > 10%
Howell-Jolly bodies	Intracytoplasmic inclusions 1–2 μm in size; occur in asplenic states
Nucleated erythrocytes	Immature red blood cells still containing nuclei

day 2 or 3 of hospitalization, 5% to 10% of patients with VPC develop abnormal chest radiographic findings.<sup>5</sup>

An objective measure of blood oxygenation is frequently necessary to gauge the degree of pulmonary involvement in VPC. Comber and Lopez<sup>23</sup> report that pulse oximetry regularly underestimates the arterial oxygen saturation of patients presenting with VPC. Therefore, if the oxygen saturation as determined by pulse oximetry is acceptably high, an arterial blood gas analysis usually is unnecessary, saving the patient the pain, cost, and complication risk of an arterial blood draw. This may not apply in patients in whom pulse oximetry has been shown to be inaccurate, such as those with poor pulses, severe anemia (hemoglobin concentration < 5 g/dL), or nail polish.

#### TREATMENT OF PATIENTS IN VASO-OCCLUSIVE PAIN CRISIS

Appropriate treatment of the patient presenting with VPC is possible only after thorough, accurate patient evaluation. The heterogeneity of possible patient situations dictates a staggering range of treatment plans, from intensive care management with exchange

transfusions to oral outpatient rehydration or management of chronic organ failure. This article focuses on basic schemes for the treatment of VPC, classified as either acute pain control or preventive treatment.

#### **Preventive Treatment**

Preventive treatment is of paramount importance as it may mitigate many possible adverse outcomes and improve quality of life. Behavioral interventions (eg, avoidance of high altitudes, cold weather, and smoking) may be just as important as medical interventions (eg, vaccination, prompt treatment of infection, folate supplementation). Other useful nonpharmacologic techniques include transcutaneous electrical nerve stimulation, heating pads, massage, relaxation therapy, diversion, and biofeedback.<sup>20</sup>

Hydroxyurea shows much promise in long-term management of patients with SCD. Charache et al<sup>11</sup> showed in a large randomized controlled trial that administration of hydroxyurea significantly decreased the incidence of VPC, acute chest syndrome, and transfusions. Proposed mechanisms of action include raising the level of hemoglobin F, decreasing the reticulocyte count (these erythrocytes are the most adherent to endothelium), and reducing neutrophil numbers (thereby lowering fibronectin and endothelial adhesiveness).

Sadly, hydroxyurea is not a panacea for SCD. As Ho and Murgu<sup>24</sup> noted, the potential risks of secondary neoplasms are not yet fully defined. The Polycythemia Vera Study Group<sup>25</sup> has produced the most data on hydroxyurea safety so far, showing a 5.9% acute leukemia incidence after 8.6 years compared to 1.5% in the control group. This result was just short of statistical significance, possibly as a result of small sample size. Therefore, guidelines for hydroxyurea therapy include obtaining informed consent after a discussion of the risks and benefits, monitoring for myelotoxicity with twice-monthly CBCs, and committing to long-term therapy and follow-up such that this drug is prescribed only in the context of regular clinic visits and not on the basis of an emergency department visit.<sup>26</sup>

#### **Acute Pain Relief**

The multitude of analgesics available for acute treatment of VPC provides options but has created controversy regarding which strategy is best. A reasonable approach is similar to the World Health Organization pain ladder<sup>27</sup> and starts with nonopioid analgesics such as acetaminophen and nonsteroidal anti-inflammatory drugs.<sup>20</sup> Nonopioid agents work as peripheral analgesics, affecting prostaglandin synthesis and diminishing nociceptor sensitization. Risks may include hepatotoxicity,

analgesic nephropathy, gastropathy, coagulopathy, and overdosage. These analgesics have a ceiling above which even very large doses provide no additional analgesic benefit. However, when patients require narcotic analgesia for severe pain, nonopioids should be continued as adjuncts because they may decrease the narcotic dosage necessary for pain relief.

If opioid analgesia is necessary, weak opioids should be tried before strong opioids unless pain is extreme. Oxycodone is the most-used opioid in outpatient sickle pain management; its advantages are availability in combination with either aspirin or acetaminophen, duration of 3 to 5 hours, and good oral bioavailability. Codeine preparations are also very useful. The major side effects of all opioids necessitating close monitoring are respiratory depression, excess sedation, and hypotension. Whenever opioids are used, adjuvants to combat minor side effects should be considered, such as laxatives for constipation, antihistamines for pruritus, and antiemetics for nausea.

Strong opioids are frequently necessary for pain control. Meperidine, morphine, and hydromorphone are the most popular choices, although there is much debate over which has the best risk/benefit ratio.<sup>20</sup> Meperidine currently is the most prescribed of these choices in the United States and the United Kingdom. Meperidine's popularity is supported by its quick onset, and compared with morphine, it is less associated with nausea/vomiting, rash, and itching. However, its metabolite, normeperidine, has a half life of 18 hours (compared with 3 hours for the parent compound) and may accumulate even in people with normal kidneys. Repetitive meperidine dosing has caused generalized seizures (reported in 1%–12% of patients), myoclonus, tremors, anxiety, and death.<sup>28</sup>

Morphine has the advantage of the most clinical experience over centuries of usage for cancer, trauma, and postsurgically. Morphine has an excellent safety record, and its availability in many preparations ensures a wide variety of routes and schedules. Morphine-6-glucuronide is formed from hepatic metabolism, is more potent than morphine, and has a slightly longer half-life than morphine if kidney function is normal. Conversely, in patients with renal failure, morphine-6-glucuronide accumulates and may cause marked sedation and respiratory depression; however, it is not a neuro-excitotoxin as is normeperidine.

Hydromorphone is attractive because of its high potency and solubility, which are especially favorable if subcutaneous or intramuscular routes are used; importantly, it does not accumulate in the presence of renal failure. Because hydromorphone is relatively new, there

is not as much safety nor metabolic information as is available for the older opioids.

Considering all factors, morphine may be the best strong opioid in patients without renal compromise, whereas hydromorphone is best in patients with renal insufficiency. Frequent allergies or claims of allergies may necessitate a switching between classes of narcotics.

#### Other Treatment Options

Other interventions include administration of fluids, clotrimazole, and magnesium, all of which may increase intraerythrocyte free water, thereby decreasing intraerythrocyte hemoglobin and hindering sickling. In an intravascularly euvoletic patient, a goal of mild hyponatremia (sodium concentration 130 to 135 mEq/L) attained by administering oral free water,  $1/2$  normal saline solution (0.45% NaCl), or 5% dextrose in water promotes erythrocyte water uptake.

Clotrimazole inhibits the Gardos channel and magnesium retards potassium efflux, preventing erythrocyte dehydration and thereby reducing sickling.<sup>10</sup> Clotrimazole is administered via tablets given orally at 10 mg/kg body weight per day, which is increased to 20 mg/kg body weight per day on day 7 of therapy. Clotrimazole's major side effects are dysuria and elevated transaminases, which usually occur at higher doses.<sup>29</sup> Sodium cromoglycate has also been noted to have some anti-sickling properties.<sup>30</sup>

Supplemental oxygen is often administered to patients presenting with VPC; however, unless the patient is hypoxic from pulmonary pathology, it probably has little benefit because the vaso-occlusive site is devoid of blood flow and thus oxygen cannot reach the involved erythrocytes to rectify sickling.<sup>5</sup> However, it is a benign intervention and should routinely be used empirically until normal pulmonary function is ensured.

A randomized, controlled, clinical trial of SCD patients admitted with chest pain has shown that incentive spirometry (10 maximal breaths every 2 hours between 8 AM and 10 PM and while awake at night) prevents the atelectasis and infiltrates associated with acute chest syndrome.<sup>31</sup>

Short-term steroid administration decreases the inflammatory response by down-regulating the leukotrienes that promote the endothelial-erythrocyte adhesion process that initiates the VPC cascade; however, steroids further increase the infectious and aseptic necrosis risks of SCD and thus should be used with caution.

Special treatments for SCD include bone marrow transplant, which is curative but is not regularly chosen because the short-term mortality risk of 5% to 10% outweighs the benefit unless severe consequences (eg,

recurrent stroke) are likely.<sup>1</sup> Treatments for priapism include standard VPC treatment and, additionally, administration of calcium channel blockers, spinal anesthesia, and prompt drainage if necessary. Transfusions may be necessary during aplastic, sequestration, or acute chest crises; however, transfusions may lead to infections, transfusion reactions, alloimmunization, and iron overload.

#### SUMMARY

SCD is a common genetic disease and causes significant morbidity and mortality. It produces multiple characteristic effects in virtually every organ in the body. Vaso-occlusive pain crises, which may be precipitated by many factors, are the most notable feature of SCD. Other acute pain states include priapism and sequestration, usually of the spleen or liver. Other clinical manifestations of SCD include anemia, progressive organ damage, infection, acute chest syndrome, bone and joint damage, and leg ulcers. Patients with SCD are prone to stroke at a young age—8% of sickle cell anemia patients experience stroke by the age of 14 years.

A diagnosis of SCD is confirmed by hemoglobin electrophoresis or isofocusing. Evaluation of the patient in VPC should include a thorough history and physical examination. The use of a written pain scale can help assess treatment progress over time. Laboratory evaluation of a patient in VPC should include CBC, peripheral blood smear, reticulocyte count, and urinalysis/culture. If pneumonia is suspected, a chest radiograph should be taken.

Treatment of patients in VPC consists mainly of palliation of pain and any interventions necessitated by the manifestations of the disease (eg, pneumonia, organ failure, anemia). The prevention of VPC is of paramount importance, and is a primary goal of long-term management of SCD. Unfortunately, the interventions available for preventing pain crises are fairly limited. Along with standard medical measures such as vaccinations, behavioral changes to avoid VPC triggers are extremely important and may give a patient some sense of control over his or her disease. Hydroxyurea therapy shows great promise in the treatment of SCD; however, it poses risks of bone marrow suppression and acute leukemia, and thus intensive monitoring and follow-up is required. HP

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