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Objectives

After completing this article, readers should be able to:

1. Recognize the signs and symptoms of sickle cell vaso-occlusive crisis.
2. Explain the factors contributing to the pathogenesis of sickle cell vaso-occlusion.
3. Delineate the reasons for the heightened susceptibility to infection in sickle cell disease.
4. Describe the biochemical basis for hemolysis in glucose-6-phosphate dehydrogenase deficiency.
5. Compare and contrast Diamond-Blackfan anemia and transient erythroblastopenia of childhood.

Introduction

Children's hematologic and oncologic problems often present initially to the pediatrician. This article provides guidance for the diagnosis and office treatment of anemia and guidelines for follow-up and, where appropriate, referral to a subspecialist. Last month, part 1 considered iron deficiency, beta- and alpha-thalassemia trait, and hereditary spherocytosis. This month, part 2 considers sickle cell syndromes, glucose-6-phosphate dehydrogenase (G6PD) deficiency, and transient erythroblastopenia (Table 1). These topics were proposed by practicing pediatricians in our communites as those of particular concern in their office practices.

Sickle Cell Anemia and The Severe Sickle Cell Syndromes

History and Physical Examination

The severe sickle syndromes are most common among people of African or mixed African and Hispanic descent. Many states have newborn screening programs that detect hemoglobinopathies at birth. Beta-chain abnormalities, such as hemoglobins S, C, E, and beta-thalassemia, do not cause symptoms until the change from gamma-chain (fetal hemoglobin, $alpha_2$ $gamma_2$) production to beta-chain ($alpha_2beta_2$) production is nearly complete between the ages of 6 and 12 months. Therefore, children who have severe sickle syndromes and are homozygous for hemoglobin S or who are double heterozygous for hemoglobin S and other hemoglobins such as C, D, O-Arab, or beta-thalassemia usually develop symptoms during the second half of the first year of life. Symptoms of sickle cell diseases may result from the occlusion of blood vessels by sickling, from the anemia itself, or from a heightened susceptibility to infection.

The vaso-occlusive symptoms can arise in almost any organ system. Patients who have homozygous SS disease initially may present with dactylitis manifested by swelling and pain in the hands and feet and extreme pain in the bones (Table 2). The arms, legs, back, abdomen, and joints also can be sites of vaso-occlusion with resultant painful crises. Other common vaso-occlusive episodes include stroke, priapism, and infarction of lung, resulting in an acute chest syndrome. Results of the physical examination in each of these conditions reflect the underlying pathophysiology and location. Joint, muscle, and abdominal tenderness are common findings. Neurologic signs may be present with either transient ischemic episodes or stroke. Examination of the chest may reveal lung congestion or consolidation.

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Table 1. Red Blood Cell (RBC) Disorders

Disease	Clinical Presentation: History	Clinical Presentation: Physical Findings	Laboratory Diagnosis	Treatment
Severe Sickle Cell Syndromes	Neonatal screen Fatigue Abdominal, bone pain Headache Chest pain, cough, dyspnea Central nervous system complaints Hematuria Dactylitis	Pallor, jaundice Nonspecific abdominal signs Joint pain/swelling Evidence of pulmonary infiltrate Priapism Neurologic signs Splenomegaly—early	Neonatal screen Sickledex positive in trait and disease Hemoglobin electrophoresis Reticulocyte % ↑ Irreversibly sickled cells (ISCs)	Symptomatic care Folic acid (0.5 mg qd <5 y of age; 1.0 mg qd ≥5 y of age) Pencillin prophylaxis (125 mg bid <3 y of age; 250 mg bid ≥3 y of age) Analgesia Hydration Transfusion and chelation Hydroxyurea
Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency	None without oxidant stress (A-variety) Chronic anemia Neonatal jaundice	Pallor, jaundice, orthostasis	Precipitous anemia Reticulocyte % ↑ Hemoglobinemia ± hemoglobinuria G6PD assay	Remove precipitating agent Supportive Transfusion
Transient Erythroblastopenia of Childhood (TEC)	Fatigue, irritability	Pallor	Reticulocyte <0.5% Profound anemia White blood cells + platelets normal	Supportive Transfusion

The chronic anemia, if severe, may produce fatigue, exercise intolerance, lethargy, and limitation of activities. During the first year, the spleen may be palpable, although palpability usually disappears during the first few years of life. Pallor and jaundice are common. Profound anemia with cardiovascular instability may result acutely from sequestration of blood within the spleen or from red cell aplasia due to parvovirus or other viruses.

Patients who have severe sickle cell syndromes are particularly susceptible to infection with encapsulated organisms such as pneumococcus because of splenic hypofunction. Some patients also have an opsonic defect in their antibody response to these infections that heightens their susceptibility. There is a susceptibility to osteomyelitis, possibly due to bone infarction, and *Salmonella* and *Staphylococcus* are common infecting organisms.

Table 2. Sickle Crises

Pain (vaso-occlusive)
- Bone
  - Marrow ischemia or infarction (eg, hand-foot syndrome)
- Abdominal
  - Mesenteric sickling

Stroke
- Stenosis of the internal carotid, anterior, and middle cerebral arteries

Priapism
- "Stuttering," intermittent, or prolonged >24 h

Acute Chest Syndrome
- Infarction and/or infection

Splenic Sequestration
- Massive enlargement and red cell trapping

Aplastic
- Parvovirus

Pathogenesis, Signs, and Symptoms

The vaso-occlusive symptoms and signs of severe sickle syndromes result primarily from the interruption of flow in the microvasculature by sickle hemoglobin-containing red cells. Although strenuous exertion, dehydration, exposure to cold, and infections appear to precipitate painful or vaso-occlusive crises, the precise mechanism is unknown; often there is no obvious precipitating event. A certain time is required for red cells to traverse the capillary bed, and if sickling occurs prior to entry into the venous system, capillary occlusion may occur. A long delay time for sickling, therefore, would improve flow through the capillary bed. The delay time for sickling is shortened markedly if the sickle hemoglobin concentration is high. Thus, dehydrated red cells are more disposed to rapid sickling. Further, sickle hemoglobin-

containing red cells are much more adherent to endothelium than are normal red cells. Adherence to endothelium, like sickling within the capillary bed, tends to obstruct blood flow. Other factors, such as low pH and hyperosmolality, also enhance intravascular sickling, and a proportion of the red cells are irreversibly sickled (ISCs), heightening the risk of vaso-occlusion. Furthermore, patients who have severe sickle syndromes may be hypercoagulable because of decreased levels of the anticoagulant proteins C and S, hyperhomocysteinemia, and the presence of antiphospholipid antibodies. Alternatively, increased hemoglobin F concentration within each cell tends to inhibit the sickling process. The capillary beds of all organs are susceptible to vaso-occlusion in patients who have severe sickle cell syndromes. Stroke affects approximately 10% of patients by the time they reach age 20 years. Hepatic, renal, splenic, and lung injury are frequent complications of vaso-occlusion. Sickling within the splanchnic bed of the abdomen and within the vessels supplying bones, joints, and muscle precipitates the classic syndrome of sickle cell crisis. Abdominal pain also may be related to cholelithiasis resulting from the chronic hemolysis and heightened bilirubin turnover.

Infants identified by newborn screening should be administered penicillin prophylaxis 125 mg bid until age 3 years.

Three primary factors contribute to the susceptibility to pyogenic infections observed in patients who have severe sickle syndromes. First, splenic hypofunction results initially from intrasplenic sickling and shunting as well as from mononuclear phagocyte system saturation due to red cell destruction and ingestion of cell debris. Repeated episodes of splenic sickling throughout the first decade usually cause repeated splenic infarction and little residual splenic tissue in SS disease by the time of adolescence. Thus, children and adults who have sickle cell anemia are essentially asplenic and susceptible to encapsulated pyogenic bacteria. Although the spleen often remains palpable in sickle thalassemia, phagocytic function is impaired because of the red cell destruction and consequent ingestion of debris.

Second, approximately 10% of patients who have homozygous sickle disease have a defect in the complement opsonic system that results in markedly heightened susceptibility to infection by encapsulated organisms. In the era prior to the availability of pneumococcal vaccines and prophylactic penicillin, these patients presented early with pneumococcal pneumonia, pneumococcal meningitis, and pneumococcal sepsis and experienced repeated episodes. Current prophylactic treatment has reduced the morbidity from these agents markedly.

Third, a number of organ systems appear susceptible to infection because of underlying vaso-occlusive damage. These include the bones, in which microinfarction may be infected secondarily by *Staphylococcus aureus* or *Salmonella* sp, and the lungs by *Mycoplasma pneumoniae* or pyogenic bacteria.

The diagnosis of a severe sickle syndrome often is established through a newborn screening program. The clinical features that suggest the diagnosis in an undiagnosed child include signs and symptoms of a vaso-occlusive crisis and infection in children of African descent, often in the presence of splenomegaly during the first year. The occurrence of stroke, pulmonary symptoms, pain and swelling in the hands and feet, or a severe worsening of anemia should suggest a hemoglobinopathy.

Laboratory Evaluation

Patients who have severe sickle syndromes are invariably anemic, exhibiting hemoglobin values of 6 to 10 g/dL (60 to 100 g/L). The mean cell volume (MCV) of the cells is greater than 80 fL/cell unless there is a concomitant thalassemic gene. The reticulocyte percentage is elevated, reflecting the heightened marrow activity to compensate for the red cell destruction. The blood film contains irreversibly sickled cells (ISCs) or dense elliptocytes in varying amounts in all of the severe sickle syndromes. The size and shape of the red cells vary markedly, and nucleated red cells may be present. The type of hemoglobinopathy is diagnosed definitively by hemoglobin electrophoresis in conjunction with the blood counts and blood film. A summary of the laboratory diagnostic tests for hemoglobinopathies is shown in Table 3.

Treatment

The pediatrician should provide primary care for these patients and is an integral member of the multidisciplinary care team of the hematology/oncology unit or sickle cell clinic. Infants identified by newborn screening should be administered penicillin prophylaxis immediately at 125 mg twice a day by mouth until age 3 years,

Table 3. Laboratory Diagnosis of Sickle Syndromes

Hemoglobin	Chain Structure	Normal	Sickle Trait	SS	S-Beta^0 Thalassemia	S-Beta$^+$ Thalassemia	SC
A	$Alpha_2$ $Beta_2$	>95%	52% to 65%	–	–	10% to 30%	–
F	$Alpha_2$ $Gamma_2$	<2%	<2%	<10%	<20%	<20%	<5%
A_2	$Alpha_2$ $Delta_2$	<3.5%	<3.5%	<3.5%	>3.5%	>3.5%	<3.5%
S	$Alpha_2$ $Beta^S_2$	–	32% to 45%	>90%	>80%	>60%	50%
C	$Alpha_2$ $Beta^C_2$	–	–	–	–	–	50%
Hemoglobin level	–	Normal	Normal	6 to 10 g/dL (60 to 100 g/L)	6 to 10 g/dL (60 to 100 g/L)	8 to 12 g/dL (80 to 120 g/L)	10 to 12 g/dL (100 to 120 g/L)
MCV (fL/cell)	–	78 to 90	78 to 90	>80	<80	<75	>75
Morphology	–	Normal	Normal	ISCs Polychromasia Variation in size and shape Nucleated red cells Target cells	ISCs Polychromasia Variation in size and shape Nucleated red cells Target cells	ISCs Polychromasia Variation in size and shape Nucleated red cells Target cells	ISCs Polychromasia Variation in size and shape Target cells

MCV = mean cell volume, ISC = irreversibly sickled cells.

then 250 mg twice a day continued indefinitely. Immunizations are required on the schedule shown in Table 4. They include pneumococcal and meningococcal vaccine, the routine childhood immunizations, and a yearly vaccination for influenza virus. Prevnar, a heptavalent conjugate pneumococcal vaccine, produces immunity to seven strains that account for approximately 80% of pneumococcal disease and can be administered as early as age 2 months (Table 5). The 23-valent polysaccharide pneumococcal vaccine is recommended after age 2 years. Those children starting immunization after age 6 months or requiring "catch-up" immunization should be treated according to Table 5. Oral folic acid may be prescribed to prevent secondary folic acid deficiency (0.5 mg/d before age 5 years and 1.0 mg/d after age 5 years).

Family education regarding the nature and complications of sickle syndromes should be provided in conjunction with the hematology consultants. Discussion should include the risk of overwhelming infection, dactylitis, splenic sequestration, stroke, and priapism. The parents should be instructed to seek medical attention promptly in the event of fever, pulmonary symptoms, severe pain, neurologic signs, or priapism. A precipitous fall in hemoglobin secondary to splenic sequestration or an aplastic crisis also requires expeditious evaluation and referral to a medical center. It is helpful to teach the parents to

Table 4. Immunizations for Patients Who Have Severe Sickle Syndromes

Age	Vaccine*	Recommendation
2 to 6 mo	Prevnar (PCV7)	Primary series: 3 doses 6 to 8 wks apart Booster: 1 dose at 12 to 15 mo of age
2 y	Multivalent (23PS) Pneumococcal	Booster: 1 dose 3 to 5 y after primary dose
>2 y	Meningococcal	No booster recommended
6 mo	Influenza	Yearly vaccination

*Routine immunizations also should be administered according to the recommendations of the American Academy of Pediatrics.

Table 5. Prevnar (PCV7) Dosing Recommendations for Children Who Have Sickle Cell Disease

Age	Previous Doses	Recommendations		
≤23 mo	None	Age at first dose	Primary Series of PCV7	Booster Dose of PCV7*
		7 to 11 mo	2 doses, 6 to 8 wks apart	1 dose at 12 to 15 mo of age
		12 to 23 mo	2 doses, 6 to 8 wks apart	
		>24 mo	1 dose	
24 to 59 mo	4 doses of PCV7	1 dose of 23PS vaccine at 24 mo, at least 6 to 8 wk after last dose of PCV7 1 dose of 23PS vaccine, 3 to 5 y after the first dose of 23PS vaccine		
24 to 59 mo	1 to 3 doses of PCV7	1 dose of PCV7 1 dose of 23PS vaccine, 6 to 8 wk after last dose of PCV7 1 dose of 23PS vaccine, 3 to 5 y after the first dose of 23PS vaccine		
24 to 59 mo	1 dose of 23PS	2 doses of PCV7, 6 to 8 wks apart, beginning at least 6 to 8 wk after the last dose of 23PS vaccine 1 dose of 23PS vaccine, 3 to 5 y after the first dose of 23PS vaccine		
24 to 59 mo	None	2 doses of PCV7, 6 to 8 wks apart 1 dose of 23PS vaccine, 6 to 8 wk after the last dose of PCV7 1 dose of 23PS vaccine, 3 to 5 y after the first dose of 23PS vaccine		

*Booster doses to be given at least 6 to 8 wk after the final dose of the primary series.
The recommendations for pneumococcal immunization are taken from the Policy Statement of the Committee on Infectious Diseases of the Academy of Pediatrics. *Pediatrics.* 2000;106:362–366.

palpate the left upper quadrant so they can detect an enlarging spleen that may herald splenic sequestration. Mild-to-moderate painful crises may be managed initially with fluids, hydration, and analgesics that can be taken orally. If the pain persists or worsens, hospital care may be necessary. The febrile child who has a severe sickle syndrome should have an immediate blood culture and be administered broad-spectrum parenteral antibiotics that are continued for 48 hours as an outpatient. If the child appears septic or deteriorates, hospitalization is required. Positive cultures require a full course of intravenous antibiotics.

Hospital management of patients who have severe sickle syndromes and vaso-occlusive or anemic crises includes the use of intravenous analgesia, judicious transfusion, exchange transfusion, and if necessary, cardiorespiratory support. It is useful to perform complete blood typing prior to the need for transfusion of red cells so blood for transfusion can be restricted to types more common among patients of African descent to avoid alloimmunization. Treatment for sickle cell disease remains investigative because no medication prevents or aborts a painful crisis. Hydroxyurea may be useful in some patients to heighten the proportion of hemoglobin F red cells and raise the hematocrit modestly. Hydroxyurea reduces the frequency of painful crises, but it inhibits DNA synthesis and may cause marrow suppression with neutropenia and thrombocytopenia. If a patient who has a sickle syndrome is taking this agent, blood counts should be monitored at least monthly. A number of patients now have been cured with allogeneic bone marrow transplantation. This, of course, carries with it an approximate 20% risk of severe graft-versus-host disease, transplant failure, or death resulting from the procedure. It has not become a widely accepted practice in the United States. The successful use of matched cord blood transplantation has been reported, and this procedure may reduce the morbidity and mortality from graft-versus-host disease. This requires collection, processing, human leukocyte antigen typing, and storage of cord blood from siblings of a child who has sickle cell disease. Alternatively, there is the possibility of "nonmyeloablative" marrow transplants that have significantly less morbidity. This type of transplant requires little preparative chemotherapy and radiotherapy. The recipient's marrow is preserved, and the transplant results in a mixture of the donor and recipient marrow that is beneficial because of the longevity of the normal cells that are produced compared with the patients' cells. Thus, 20% normal hemoglobin A-producing cells in the marrow may result in 80% hemoglobin A-containing cells in the blood.

A transcranial Doppler examination at appropriate intervals is essential to monitor intracranial vascular flow. Transcranial Doppler is performed initially at age 2 years and then yearly thereafter. If the blood velocity is greater than 200 cm/sec, and it is confirmed 4 to 6 weeks later, the patient has a very high risk of stroke and warrants institution of chronic transfusion and iron chelation ther-

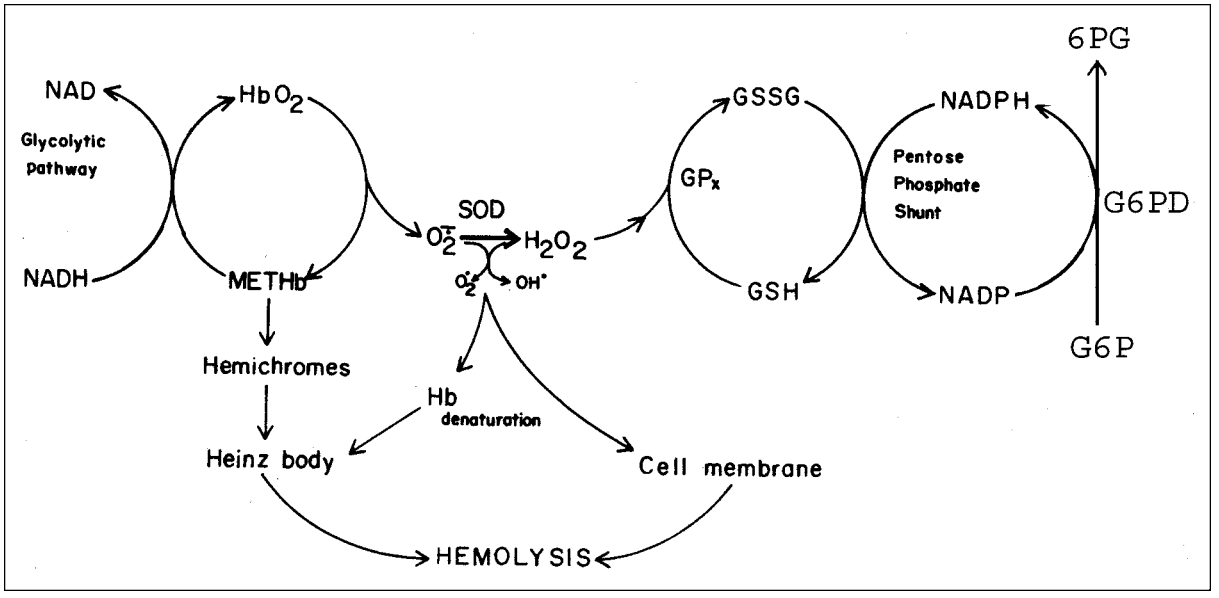

Figure. The central role of the production and reduction of activated oxygen and its link to red cell glycolysis and the pentose phosphate pathway. The accumulation of activated oxygen (O_2^-) and free radical species (O_2, $OH^•$) that results from exposure to oxidant drugs or infection may cause hemolysis by denaturing hemoglobin or by injuring the red cell membrane. SOD=superoxide dismutase, GPx=glutathione peroxidase, Hb=hemoglobin, GSSG=oxidized glutathione, GSH=reduced glutathione, NADP=nicotinamide adenine dinucleotide phosphate, NADPH=nicotinamide adenine dinucleotide phosphate (reduced form), G6PD=glucose-6-phosphate dehydrogenase. Modified from Oski FA, Naiman JI, eds. *Hematologic Problems in the Newborn.* 3rd ed. Philadelphia, Pa: WB Saunders Co; 1982.

apy. A blood velocity of 170 to 200 cm/sec is considered conditional and should be reassessed in 3 to 4 months. Intractable painful crises, stroke, recurrent acute chest syndrome, and anemia causing heart failure also may require the institution of a chronic transfusion program.

Indication for Referral

Subspecialty consultation is necessary for all patients who have a hemoglobinopathy, and patients who have severe sickle cell syndromes should be seen in a sickle cell clinic or by a pediatric hematologist at least twice each year. This allows assistance with patient and family education, genetic counseling of the family, regular evaluation of the cardiovascular and neurologic status, and assessment of compliance with preventive measures. It is ideal for primary care to be provided by the pediatrician with subspecialty cooperation. Referral to the subspecialty service is appropriate when hospital care is warranted. The issues of infection in an immunocompromised host, severe painful crises, priapism, neurologic signs or symptoms, severe pulmonary symptoms, and marked fall in hematocrit are managed in conjunction with hematology and critical care facilities. Surgery and pregnancy are particularly complex issues in affected patients and should be managed in hospitals in which appropriate expertise is available. Hydroxyurea therapy or a chronic transfusion program should be instituted by a pediatric hematologist and administered and monitored by the pediatrician and the subspecialty service.

Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency

History and Physical Examination

The presenting manifestations of G6PD deficiency are neonatal jaundice, acute intravascular hemolytic crises on exposure to oxidant stress, an insidious decrease in hemoglobin in an otherwise moderately to severely ill patient, and chronic hemolytic anemia (seen with certain variant enzymes). A careful history to establish exposure to inciting agents is required. Oxidant drugs interact with oxyhemoglobin to produce free radicals (Figure). Infection alone, particularly hepatitis, may be an oxidant stress of sufficient intensity to cause acute hemolysis. Most G6PD-related hemolysis in the United States occurs in susceptible African-American males who are ill with an infection or metabolic disease such as diabetes mellitus or are exposed to an oxidant medication (Table 6).

G6PD-deficient patients do not have hepatomegaly

Table 6. Agents Precipitating Hemolysis in G6PD Deficiency

Medications
• Antibacterials
Sulfonamides
Trimethoprim-sulfamethoxazole
Nalidixic acid
Chloramphenicol
Nitrofurantoin
• Antimalarials
Primaquine
Pamaquine
Chloroquine
Quinacrine
• Other Medications
Phenacetin
Vitamin K analogs
Methylene blue
Probenecid
Acetylsalicylic acid
Phenazopyridine
Chemicals
• Phenylhydrazine
• Benzene
• Naphthalene
Illness
• Diabetic acidosis
• Hepatitis
• Others
Foods
• Fava beans in susceptible patients (Mediterranean type)

Modified with permission from Asselin BL, Segel GB. In: Rakel R, ed. *Conn's Current Therapy*. Philadelphia, Pa: WB Saunders; 1994:341.

or splenomegaly, but pallor and jaundice may be present if there is chronic hemolysis. With an acute hemolytic crisis, patients often report red, clear urine; jaundice; pallor; lethargy; and headache. In extreme cases, patients may present in shock.

Pathogenesis, Signs, and Symptoms

G6PD is a central enzyme in the pentose phosphate shunt of glucose metabolism (Figure). It catalyzes the conversion of glucose-6-phosphate (G6P) to 6-phosphogluconic acid (6PG) and generates NADPH in the process (Figure). NADPH is necessary to maintain glutathione in the reduced state, that is, GSSG→GSH. Glutathione is present in the red cell in millimolar amounts and acts as a "sponge" to neutralize agents that threaten to oxidize either hemoglobin or components of the red cell membrane. If reduced glutathione cannot be sustained to remove the oxygen radicals resulting from oxidant drugs, the hemoglobin precipitates, forming Heinz bodies that can be characterized as "rocks in the red cell," and the red cell membrane is critically damaged. The precipitation of hemoglobin and damage to the membrane result in premature red cell destruction or hemolysis.

The most common type of G6PD deficiency seen in the United States is the A-minus variety, which is inherited as an X-linked condition affecting primarily African-American males. Females sometimes are affected if they are homozygous for G6PD deficiency or if random X chromosome inactivation results in a large proportion of deficient red cells. The A-minus mutant enzyme is unstable and diminishes as red cells age in the circulation. Persons who have this disorder have little or no problem unless they are exposed to an oxidant drug or chemical or they acquire a severe illness or infection. Oxidant exposure causes lysis of the susceptible older population of red cells and a fall in hemoglobin and hematocrit, followed by a rise in the percentage of reticulocytes. Weakness, pallor, jaundice, fatigue, and even cardiovascular collapse can accompany the precipitant anemia. Jaundice occurs because of heightened indirect bilirubin production, and the urine may become dark as the bilirubin is conjugated to direct bilirubin and excreted. If the hemolysis is severe, the binding proteins for free hemoglobin in the plasma, such as haptoglobin and hemopexin, may be saturated, and hemoglobin may appear in the urine (without red cells). The young reticulocytes that appear in the blood are replete with G6PD in the A-minus variety, allowing some degree of spontaneous recovery. In contrast to oxidant-induced acute hemolysis, the hemoglobin commonly falls insidiously in a G6PD-deficient patient hospitalized for other illnesses. G6PD deficiency may remain unrecognized because the oxidant stress is modest, the hemoglobin fall is gradual, and the reticulocyte response is blunted by the primary illness.

Patients who have G6PD deficiency of the Mediterranean type can develop severe hemolysis when exposed to oxidant drugs. This G6PD variety is characterized by enzyme deficiency in red cells of all ages, including reticulocytes, and shows no evidence of spontaneous recovery. Other varieties of G6PD deficiency may cause a chronic hemolytic anemia without external oxidant exposure. Patients who have chronic hemolytic anemia are susceptible to development of cholelithiasis because of heightened bilirubin turnover. Complaints of abdominal pain or fatty food intolerance warrant evaluation of the gall bladder by ultrasonography.

Unexplained anemia in a patient of African descent should suggest consideration of G6PD deficiency. Other acquired causes of acute hemolysis include acquired immune hemolytic anemia and microvascular hemolytic anemias due to the hemolytic-uremic syndrome, thrombotic thrombocytopenic purpura, or vasculitis.

Laboratory Testing

In acute hemolysis resulting from G6PD deficiency, the blood count reveals a fall in hemoglobin and hematocrit and a subsequent rise in the reticulocyte percentage. The bilirubin, particularly the indirect fraction, may be elevated, and haptoglobin is reduced as it binds free hemoglobin and is removed from the circulation. The urine may contain free hemoglobin if the tubular reabsorptive capacity for hemoglobin is exceeded. There are no definitive findings on the blood film, although some fragmented red cells or "bite cells" may be present.

The definitive diagnostic test involves assay of G6PD enzyme activity in the red cells. In A-minus G6PD deficiency, the enzyme is age-labile, deteriorating as the red cells age in the circulation. During the acute stage of hemolysis in A-minus type deficiency, G6PD activity will be higher than the patient's baseline because the reticulocytes are replete with enzyme, and the cells that have low enzyme levels have hemolyzed. Assay values determined during hemolysis of A-minus G6PD often are above the deficient range. This measurement can be repeated several months after the hemolytic episode has resolved when the normal distribution of red cell age is restored. A deficiency should be evident at this time. Other types of G6PD deficiency show diminished G6PD activity even during acute hemolysis.

Treatment

In newborns who have G6PD-related hemolysis, both the anemia and the indirect hyperbilirubinemia must be addressed. Phototherapy usually controls the level of indirect hyperbilirubinemia. However, exchange transfusion may be necessary if lights are ineffective in controlling the bilirubin or if the anemia is severe. Exchange transfusion permits the removal of endogenous G6PD-deficient red cells that are susceptible to further hemolysis. If G6PD deficiency or other intrinsic abnormality of the red cells is suspected, a sample of blood for enzyme analysis should be obtained prior to transfusion or exchange transfusion.

The management of acute hemolysis in older children requires hemodynamic stabilization of the patient with fluids and red cell transfusions as needed, as well as removal of the oxidant agent that has precipitated the hemolysis. All patients who have G6PD deficiency should be provided with a list of medications to avoid (Table 6). They also need to understand the nature of this problem so they can inform physicians who prescribe medications for them.

Indication for Referral

The precise diagnosis of G6PD deficiency may be complex, and there are literally hundreds of variant defective enzymes. The initial diagnostic data should be reviewed by a specialist and diagnostic confirmation and delineation of the specific enzyme defect provided at consultation. The consultation also provides the opportunity to explain the genetics of G6PD deficiency (ie, X-linked), to test other family members who may be at risk, and to teach the patient and family about the avoidance of agents that might precipitate a hemolytic episode.

Diamond-Blackfan syndrome is due to a relative insensitivity to erythropoietin and presents during the first year of life.

Aregenerative Anemias: Parvovirus, Diamond-Blackfan Syndrome, Transient Erythroblastopenia of Childhood

History and Physical Examination

Aregenerative anemia or pure red cell aplasia due to prenatal parvovirus infection or rarely Diamond-Blackfan anemia (DBA) may present in the neonate as hydrops fetalis and requires prompt intervention with exchange transfusion. Parvovirus causes a significant fall in hemoglobin in patients who have a history of chronic hemolysis. Physical examination reveals pallor without jaundice or organomegaly in parvovirus infection. DBA usually develops insidiously during the first year of life because of the relatively long circulation time of the red cell. Affected children develop pallor, lethargy, and decreased energy and may progress with symptoms of congestive

heart failure. Approximately 25% of affected patients have dysmorphic features (eg, short stature, abnormal facies with cleft palate, or eye abnormalities), abnormalities of the thumb, congenital heart disease, or mental retardation. Transient erythroblastopenia of childhood (TEC) also evolves slowly, usually after age 1 year, and there are no abnormal physical findings except pallor.

Pathogenesis, Signs, and Symptoms

The differential diagnosis of isolated aregenerative anemia includes parvovirus, DBA, and TEC. In each case, anemia does not produce the expected increase in erythropoiesis and, therefore, becomes progressively more severe. In the newborn, aregenerative anemia may result from an intrauterine infection with parvovirus or from DBA. In contrast to newborns who have hemolytic disease, these patients may be pale, anemic, and reticulocytopenic, but they do not have significant jaundice. If severe, the anemia may progress to heart failure with tachypnea, cardiac enlargement, hepatomegaly, and anasarca.

The pathogenesis of erythroid failure in parvovirus infections is related to the erythrotropic nature of this infectious agent. Parvovirus causes several clinical syndromes, including erythema infectiosum (fifth disease) and a syndrome that includes rash and arthritis in adults. From the hematologic standpoint, it has a striking affinity for erythroid precursors and produces transient erythroid marrow aplasia. This is of little consequence when the red cell lifespan is normal, but it may cause a dramatic fall in blood hemoglobin concentration and hematocrit in patients who have hemolysis and a short red cell survival. It may affect the newborn via maternal infection and can result in hydrops fetalis.

DBA is due to a relative insensitivity to erythropoietin. A familial occurrence of the disorder has been reported, but the mode of inheritance is not clear. Some patients may show a dominant pattern with incomplete penetrance; in others, it appears to be a recessive disorder. DBA may present in the newborn or during the first year of life; the onset is rare after age 2 years. Anemia is progressive unless the diagnosis is recognized and treatment instituted.

TEC is a relatively rare disease of unknown etiology that also results in acquired erythroid marrow failure. Affected patients are older, with a median age of 2 years, compared with those who have DBA. Congenital anomalies and short stature are not part of this syndrome, and it resolves spontaneously within several months. Table 7 compares the features of TEC and DBA.

Table 7. Comparison of Diamond-Blackfan Anemia (DBA) and Transient Erythroblastopenia of Childhood (TEC)

	DBA	TEC
No. of patients	527	608
Male:female	1.1	1.2
Male age in months at diagnosis		
Mean	10	40
Median	2	23
Range	0 to 408	1 to 120
Female age in months at diagnosis		
Mean	12	40
Median	3	23
Range	0 to 420	2 to 192
Males >1 y	10%	85%
Females >1 y	15%	82%
Etiology	Inherited?	Acquired
Antecedent history	None	Viral illness
Physical examination findings abnormal	24%	<1%
Hemoglobin (g/dL) (g/L)	1.5 to 10 (150 to 1,000)	2.2 to 12.5 (220 to 1,250)
White blood cells $<3\times10^3$/mcL ($<3\times10^9$/L) or ANC <1,000 mcL	5%	19%
Platelets $>400\times10^3$/mcL ($>400\times10^9$/L)	20%	60%
Red cell adenosine deaminase	Increased	Normal
MCV increased		
At diagnosis	~80%	8%
During recovery	~100%	~90%
In remission	~100%	0%
Hemoglobin F increased		
At diagnosis	~100%	~25%
During recovery	~100%	~100%
In remission	~85%	0%
i Antigen increased		
At diagnosis	~100%	~20%
During recovery	~100%	~60%
In remission	~90%	0%

% refers to percent of patients having the characteristic.
Reproduced with permission from Alter BP, Young NS. The bone marrow failure syndromes. In: Nathan DG, Orkin SH. *Nathan and Oski's Hematology of Infancy and Childhood*. 5th ed. 1998.

Laboratory Testing

For patients who have underlying hemolytic disease, such as sickle cell anemia or hereditary spherocytosis, a marked fall in the reticulocyte percentage, even prior to a fall in hemoglobin and hematocrit, may herald the onset of aregenerative anemia. In this setting, parvovirus is the likely culprit, and its presence can by assessed by serologic measurement of specific immunoglobulin G (IgG) and IgM. The anemia is normochromic and normocytic without any characteristic findings on the blood film, and neutropenia occasionally is present. Bone marrow usually is not examined, but it would show relative erythroid hypoplasia and vacuolization of red cell precursors unless the patient already is recovering, at which time young erythroid progenitors are seen. In patients who do not have underlying hemolysis, parvovirus causes much less decrease in the hemoglobin and hematocrit because of the longevity of the normal red cells.

If congenital anomalies and short stature are present with reticulocytopenia, the child is younger than 1 year of age, and there is no underlying hemolytic anemia, DBA is most likely. This condition is characterized by macrocytosis, an increase in hemoglobin F concentration, an increase in the expression of the i antigen, and increased levels of red cell adenosine deaminase (Table 7). These markers of "fetal" or dysplastic erythropoiesis, however, may be seen in patients who manifest stress erythropoiesis, such as when recovering from transient aplasias. The hallmarks of DBA are the marked reticulocytopenia and red cell macrocytosis. Bone marrow examination shows marked erythroid hypoplasia or total erythroid aplasia in greater than 90% of patients. Rarely, normal numbers of erythroblasts are seen, or there is an erythroid hyperplasia with a maturation arrest. In the two latter conditions, reticulocytopenia still is profound.

TEC occurs in an older but otherwise healthy group of children (Table 7). Unlike DBA, the anemia is normochromic and normocytic, with an absence of reticulocytes. Parvovirus is not responsible for this condition, and there is no specific diagnostic test. Bone marrow examination may be helpful in establishing the paucity of erythroid precursors unless recovery already has begun. As the name implies, the anemia is short-lived. A requirement for more than one transfusion suggests that there is another problem.

Treatment

Hydrops fetalis of the neonate who has reticulocytopenia and the absence of jaundice likely is related to intrauterine parvovirus infection or DBA. This condition requires prompt hematologic consultation and exchange transfusion. The initial sample of the newborn's blood should be saved for hematologic examination and serologic evaluation. Older patients who have underlying hemolytic anemias such as sickle cell disease or hereditary spherocytosis also may present with life-threatening anemias when infected with parvovirus. Patients who have very low hematocrits or higher hematocrits and cardiovascular instability should be admitted to a pediatric intensive care unit for monitoring and transfusion. Careful exchange transfusion while maintaining the intravascular volume is recommended to raise the hematocrit slowly to greater than 15% (0.15) and stabilize the cardiovascular status. Subsequent slow transfusion is required to increase the hematocrit further during the next 24 to 48 hours to 25% to 30% (0.25 to 0.30). This provides adequate oxygenation until the erythrotropic-damaging effects of parvovirus on erythropoiesis have dissipated. An alternative approach to exchange transfusion is the careful transfusion of packed red cells in conjunction with the judicious use of diuretics to modulate intravascular volume.

For patients diagnosed with DBA, the mainstay of therapy is administration of glucocorticoids. Following administration of prednisone 2 mg/kg per day, a reticulocyte response usually is apparent in 1 to 2 weeks. When the hemoglobin level reaches 10 g/dL (100 g/L), the prednisone dose can be reduced to a level that sustains that level with a single daily dose. This dose then is doubled and administered every other day, which tends to minimize the side effects of the glucocorticoid treatment. Patients vary greatly in their response to glucocorticoids. Some who have not responded to the initial 2 mg/kg per day dose have responded to double or triple this dose. If the patient does not respond to glucocorticoid therapy, a chronic transfusion program is required, with the attendant potential complication of transfusion hemosiderosis. For the 25% to 30% of patients who are glucocorticoid-resistant, bone marrow transplantation may be a reasonable option if there is a human leukocyte antigen-compatible donor available.

The long-term prognosis for DBA is guarded, particularly if chronic transfusion therapy is required. Chronic transfusion ultimately requires chronic iron chelation and removal with deferoxamine, and affected patients are at increased risk to develop acute myelogenous leukemia.

A child who has TEC also may have extremely low hemoglobin and hematocrit values, requiring pediatric intensive care. Such patients need prompt but extremely cautious transfusion, as described previously for parvovirus. Alternatively, if the nadirs of the hemoglobin and hematocrit are greater than 5 g/dL (50 g/L) and 15%

(0.15), respectively, the patient may recover from TEC without transfusion. The prognosis in this disease is excellent, and recurrence is unlikely.

Indication for Referral

Early hematologic consultation is indicated for patients who have aregenerative anemias. If the primary care physician is in an isolated setting and transportation is not readily available, phone consultation with a pediatric hematologist or pediatric intensivist may provide the essential support for judicious transfusion and management with diuretics to minimize the risk of arrhythmia, cardiac failure, and cardiovascular collapse. Consultation with hematology/oncology also permits consideration of other marrow failure syndromes that may involve multiple cell lines, including leukemia and aplastic anemia. It is best not to transport patients who have extremely low hemoglobin levels, even if they are hemodynamically stable. Decompensation during transport would present a very difficult problem in resuscitation. Similarly, patients who have any cardiorespiratory instability and somewhat higher values of blood hemoglobin should be managed where they present until they are stabilized.

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PIR Quiz

Quiz also available online at *www.pedsinreview.org.*

1. A 28-month-old girl who has sickle cell anemia develops a fever of 104°F (40°C). She is not in distress, and her mild irritability is consistent with her degree of fever. Results of physical examination are normal. Blood counts are consistent with her baseline values, and a blood culture is obtained. The *most* appropriate next step is to:

   A. Admit her for observation for 24 hours.
   B. Ensure that she receives prophylactic penicillin and have her parents observe her at home.
   C. Observe her for 3 to 4 hours and send her home if she appears well.
   D. Obtain a chest radiograph and treat her with antibiotics if an infiltrate is present.
   E. Treat her with broad-spectrum parenteral antibiotics.

2. Transcranial Doppler in a 4-year-old boy who has sickle cell anemia reveals elevated velocities of greater than 200 cm/sec in several intracranial arteries. Results of a repeat study 5 weeks later are unchanged. The *most* appropriate next step in management is to:

   A. Obtain cerebral angiography.
   B. Obtain computed tomography of the brain.
   C. Start a chronic transfusion program.
   D. Start hydroxyurea therapy.
   E. Repeat the transcranial Doppler in another 3 months.

3. A 4-year-old boy of Greek descent develops pallor and red urine within hours of taking trimethoprim-sulfamethoxazole. Laboratory testing reveals substantially reduced levels of G6PD. In your discussion of the diagnosis of G6PD deficiency with the family, you would explain the:

   A. Absence of neonatal hyperbilirubinemia in this disorder.
   B. Autosomal recessive inheritance of this disorder.
   C. Low risk of serious hemolysis in patients of Mediterranean descent.
   D. Risk of hemolysis with a variety of drugs.
   E. Lack of hemolysis with severe infection.

4. A previously well 20-month-old boy presents with fatigue and pallor. A complete blood count reveals white blood cell count of 5.1×10^3/mcL (5.1×10^9/L), hemoglobin of 3.9 g/dL (39 g/L), mean cell volume of 82 fL, platelet count of 375×10^3/mL (375×10^9/L), and serum bilirubin of 0.7 mg/dL (12 mcmol/L). Of the following, the *most* likely diagnosis is:

   A. Anemia of chronic disease.
   B. Diamond-Blackfan anemia.
   C. Hereditary spherocytosis.
   D. Parvovirus infection.
   E. Transient erythroblastopenia of childhood.

5. Your state neonatal screening program reports that an infant in your practice has a pattern on hemoglobins F and S on newborn screening. The underlying disorder(s) that would *most* likely present with this pattern is(are):

   A. Congenital hemolytic anemia.
   B. Sickle cell anemia and sickle beta$^+$ thalassemia.
   C. Sickle cell anemia and sickle beta^0 thalassemia.
   D. Sickle cell anemia and hemoglobin S-C disease.
   E. Sickle cell trait.

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