Management and Therapy of Sickle Cell Disease

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Management and Therapy of Sickle Cell Disease

NIH Publication

No. 96-2117

Originally Printed 1984

Previously Revised 1989

Revised December 1995

(Third Edition)

National Institutes

of Health

National Heart, Lung,

and Blood Institute

Contents

Preface

We are pleased to offer the third edition of *Management and Therapy of Sickle Cell Disease*. According to all reports, previous editions have served both the lay and professional communities extremely well in sorting out various approaches to health maintenance and complications of patients with sickle cell disease. As in the past, this edition serves as a guide for the health care worker involved in the management of patients with sickle cell disease. It represents a collective summary of experiences with therapeutic regimens rather than the by-product of controlled clinical trials. Some users have referred to this booklet as the *Bible* and others a "cookbook," and while neither is an accurate descriptor, the contributors hope that the real use is somewhere in between. During this past 5-year interval, progress in clinical management of sickle cell disease has been incredible. Most of the chapters in this edition have been totally rewritten or updated to reflect these advances and modifications in practices and to describe the published results of clinical research. These include findings from the Preoperative Transfusion Study, the Prophylactic Penicillin Trial II, the Multicenter Hydroxyurea Study, as well as epidemiological data derived from the Cooperative Study of Sickle Cell Disease (CSSCD).

The forum for developing this booklet was unchanged from that used in producing previous editions. After accepting assignments to review the specific topics, a small group of pediatricians, nurses, hematologists, and internists met in Bethesda and, at the end of 1 day, had hammered out positions that could be agreed upon by most of the participants. Each 5-year period sees fewer and fewer areas of disagreement, although it is unlikely that everyone present will proceed exactly along the same pathway. We encourage you to use this booklet as you see fit and to share it with your students, house staff, and clinical colleagues. We invite questions and comments and hope that you will feel free to contact the contributors who have made their telephone numbers and addresses available.

Clarice D. Reid, M.D.

Contributors

Rita Bellevue, M.D.
New York Methodist Hospital
506 Sixth Street
Brooklyn, NY 11215-9008
718/780-5643
718/780-3529 FAX

Lennette J. Benjamin, M.D.
Montefiore Medical Center
111 East 210th Street
Central Building #221
Bronx, NY 10467
718/920-7373
718/798-5095 FAX

Oswaldo Castro, M.D.
Howard University
2121 Georgia Avenue, N.W.
Washington, D.C. 20059
202/806-7930
202/806-4517 FAX

Samuel Charache, M.D.
The Johns Hopkins University
Department of Laboratory Medicine
2006 Sulgrave Avenue
Baltimore, MD 21209
410/466-6405
410/466-4330 FAX

Wesley Covitz, M.D.
Bowman Gray School of Medicine
Department of Pediatrics/Cardiology
300 South Hawthorne Road
Winston-Salem, NC 27103
919/748-4627
919/748-4204 FAX

Ann Earles, R.N., P.N.P.
Children's Hospital Oakland
Department of Hematology/Oncology
747 52nd Street
Oakland, CA 94609
510/428-3453
510/450-5647 FAX

Stephen Embury, M.D.
San Francisco General Hospital
Building 100, Room 263
1001 Potrero Avenue
San Francisco, CA 94110
415/206-8574
415/206-3332 FAX

Cage Johnson, M.D.
University of Southern California
2025 Zonal Avenue - RMR 304
Los Angeles, CA 90033
213/342-1259
213/342-1255 FAX

Thomas Kinney, M.D.
Duke University Medical Center
Erwin Road - 5417 Duke North
Durham, NC 27710
919/681-3395
919/681-2714 FAX

Mabel Koshy, M.D.
University of Illinois at Chicago
Room 1420 CSB
840 South Wood Street (M/C 787)
Chicago, IL 60612
312/996-5680
312/996-5984 FAX

Lawrence Lessin, M.D.
Washington Hospital Center
The Cancer Institute
110 Irving Street, N.W.
Washington, D.C. 20010
202/877-8112
202/877-8113 FAX

Bertram Lubin, M.D.
Children's Hospital Medical Center of Northern California
Department of Hematology/Oncology
747 52nd Street
Oakland, CA 94609
510/428-3502
510/528-3608 FAX

Scott Miller, M.D.
SUNY-Brooklyn
450 Clarkson Avenue - Box 49
Brooklyn, NY 11203
718/270-1692
718/270-1985 FAX

Paul F. Milner, M.D.
Medical College of Georgia
Sickle Cell Clinic - FK 100
Augusta, GA 30912
706/721-2171
706/721-4575 FAX

Kwaku Ohene-Frempong, M.D.
The Children's Hospital of Philadelphia
Comprehensive Sickle Cell Center
324 South 34th Street
Philadelphia, PA 19104
215/590-3423
215/590-2499 FAX

Orah Platt, M.D.
Children's Hospital Medical Center, Boston
Division of Hematology/Oncology
Enders Research Building - Room 761
320 Longwood Avenue
Boston, MA 02115
617/355-6347
617/355-6081 FAX

Darlene Powars, M.D.
University of Southern California Medical Center
Division of Hematology/Oncology
1129 North State Street
Los Angeles, CA 90033
213/226-3853
213/226-5049 FAX

Clarice D. Reid, M.D.
National Institutes of Health
National Heart, Lung, and Blood Institute
Division of Blood Diseases and Resources
Two Rockledge Centre
MSC 7950 - Room 10160
6701 Rockledge Drive
Bethesda, MD 20892-7950
301/435-0080
301/480-0867 FAX

Wendell Rosse, M.D.
Duke University Medical Center
Department of Medicine
Hematology/Oncology
Post Office Box 3934
Durham, NC 27710
919/684-3724
919/681-8477 FAX

Jeanne A. Smith, M.D.
Comprehensive Sickle Cell Center
Harlem Hospital - Columbia University
506 Lenox Avenue - Suite 6146
New York, NY 10037
212/939-1701
212/939-1692 FAX

Gwendolyn Swinson, R.N.
Bronx Comprehensive Sickle Cell Center
Montefiore Medical Center
111 East 210th Street
Bronx, NY 10467
718/920-7373
718/798-5095 FAX

Elliott Vichinsky, M.D.
Children's Hospital Oakland
747 52nd Street
Oakland, CA 94609
510/428-3651
510/450-5647 FAX

Winfred Wang, M.D.
St. Jude Children's Research Hospital
Department of Hematology/Oncology
332 North Lauderdale
Memphis, TN 38101
901/495-3497
901/521-9005 FAX

Doris Wethers, M.D.
St. Luke's Roosevelt Hospital Center
Sickle Cell Program
1111 Amsterdam Avenue
New York, NY 10025
212/523-3103
212/523-1839 FAX

Introduction

Sickle cell disease is a generic term for a group of genetic disorders characterized by the predominance of hemoglobin S (Hb S). These disorders include sickle cell anemia, the sickle beta thalassemia syndromes, and hemoglobinopathies in which Hb S is in association with another abnormal hemoglobin that not only can participate in the formation of hemoglobin polymers but also is present in sufficient concentration to enable the red cells to sickle. Examples of the latter disorders include hemoglobin SC disease, hemoglobin SD disease, and hemoglobin S O_{Arab} disease. The sickle cell disorders are found in people of African, Mediterranean, Indian, and Middle Eastern heritage. In the United States, these disorders are most commonly observed in African Americans and Hispanics from the Caribbean, Central America, and parts of South America.

Sickle cell disorders are best classified by genotype. The type of hemoglobin produced is determined by the two beta globin genes located on chromosome 11 and the four alpha globin genes located on chromosome 16. Individuals who are homozygous for the sickle beta globin gene (β^S) have sickle cell anemia (SS disease). Individuals with sickle beta thalassemia have a β^S gene and a gene for beta thalassemia. If no beta globin is produced by the beta thalassemia gene, the individual has $S\beta^o$ thalassemia ($S\beta^o$ thal). If some normal beta globin is produced by the thalassemia gene, the individual has $S\beta^+$ thalassemia ($S\beta^+$ thal). In the case of hemoglobin (SC disease), the individual has two abnormal beta globin genes, β^S and β^C, and makes two abnormal hemoglobins, Hb S and Hb C. Because the alpha globin genes are located on a different chromosome from the beta genes, a patient with sickle cell anemia can independently inherit an alpha globin gene abnormality. A common condition in people of African descent that has clinical significance for patients with a sickle cell disorder is the deletion of two of the four alpha globin genes, resulting in alpha thalassemia trait.

In contrast to these diseases is sickle cell trait. Individuals with sickle cell trait (Hb AS) have a normal beta globin gene (βA) and a βS globin gene, resulting in the production of both normal hemoglobin A and hemoglobin S, with a predominance of Hb A. Their red blood cells sickle only under unusual circumstances such as marked hypoxia and the hyperosmolar environment of the renal medulla (resulting in hyposthenuria).

There are two cardinal pathophysiologic features of sickle cell disorders: chronic hemolytic anemia and vaso-occlusion (which results in ischemic tissue injury). Hemolytic anemia may be related to repeated cycles of sickling and unsickling, which interact to produce irreversible red cell membrane changes, red cell dehydration, and erythrocyte destruction. Tissue

injury is usually produced by hypoxia secondary to the obstruction of blood vessels by an accumulation of sickled erythrocytes. The organs at greatest risk are those with venous sinuses where blood flow is slow and oxygen tension and pH are low (spleen and bone marrow) or those with a limited terminal arterial blood supply (eye, head of the femur and humerus). The lung, as the recipient of deoxygenated sickle cells that escape from the spleen or bone marrow, may be at special risk for vaso-occlusion and infarction. No tissue or organ is spared from this injury. Symptoms of the hypoxic injury may be either acute (e.g., painful events, acute chest syndrome) or insidious in onset (e.g., aseptic necrosis of the hips, sickle cell retinopathy). The effects of acute and chronic tissue injury may ultimately result in failure of organs like the kidney, particularly as the patient ages.

An additional and less recognized problem is that sickle cell patients live under considerable psychosocial stress. Not only do they experience stresses common to other painful chronic illnesses, but they must also cope with the unpredictable nature of their illness. The recurrent and unpredictable nature of the disease can adversely affect both school and work attendance and has the potential of reducing the patient's sense of self-esteem.

Appropriate counseling and management requires definitive diagnosis. The diagnosis of sickle cell disease is primarily based on hemoglobin electrophoresis. In those instances where Hb S is found in association with another abnormal hemoglobin such as Hb C, the diagnosis can be made by electrophoresis alone. In those instances, however, when the electrophoresis reveals only Hb S, Hb F (fetal hemoglobin), and Hb A_2, there can be difficulty in distinguishing between sickle cell anemia and some of the sickle beta thalassemia syndromes, including Sβ^o thal and sickle cell trait, in association with hereditary persistence of fetal hemoglobin (S HPFH). It is important that distinctions be made because these disorders differ markedly in their clinical expression. For example, symptoms of patients with Hb Sβ^o thal are similar to those of Hb SS; patients with Hb Sβ^+ thal have less associated symptoms, and those with Hb S HPFH are asymptomatic and not anemic.

Patients with SS or Sβ^o thal disease or S HPFH all have similar electrophoretic patterns. Mean corpuscular volume (MCV) is definitely decreased in thalassemia syndromes and is somewhat decreased in S HPFH. Measurement of Hb A_2 and Hb F may help in distinguishing between these conditions. In general, Hb A_2 levels are elevated above 3.5 percent in Sβ^o thal and are low in patients with S HPFH. Hb F levels are generally higher in the sickle beta thalassemic disorders than in SS disease, although there is considerable overlap between these diagnostic groups. In those instances where S HPFH is suspected, measurement of Hb F in the parents and/or siblings can be valuable.

The diagnosis of sickle cell disease cannot and must not be made from either a sickle cell preparation or solubility test because neither of these tests will reliably distinguish sickle cell trait from sickle cell disease. The diagnosis of a specific sickle cell disorder can be readily established through an analysis of the alpha and beta globin gene complex by using techniques of molecular biology; however, these are not usually required. The clinician should rely on the clinical history, blood counts, peripheral blood smear, hemoglobin electrophoresis

with measurement of the minor hemoglobins A_2 and F, and, when available, family studies that include hemoglobin electrophoresis and measurement of Hb A_2 and Hb F.

Table 1 summarizes the relationships between the clinical severity, blood counts, peripheral smear, Hb A_2 levels, and Hb S levels for the more common sickle cell disorders.

Table 1

Clinical and Hematologic Findings in the Common Variants of Sickle Cell Disease After the Age of 5 Years*

		HEMOGLOBIN ELECTROPHORESIS				HEMATOLOGIC VALUES			
Disease Group	**Clinical Severity**	**S (%)**	**F (%)**	**A_2 (%)**	**A (%)**	**Hb g/dL**	**Retic (%)**	**MCV (fl)**	**RBC Morphology**
SS	Usually marked	>90	<10	<3.5	0	6-11	5-20	>80	sickle cells nrbc normochromia anisocytosis poikilocytosis target cells Howell-Jolly bodies
$S\beta^o$ Thal	Marked to moderate	>80	<20	>3.5	0	6-10	5-20	<80	sickle cells nrbc hypochromia microcytosis anisocytosis poikilocytosis target cells
$S\beta^+$ Thal	Mild to moderate	>60	<20	>3.5	10-30	9-12	5-10	<75	no sickle cells hypochromia microcytosis anisocytosis poikilocytosis target cells
SC	Mild to moderate	50	<5	†	0	10-15	5-10	75-95	"fat" sickle cells anisocytosis poikilocytosis target cells
S HPFH	Asymptomatic	<70	>30	<2.5	0	12-14	1-2	<80	no sickle cells anisocytosis poikilocytosis rare target cells

Hematologic values are approximate.

*For findings in younger children, see Brown AK, Sleeper LA, Miller ST, et al. Reference values and hematological changes from birth to five years in patients with sickle cell disease. *Arch Pediatr Adolesc* 1994;48:796-804.

† = 50 percent Hb C.

nrbc = nucleated red blood cells.

There is tremendous variability between disease groups and between individual patients of the same group, particularly regarding clinical severity.

Chapter 1
Child and Adolescent Health Care Maintenance

During the past several decades, there have been substantial advances in the management of patients with sickle cell disease. For example, infant morbidity and mortality from overwhelming pneumococcal infection have been reduced by the administration of prophylactic antibiotics, and some individuals have been cured of their disease by bone marrow transplantation. Enhanced testing of blood products for infectious agents and more careful attention to crossmatching for minor red blood cell antigens have reduced complications from blood transfusion. Comprehensive sickle cell programs can reduce morbidity and mortality by providing easily accessible health care services administered by individuals knowledgeable about the disease and its complications. As a result of these advances, children with sickle cell anemia have about an 85 percent probability of reaching 20 years of age.

At the crux of effective health care maintenance is a strong patient-provider relationship built on trust, respect, open communication, and mutual understanding. The child and family should be encouraged to be active participants in the health care program, to be candid in expressing their concerns, and to work closely with the provider in all areas. In turn, the provider must be sensitive to the child's development and be willing to offer counseling and education that is age appropriate, realizing that the child's need for information will change with age. Providers who speak only to the parents and fail to incorporate the child or adolescent into the management plan will foster dependency in the child, ultimately hindering the transition to adulthood. The provider also must be knowledgeable about existing medical and psychosocial resources within the community and assist the patient in accessing these services when appropriate.

DEFINITIVE DIAGNOSIS

When a newborn's screening test indicates "sickle cell disease," it is the primary physician's responsibility to either establish a definitive diagnosis or to refer the patient to a pediatric hematologist for this purpose. As discussed in Chapters 1 and 5, establishing a definitive diagnosis requires accurate characterization of the hemoglobin phenotype and correlation of the phenotype with the clinical history, blood counts, and red blood cell morphology. Recent advances in molecular biology techniques have identified many variations in the beta globin gene area (beta globin gene haplotype) that may modify the clinical expression of sickle cell disease. Studies of the child's parents are useful in establishing a definitive diagnosis but must be undertaken with caution as the tests may disclose mistaken

paternity. As in all inherited disorders, thorough counseling of the mother is recommended before performing extensive family testing, and family testing should not be performed if the mother objects.

Once the definitive diagnosis is established, the parents should be provided with appropriate education and counseling about the specific form of sickle cell disease affecting their child. Providers must explain things carefully, avoiding medical jargon and allowing ample time for questions. Practitioners should not "overload" parents by providing them with too much detail during initial visits. More than one counseling/education session is required to ensure that parents adequately understand the information. A practitioner should not hesitate to refer the patient and family to a specialist for counseling. Many community-based sickle cell organizations are available to help with patient education and the acquisition of social services.

The definitive diagnosis should be recorded on the child's immunization record and in other key medical records. A copy of the diagnostic information also should be given to the parents so that information can be shared with other health professionals involved with the infant's care.

MAINTENANCE HEALTH CARE SERVICES

General Issues

Health care maintenance services for children and adolescents with sickle cell disease include those services provided to healthy children and services specifically provided for sickle cell disease. Routine services include immunizations and dietary counseling as well as education about preventive health measures. The frequency of visits should depend on the needs of the child and family. During the first 2 years of life, health care maintenance visits should be scheduled concurrently with needed immunizations. Older patients who are doing well can be seen semi-annually. Children also should be seen within a short time after a hospitalization or emergency room visit so the physician can review the situations that may have precipitated the event and make any necessary changes in the treatment plan.

Immunizations should be administered according to schedules recommended by either the American Academy of Pediatrics or the American Academy of Family Practice. In addition, all children with sickle cell disease should be immunized against hepatitis B virus and should receive the polyvalent pneumococcal vaccine at age 2 years, with a booster at age 5 years. Seasonal influenza vaccines are recommended.

Dietary counseling is an important part of routine health care. Mothers should be encouraged to breastfeed their infants, although iron-fortified formulas are an alternative. Supplemental iron should not be prescribed unless the patient is documented to have reduced iron stores by specific assessments of the serum ferritin level or measurement of serum iron and iron-binding capacity. Children with hemoglobin SC disease are often microcytic in the absence of iron deficiency or concomitant alpha thalassemia. Similarly, the incidence of alpha thalassemia trait is quite high in the African-American population and may produce microcytosis in the absence of iron deficiency. Routine administration of supplementary folic acid may not be necessary unless the dietary history reveals inadequate folate intake. Particular attention

should be paid to the diet if education, unmet economic needs, or cultural patterns place the child at risk for dietary deficiencies.

All children, including those with sickle cell disease, need regular dental care. Supplemental fluoride given topically, in vitamins, or in the drinking water, should be provided when indicated. Cleaning and dental fillings do not require special care. Operative procedures such as extractions and root canal therapy should be preceded and followed by standard rheumatic fever antibiotic prophylaxis to lessen the risk of bacteremia/sepsis. If general anesthesia is required, the child should be hospitalized, and preoperative transfusion should be considered if the surgery is extensive (see Chapter 10).

Other health care maintenance services include routine hearing and vision screening and periodic skin tests for tuberculosis. Because of the ocular complications of sickle cell disease, adolescents and adults should be seen annually by an ophthalmologist. Providers must also counsel patients and parents about the adverse health effects of illicit drugs, including tobacco and alcohol. Teenagers should be counseled about safe sex practices, including abstinence. If sexually active, they should be encouraged to use condoms to prevent getting sexually transmitted diseases, including acquired immunodeficiency syndrome (AIDS). Adolescent girls should receive additional counseling on birth control practices and be provided with birth control pills or other effective contraceptives when requested, given that there are no specific contraindications (see Chapter 13, Contraception and Pregnancy).

Sickle Cell-Specific Issues

In addition to the general health maintenance issues, there are health maintenance issues specific for sickle cell disease. These include the need for parents to learn specific physical assessment skills, to administer prophylactic antibiotics, to implement measures that minimize the risk of vaso-occlusive complications, and to use analgesics and comfort measures to minimize pain. During health maintenance visits, providers also should carefully review the history and physical examination for evidence of organ dysfunction.

When performing the physical examination, providers should pay attention to growth parameters and physical development. Physical growth and sexual maturation are delayed in sickle cell anemia patients compared with normal children, but the child eventually will "catch up" during the late teenage years. Common physical findings in children with sickle cell disease include mild generalized lymphadenopathy, functional systolic murmurs, and slight hepatic enlargement. Splenomegaly is often seen in infants and young children but is uncommon in children with SS disease and $S\beta^0$ thalassemia after age 6 years. Splenomegaly, however, is frequently observed in patients of all ages with Hb SC disease and $S\beta^+$ thalassemia. Because limitation of motion and pain are common signs of aseptic necrosis, the range of motion of the hips of older children and adolescents should be assessed. Scleral icterus is another common physical finding. Because children and adolescents are often teased about their "yellow eyes," they should be taught the nature of this characteristic and reassured

that it will not affect their visual acuity and does not necessarily reflect liver disease.

Blood counts should be done frequently during the first year of life to establish the patient's baseline, but after 12 months of age, the hemoglobin and hematocrit are relatively stable and need to be checked only once or twice a year in uncomplicated patients. For patients who are doing well, an annual urinalysis and measurement of blood urea nitrogen (BUN), serum creatinine, and liver enzymes are adequate for monitoring the patient for evidence of organ damage. Before the administration of the first transfusion, the patient's red blood cell antigens should be determined and recorded in the patient's permanent medical record.

Specific physical assessment skills that should be taught to parents include taking the body temperature and assessing respiratory effort, degree of pallor, and spleen size. Parents of children who have an enlarged spleen should be taught to palpate the spleen and may be given a tongue depressor that indicates the level at which the spleen extends below the left costal margin in the mid-clavicular line. The parent can use this "spleen stick" to determine if the spleen size has changed and can provide the stick to other health care providers who assess the child. The skin around the ankles of adolescents should be examined carefully for ulcers, and patients should be reminded to avoid trauma to the lower extremities because this may precipitate ulcerations. Parents should also be told that the child may have repeated episodes of enuresis or nocturia as a result of the renal concentrating defect and should be provided with suggestions on how to manage this rather difficult problem. Parents should remind school officials that their child will need access to fluids while at school and will also need to be excused periodically from class to use lavatory facilities.

One of the major advances in the care of infants with sickle cell anemia has been the recognition that oral penicillin given twice a day will reduce morbidity and mortality from pneumococcal infections. Prophylactic penicillin is recommended for all patients with SS disease and $S\beta^o$ thal until they are 5 years of age. For patients who are allergic to penicillin, erythromycin ethyl succinate (20 mg/kg) divided into two daily doses can provide adequate prophylaxis. The importance of administering the prophylactic antibiotics should be addressed at all visits because parents may become lax in dispensing this essential treatment over time. Penicillin may be prescribed in either liquid or tablet form; finely crushed pills may be given to young children. Pills have an important advantage over liquid penicillin preparations because pills are stable for years compared with liquid forms of penicillin that must be discarded after 2 weeks. An alternative to oral penicillin is injections of 1.2 million units of long-acting Bicillin® every 3 weeks. A recently concluded randomized trial demonstrated that penicillin prophylaxis may be safely stopped after the patient's fifth birthday. Concerns regarding the development of penicillin-resistant pneumococcal infections should not prevent the use of prophylactic penicillin, but appropriate measurements of antibiotic sensitivity are required in treating patients who have pneumococcal infections (see Chapter 6).

The role of prophylactic penicillin in SC disease and $S\beta^+$ thal is less well established. Although these latter two groups of patients are not at the same risk as children with SS disease for overwhelming infection

by encapsulated organisms because they have better preservation of splenic function, a significant number of pneumococcal infections have been reported. Regardless of whether a sickle cell patient is receiving prophylactic antibiotics, these patients should be evaluated promptly when they develop a fever greater than 38.5 $^{\circ}$C (101 $^{\circ}$F) (see Chapter 6, Infection).

Parents and patients should be instructed in the proper use of analgesia. Fear of addiction may prevent parents from administering adequate analgesics to their children. Similarly, older patients may undermedicate themselves for fear of becoming addicted to the analgesic (see Chapter 7, Painful Events). Discussing these issues with the patient and parents and using nonaddictive analgesics where possible should minimize the risk of drug dependency. Providers can explore various ancillary measures with the patient to assist with pain management, including biofeedback and relaxation techniques. The provider can also address health care practices that minimize the risk of painful events such as maintaining adequate hydration, treating infections promptly, and avoiding temperature extremes. Patients can often predict that a painful event is about to happen and can frequently help themselves by implementing treatment before the pain becomes too severe. Deterioration in school performance or changes in behavior may be early signs of cerebrovascular disease and should be evaluated promptly by physicians knowledgeable about sickle cell disease.

Primary care providers should identify physicians with expertise in sickle cell disease to assist them in managing sickle cell patients under their care. Cost-effective care can be provided when there is close collaboration and communication between primary care providers and consultant specialists.

Adolescents

Those who treat adolescents should realize that these individuals are coping with a very difficult time in their life, and the multiplicity of problems confronting healthy adolescents also exists for individuals with sickle cell disease. All health professionals who care for adolescents must be particularly attuned to the range of their problems and to the local resources available for assistance (see Chapter 4). Compliance with medication regimens and clinic visits can be a problem at any age but is a particular problem in this age group. Health care providers should identify ways to motivate such patients, including peer support groups and one-on-one guidance by a knowledgeable staff member.

The transition from a pediatric medical setting to the adult care setting is often difficult for the patient. Ideally, adolescents in the pediatric setting should be given assistance in learning how to use the adult care facility and be introduced to their new providers by those who have cared for them as children (see Chapter 3, Patient Care Coordination). In some hospitals, this transition is greatly eased by holding concurrent pediatric/adolescent/adult sickle cell clinic sessions.

COUNSELING

In addition to genetic counseling, sickle cell patients and their families may need counseling in academic and vocational guidance as well as counseling related to recreational activities and travel. The basic premise, however, is that parents should

treat their affected child as normally as possible. Parents should encourage activities that foster self-esteem and self-reliance. A positive self-image and a feeling of self-worth will help children and adolescents to cope more effectively with their illness.

Academic and Vocational Counseling

Providers should be prepared to counsel teachers and other school officials as well as patients. Narcotic analgesic usage and repeated absences may impair school performance, necessitating the need for specialized tutoring or the development of an individualized educational plan. Unless impaired by cerebrovascular disease, children with sickle cell disease have the usual range of intelligence and should be encouraged to develop their full potential. With additional tutoring or other assistance to compensate for time lost from school, they can often remain at grade level. Appropriate counseling and anticipatory guidance may minimize academic difficulties.

Vocational counseling is very important for adolescents and adults with sickle cell disease. Gainful employment is possible, despite the unpredictable nature of vaso-occlusive complications. The adoption of flexible work hours is an example of a strategy that will help patients in the workforce. Referral to community resources, including school guidance and vocational rehabilitation counselors, is another way to assist the patient in assessing and obtaining goals. Introducing children and adolescents to adults with sickle cell disease who have successfully coped with their illness has a very positive effect. Health care providers should be familiar with legal protection against discrimination in the workplace, provided by the Americans With Disabilities Act.

Recreation and Travel

There is often a need to provide counseling in the area of recreation and physical activities. Patients should be encouraged to get regular exercise. School-age children should participate in physical education classes, but they should be allowed to rest if they tire, and they should be encouraged to drink fluids after exercise. The potential risks of recreational activities that involve strenuous exertion should be discussed with the patient. Patients with sickle cell disease should dress warmly for cold weather and should avoid direct exposure to cold temperatures, including swimming in cold water. Children and adolescents should engage in competitive athletics with caution because it is difficult to heed the signs of fatigue in the heat of competition, and the team may find it difficult to replace an athlete sidelined by illness.

Children with sickle cell disease may benefit from a summer camping experience, either in an appropriate regular camp or through participation in a special camp for children with sickle cell disease. If the camp staff members are knowledgeable about the disease and comfortable with the care of these children, the camper can learn self-reliance and share experiences with other children about sickle cell disease while having fun. Health care providers and others who attend camp with sickle cell children typically find this a rewarding experience.

Patients and families often seek advice on the best methods of travel. Flying in a pressurized aircraft usually poses no special problems for sickle cell patients, provided

that fluids are liberalized and the patient dresses warmly to accommodate for the low humidity and cool temperature of the aircraft. On the other hand, air travel above 15,000 feet in nonpressurized planes can induce vaso-occlusive complications. Land travel by bus or automobile is not associated with any increased risk of sickle cell-related complications, although frequent rest and refreshment stops should be included in the travel plans. Patients should be encouraged to consult their physician before traveling and should be advised to carry with them specific medical information that includes their diagnosis, baseline hematologic values, a list of current medications, and the name and telephone number of their physician. Providers should give their patients the names of physicians or care facilities to contact in the event of problems.

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Chapter 2
Adult Health Care Maintenance

Many patients can live for long periods without experiencing acute or severe exacerbations of sickle cell disease. Increased awareness of the disease's complications and improved use and availability of health care are positive contributors to patient longevity and productivity. Contrary to previous estimates that one-half of all sickle cell disease patients die before age 20 years, about 90 percent of patients now survive past that age. Recent studies indicate that the mean age at death for SS patients is 42 years for males and 48 years for females. Most patients with SC and $S\beta^+$ thalassemia can be expected to reach age 70 years and older. Many patients live a full life, and patients age 50 years now constitute a large segment of the adult population with sickle cell disease.

Common practices and approaches to optimal health care maintenance of adults are reviewed in this chapter, with an emphasis on developing a useful operational strategy for clinicians. Health maintenance includes prevention, early recognition and treatment of complications, and continuing patient education. In contrast to the stress of acute crises, well-patient visits provide a better psychological setting for the development of effective doctor-patient relationships and effective coping skills. The development of such relationships may result in fewer visits to the emergency room and fewer hospitalizations.

INITIAL PATIENT VISIT

During the initial patient visit, a complete medical history should be taken, and a physical examination should be performed. A patient should have a complete blood count, reticulocyte count, and hemoglobin electrophoresis if this information is not already available. Laboratory tests, including urinalysis, liver function, urea, creatinine, electrolytes, and chest x-ray, should also be obtained. Certain laboratory tests, although not routinely performed, may be indicated by the presence of specific complications. These tests include screening for red cell antibodies, measurement of arterial blood gases, pulmonary function tests, electrocardiograms (EKGs), studies to detect the presence of gallstones, and radiographs or magnetic resonance imaging (MRI) scans of the femoral and humeral heads to detect aseptic necrosis. Previous medical records should be requested as well. If the patient has never received the pneumococcal vaccine, immunization should be offered.

Patients with sickle cell disease are at high risk for developing sickle cell retinopathy. Patients should see an ophthalmologist for retinoscopy; the ophthalmologist should conduct followup examinations of patients diagnosed with significant proliferative retinopathy, at regular intervals.

Also during the initial visit, health providers should assess the patient's understanding of the disease and its complications (see "Patient Education" in Chapter 3, Patient Care Coordination). Family planning and genetic counseling services should be discussed, and the availability of prenatal diagnosis should be mentioned when appropriate (see Chapter 13, Contraception and Pregnancy). Asymptomatic patients often have a false feeling of security about their disease. They should be cautious particularly regarding the choice of a profession and jobs requiring strenuous exercise and exposure to high altitudes.

PATIENT FOLLOWUP VISITS

Most patients with sickle cell disease should have regular medical evaluations approximately every 3 to 6 months; certain patients need to be seen more frequently as symptoms dictate. Others, including asymptomatic patients with SC disease or $S\beta^+$ thal, should be seen every 6 months. A blood count as well as a reticulocyte count should be performed, and a urinalysis and routine chemistry tests should be repeated annually. With advancing age, complications such as chronic organ failure often require more frequent visits and more extensive laboratory evaluations.

Attention should be focused particularly on abnormalities of renal function such as renal tubular acidosis and hyperuricemia (see Chapter 18, Renal). During initial and followup visits, it is important to discuss the general nature and variability of the disease with the patient and to explain the significance of symptoms. Specifically, complications such as gallstones, aseptic necrosis, and priapism should be mentioned. Also, the issues of childbearing and birth control should be addressed, and the patient's spouse or partner probably should be included in these discussions (see Chapter 13, Contraception and Pregnancy).

It is particularly important to instruct patients about how to respond to acute illness. They should be instructed to seek immediate care for events such as high fever, productive cough, and symptoms of acute anemia such as sudden dyspnea, weakness, or dizziness. Discussion with the patient should include the identification of available means of transportation to the emergency room. Painful episodes should initially be managed at home with rest, a warm environment, increased oral fluids, and mild analgesia or other modalities of pain management (see Chapter 7, Painful Events). If pain persists or fever develops, the patient should contact his or her physician or go to an emergency department. The procedure to be followed for a particular emergency department should be discussed in detail; if a prior call from the physician can facilitate the visit, the patient should know whom to call at night or on weekends and holidays.

Patients should keep a small supply of an intermediate strength oral narcotic analgesic (codeine, hydrocodone, or oxycodone) and should be instructed to use it for attacks of pain that do not respond to aspirin, acetaminophen, or ibuprofen. They should be informed that most pharmacists will not accept a telephone prescription for a narcotic and should be instructed on how to obtain another supply.

Certain matters of general health care are particularly important to patients with sickle cell disease; for example, it is important for the physician to discuss the hazards of cigarette smoking and excessive alcohol

intake. Although strenuous exercise may have to be avoided in most patients, a well-planned exercise program should be encouraged (see "Counseling" in Chapter 1, Child and Adolescent Health Care Maintenance).

Most patients eat poorly during painful crises, and because patients with hemolytic anemia have an increased need for folic acid, daily supplements of 1 mg should be prescribed at those times. The danger of masking a vitamin B_{12} deficiency is small, but even young African-American patients are at risk. There is no evidence that any other form of vitamin supplementation is of value in sickle cell disease.

The patient's employment should also be discussed. Arrangements for obtaining "doctor's notes" after an absence from work, filling out forms, and refilling prescriptions should be outlined for all patients with a chronic disease. Medical providers should be familiar with procedures for seeking legal assistance if workplace discrimination because of disability is perceived.

VOCATIONAL GOALS

Individuals with sickle cell disease can pursue a variety of vocations and professions, and they should be encouraged to do so. There are very few vocational choices that should be discouraged, except jobs requiring strenuous physical exertion, exposure to high altitudes, or extreme temperature variations (see Chapters 1 and 4).

Students should not be discouraged by rigorous academic programs or long courses of study; instead, they should be encouraged and supported. However, individuals with sickle cell disease should be informed of any special considerations that are needed to facilitate their studies. For instance, they should be encouraged to inform their education program director or their employer that they have sickle cell disease and that students with sickle cell disease may take longer to complete their academic program or may require special considerations in completing their course of study.

PSYCHOSOCIAL COUNSELING

Intervention by a social worker or mental health professional is often indicated for a variety of psychosocial concerns and problems that affect sickle cell patients and their families. Physicians in private practice may not have direct access to the services of psychologists or social workers. Such services may be available, however, through local social service agencies.

The nurse's role in the management of psychosocial issues is equally important. The responsibility of nurses—often the primary providers of care and the health professionals most often seen by patients—includes the integration of other professionals into health care efforts and the identification of special patient needs. Also, nurses can provide psychosocial counseling, preventive health care information, and patient and community education (see Chapter 3, Patient Care Coordination).

DENTAL CARE

Dental procedures requiring local anesthesia can be performed in the dentist's office as with any other patient, but procedures requiring general anesthesia necessitate hospitalization. The use of nitrous oxide as an anesthetic agent for office dental procedures is controversial and requires consultation between the physician and dentist. The customary administration of at least 50

percent oxygen with nitrous oxide alleviates the risk of sickling. Concentrations of less than 20 percent oxygen should be avoided. Patients should be fully alert before leaving the office. Prophylactic antibiotics should be used with operations such as extractions or root canal therapy, if there is a question of rheumatic heart disease or mitral valve prolapse or if an orthopedic prosthesis has been implanted.

SURGERY AND ANESTHESIA

The question of prophylactic preoperative blood transfusion is addressed in Chapter 10. Intraoperative overexpansion of blood volume should be prevented, particularly in patients whose cardiac status is precarious. No special precautions are needed for local or regional anesthesia such as a pudendal block. Careful epidural anesthesia can be a good compromise for gynecologic or proctologic procedures. Operation in a "bloodless field" with the use of tourniquets may be hazardous. If possible, an alternative technique or prior exchange transfusion, or both, should be used. With all types of anesthesia, intraoperative hypothermia should be prevented.

After surgery, it is extremely important to ensure hydration and, at the same time, prevent circulatory congestion. Adequate records of the amount of intravenous and oral intake should be maintained; urine output and fluid drainage should be measured and recorded, and patients should be weighed daily. Minor hyponatremia (130-140 meq/L) can be tolerated but care should be taken to avoid hypernatremia (see Chapter 21, Surgery and Anesthesia). Efforts should be made to ensure deep breathing and coughing, to avoid atelectasis.

EXPERIMENTAL THERAPY

There has been no established method of treatment for the prevention of vaso-occlusive pain crisis and other complications of sickle cell disease. A number of experimental therapeutic approaches, including use of hydroxyurea, erythropoietin combined with hydroxyurea, short-chain fatty acids (such as butyrate derivatives), and clotrimazole, are currently under investigation (see Chapter 23, Experimental Therapy).

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Chapter 3
Patient Care Coordination

The complexities of sickle cell disease demand intricate coordination of health care services. Because of their unique educational preparation, mid-level practitioners (MLPs) (i.e., nurses, physician assistants (PAs), clinical nurse specialists, and nurse practitioners) are best suited for assuming this responsibility. Discussion of patient care coordination; preventive health care; home management, including pain management and comfort measures; patient education; and education of other health care providers will be included in this chapter. Inpatient, outpatient, and emergency department care also will be highlighted.

PATIENT CARE COORDINATION

Because of the chronic nature of sickle cell disease, multidisciplinary and subspecialty referrals are often necessary. The MLP may serve as the liaison among the patient, the primary care provider, and the specialist. All individual treatment plans must be developed with patient and parent participation to identify problem areas that may adversely affect compliance with required care. Ongoing assessments are necessary to identify the need for referrals to other professionals for further interventions.

PREVENTIVE CARE

At each visit, MLPs should emphasize the importance of regular health care examinations to patients during steady states. The expected schedule of visits, routine tests, and immunizations should be carefully outlined. Special procedures that are part of the standard of care such as EKGs, pulmonary function tests, neuropsychiatric testing, and necessary immunizations should be discussed. The patient or parent must be able to demonstrate an understanding of these procedures before being asked to sign a consent form.

Preventive care also includes education about recognizing acute and life-threatening events associated with sickle cell disease. Early recognition and prompt reporting of symptoms may prevent or minimize complications. The parents of children with sickle cell disease must be taught how to use a thermometer and palpate the spleen, and they should be asked to demonstrate their ability to perform these procedures. Reinforcing the need for prophylactic penicillin may improve compliance. In addition, the MLPs should talk with patients about when to call for advice and when to seek immediate medical attention. Transportation planning should be discussed before an emergency situation arises.

Age-appropriate education should continue into adulthood along with an emphasis on preventive health care. The importance of regular health care maintenance and visits other than for episodic acute care cannot be overemphasized. Reviewing the symptoms of acute events and the significance

of early treatment of complications are crucial and can be provided by the MLP.

PATIENT EDUCATION

The complexity of sickle cell disease mandates ongoing patient education. Specific medical treatment modalities such as those outlined in this management guide will require the development of appropriate interventions individualized to maximize compliance. During the initial assessment, the patient's and/or family's understanding of the disease should be explored as well as their understanding of general and specific treatment plans. It is important that the family thoroughly understands both the general and specific treatment plans before they are implemented. The MLP must assess the patient's and family's knowledge base of sickle cell disease regularly.

TRANSITION FROM PEDIATRIC TO ADULT CARE

Many factors must be considered before the transition from pediatric to adult health care can occur. The process can be traumatic for medical staff members and the family as well as the patient. The patient must be ready developmentally and must have the full support of the family as well as the pediatric and adult staff members. As patients leave the pediatric setting, they will have to learn how to assume increasing responsibility for their own health care. This move toward independence will be reflected in other aspects of their life such as in their job, school, and relationships. Ideally, patients should attend joint pediatric/adult sessions and then move gradually to full adult care. Participation in a support group may help the patient through the transition. Efforts must be made to transfer medical records and other pertinent information to the adult care practitioner.

EDUCATION OF OTHER HEALTH CARE PROVIDERS

Understanding the pathophysiology, treatment, and complications of sickle cell disease is important so that health caregivers can provide optimal care. MLPs should be a resource for house staff members, inpatient and outpatient nursing staff members, and public health, school health, and other health staff members. Management conferences and workshops are effective methods of education. A comprehensive health care team, including physicians, social workers, genetic counselors, and MLPs, offers the best approach to effective health care delivery and education.

HOME HEALTH CARE MANAGEMENT OF PAINFUL EPISODES

Painful episodes are the most common complication of sickle cell disease. Home health care management and close telephone followup can reduce the need for frequent hospital visits. Because fever can be a sign of infection or extensive tissue damage, patients should be urged to purchase thermometers and learn how to use them prior to telephone contacts. The health care practitioner can provide information about home comfort measures such as warm baths or showers, massages, and relaxation therapy. Pain that requires medical evaluation rather than home care should be carefully reviewed with the patient (see Chapter 7, Painful Events).

LEG ULCER CARE

Evaluation of the patient's understanding of the prescribed treatment plan (see Chapter

16, Leg Ulcers) should be done at each contact. Demonstration of how the treatment plan will be administered at home should help to increase compliance. Home care referral should be made if indicated. Successful outpatient and home management for chronic, recurring leg ulcers reduces the need for hospitalization.

CHELATION THERAPY

A chronic transfusion program may be instituted to treat severe complications of sickle cell disease (see Chapter 10, Transfusion). Patients on chronic transfusion programs should be evaluated for iron overload (hemosiderosis). When iron overload is documented, chelation therapy with deferoxamine mesylate (Desferal®) may be initiated. The MLP should develop a teaching plan for home chelation, and written instruction must be provided to assist the patient or parent through each step of the procedure. Compliance with home chelation therapy must be monitored carefully. The MLP should coordinate yearly visits to ophthalmology and audiology specialists for early detection of possible adverse effects of deferoxamine mesylate.

INPATIENT CARE

After a careful history and physical assessment are done, a health care plan using techniques proven effective in the past can be instituted and appropriate goals for hospitalization established. Continuity of care is important for the hospitalized patient. Thus, the assignment of a primary caregiver can help to reduce the stress of the hospitalization and associated fears. This individual should explain hospital procedures and specific treatment modalities to the patient carefully. Finally, the primary caregiver should also participate in discharge planning and referral to appropriate resources when indicated.

OUTPATIENT CARE

In the outpatient setting, the MLP should focus on health maintenance, prevention, early recognition, treatment of complications, and patient education. Evaluations should identify patient and practitioner concerns about illness, analgesic therapy, management, compliance, social adjustment, and school and/or work performance. Health care plans are developed to help patients maintain wellness and to be active participants in receiving the best possible care. A close relationship with school health faculty is beneficial for school-age patients.

EMERGENCY DEPARTMENT CARE

MLPs must identify and promptly treat acute events associated with sickle cell disease. Proper education of emergency room staff members will ensure a timely response to life-threatening complications (i.e., sepsis, acute anemic events). To help provide continuity of care, an updated database that includes baseline hematologic values and other pertinent information necessary for providing emergency care should be maintained. Communication is essential between emergency department staff members and the sickle cell clinic or physician's office.

SUMMARY

Patient care interventions for individuals with sickle cell disease are both supportive and treatment oriented. A delicate balance must exist between providing supportive care and fostering independence to ensure that patients become well-informed, active participants in their care.

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Chapter 4

Psychosocial Management

As in other chronic illnesses, psychosocial issues affect social, emotional, academic, and vocational adaptation to sickle cell disease throughout the patient's life cycle. The patient's care providers must be aware of these factors and respond appropriately. Many of the psychosocial factors are associated with developmental life stages. The following is a developmental framework for examining the psychosocial aspects of sickle cell disease. Suggestions for appropriate interventions are offered.

THE INFANCY THROUGH PRESCHOOL STAGE

Early and appropriate psychosocial counseling for the family of a newly diagnosed infant with sickle cell disease is extremely important. Parents may have a number of concerns pertaining to social, emotional, and environmental issues related to their baby's diagnosis. Such issues may include nutrition, health insurance, the need for adequate housing, and assistance in dealing with feelings ("genetic guilt") about having a child with a chronic hereditary illness.

To assist families with the multiple nonmedical issues that might confront them, health care providers need to know about available community resources. For example, the local social services department or a State government's Crippled Children's Program may be able to identify potential housing, medical, and financial assistance. The social services department may also provide case management services that link and coordinate counseling and support services for the family.

In addition to addressing the concrete medical needs of the patient and family, attention must be given to their emotional and psychological needs. The physician should provide an opportunity for the parents to talk, ask questions, and express their feelings (anger, guilt, fear, denial, helplessness, etc.). These sessions should be repeated as necessary. Parents should be given factual information about their child's condition, its inheritance, and problems that may occur in the future. Parents also need information and instruction on how best to provide home management and care of their infant. With sound teaching, encouragement, and support, the parents can become effective participants with health care professionals in the care of their child. This approach can have a positive influence on parental coping and compliance.

In some cases, counseling and reassurance of parents by the physician is not sufficient to allay anxiety and reduce guilt or resolve deep-seated emotional and psychological conflicts. Referral to a family and child services agency or other community mental health facility can be helpful in this situation. With specialized individual, family,

and group counseling, parents together or individually are usually able to work through social, emotional, and environmental conflicts. Often, parental understanding and comprehension of the genetic implications of their child's medical condition remain inadequate. If so, ongoing association with genetic counseling services should be considered.

Established programs in the community that provide services to patients and families affected by sickle cell disease or other genetic disorders should be used. Parents can also benefit from interacting with other parents in mutual support and self-help groups.

THE SCHOOL-AGE STAGE

Children with sickle cell disease should be enrolled in a regular classroom unless there are specific reasons to do otherwise. Parents should notify appropriate school officials of their child's condition. It is helpful to have written information that can be shared with the teacher, school nurse, and other school officials. This information can be in the form of a brochure or pamphlet containing general information about sickle cell disease or a letter from the patient's physician specifically describing the child's condition and any special needs. Medical or nursing staff should be available to provide consultation and education to teachers about sickle cell disease.

Parents may ask the physician to complete a variety of forms or write letters describing their child's illness and its management or requesting special bus transportation, the use of special school facilities (such as an elevator), exemption from certain physical education activities, or home or hospital school instruction. The physician should consider these requests carefully, discuss them fully with the parents and others involved, and understand completely the nature of the request. Although these requests relative to their child's school may be appropriate and valid, they may also be indicative of the parents' need for a better understanding of their child's health status and his/her actual limitations. Children should be encouraged to study and remain in school. Although school attendance may be interrupted periodically due to illness (usually infections and painful episodes), once the illness is resolved the child should return to school and other usual activities. Hospital-based school programs can assist the child who has frequent hospitalizations to maintain age-appropriate school performance.

To accommodate the child's school program, physician visits should be scheduled after school hours when possible. Telephone followups are often helpful. Socialization and peer interaction are important functions of the educational system, and inappropriate use of a home tutoring program during and following illnesses can interfere with the child's social and psychological development. Usually this service is not needed unless the child is convalescing at home for more than 2 weeks. During brief illnesses at home, parents can request that the child's teacher assign a study partner to bring assignments home to the patient and keep him or her abreast of school activities. Because school policies vary, parents should check with the school or school board to find out what services or resources are available. The physician and nurse practitioner can be extremely important advocates.

Recognition of the importance of school does not negate the importance of other activities of a growing child. Like all

children, children with sickle cell disease should be encouraged to have hobbies and other age-appropriate interests. Parents should understand that children with sickle cell disease need not be treated any differently from unaffected children. This is especially true during the quiescent periods when there are no sickle cell-related problems. Keeping the child's lifestyle as normal as possible helps in development of a positive self-image. Many children with sickle cell disease have successfully attended summer camp, some camps specifically for children with sickle cell disease and others unrelated to sickle cell disease. Such activities foster independence and provide the child with an opportunity to be more similar to his or her peers.

THE ADOLESCENT STAGE

Adolescence (ages 13 to 19) represents a period of transition marked by physical, emotional, and social changes. There may be concerns for adolescents with sickle cell disease in this age group. This is the stage when concerns about body image, peer group acceptance, and physical attractiveness are very important. Specific physical characteristics and complications of sickle cell disease can hinder the social and emotional adjustment of the affected teenager. Such characteristics as jaundiced eyes, enuresis, delayed physical maturation and growth retardation, unpredictable pain episodes, and complications such as avascular necrosis of the hip joint, chronic leg ulcers, and the residual effects from stroke can make coping very difficult. Episodes of priapism require both medical and psychological care, especially in adolescents. Fortunately, only a few teenage sickle cell patients are faced with these complications, and they may benefit from individual or group counseling. Therapy groups that include teenagers with the same or similar disabilities can be very successful. A support group for adolescent patients is especially important because they may hide their disease from peers and teachers. Such groups help teenagers learn how peers cope with common problems and concerns.

Overprotection by parents, family, and friends can pose very serious problems for some adolescents. They want to be independent but are forced to be dependent when they become ill. Sensitive counseling of both parents and the adolescent can be helpful. The physician dealing with the adolescent must keep the parents informed and give them an opportunity to participate in medical decisions.

Delayed development of secondary sexual characteristics and/or slow physical growth in adolescent patients requires counseling and reassurance. Just like other teenagers, teenage patients with sickle cell disease want to resemble their unaffected peers in every way, including capabilities and interests.

Often the physician is asked by the adolescent with sickle cell disease if he or she can participate in sports or other activities that require considerable physical strength and endurance. In the absence of contraindications, participation in such activities should be encouraged. The teenager with sickle cell disease needs to be able to set his or her own pace when participating in activities such as swimming, tennis, or basketball and should be able to stop and rest when tired. Some teenagers may be able to compete in competitive sports.

Sexuality in the teenager with sickle cell disease is often no different from that in

their more healthy peers. Some will be sexually active, and it is important to provide advice on contraception and sexually transmitted diseases. Failure to acknowledge problems of sexuality and associated risks may result in serious complications later. When appropriate, adolescents should be referred to family life clinics. Pregnancy in adolescents with sickle cell disease presents medical, psychological, and social problems. Pregnant adolescents can usually benefit from counseling and services offered by a social worker.

At this stage of life, teenagers should give serious consideration to college, careers, and their future as adults. Discussion with gainfully employed adults with sickle cell disease, particularly with professionals who have sickle cell disease, can be very helpful. Adolescent sickle cell patients should be encouraged to consider careers that are consistent with their medical condition. Such career aspirations often require college or vocational training. Referral to vocational rehabilitation, precollege orientation programs, or other training and career programs can be extremely helpful. Referral to key community resource agencies such as departments of employment (job services) and social or youth services can establish important linkages.

THE ADULT STAGE

Adult patients with sickle cell disease may encounter psychosocial and socioeconomic problems, including unpredictable interruptions of social and economic life due to recurring painful episodes. Adults are often faced with unemployment, lack of health insurance coverage, and inability to qualify for public assistance or disability insurance. If the young adult is employed, frequently this employment is unstable and does not offer fringe benefits like health insurance coverage. Assistance with payment for medical services may be available for adult sickle cell patients through the local public medical assistance program, Social Security Administration, and State vocational rehabilitation services.

Most sickle cell patients do not show obvious disability, and it may be difficult for them to qualify for assistance. Eligibility for public assistance in disability and Supplemental Security Income programs is based on the extent of the disability as well as income eligibility. The patient must qualify in both categories to be determined eligible. The physician's report of the patient's physical status is crucial in helping to determine his or her eligibility. The physician should carefully document the clinical course of the patient's illness, including the number and dates of hospital admissions, emergency room visits, acute visits, organic and physical dysfunctions, and the blood count and the need for blood transfusions. To provide a comprehensive picture of the patient's condition, it may be necessary to provide more information than that specifically requested.

In addition to social and environmental difficulties, the adult patient may experience emotional and psychological problems, including relationship difficulties, loneliness, low self-esteem, and preoccupation with death. Consultation with or referral to a mental health practitioner is beneficial to the patient and physician when he or she observes patient behavior that is indicative of failure to cope, depression, or other signs of psychological or emotional dysfunction. Support and self-help groups may be beneficial for these patients.

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Chapter 5
Newborn Screening

Newborn screening for sickle cell disease is an effective first step to reduce morbidity and mortality in individuals with the disease. Parents of newborns with a positive screening test result for sickle cell disease must be contacted before the child becomes 2 months of age to confirm the diagnosis. The diagnosis should be confirmed by a laboratory with expertise in analysis of variant hemoglobins. If a child who is presumed to have sickle cell disease through newborn screening is not retested by 4 months of age, he or she should be started on penicillin VK (125 mg given orally twice a day) pending confirmation; the medication can be discontinued in the rare instance that the hemoglobin screening test result was erroneous or is found to represent a benign disorder. Once the disease diagnosis is confirmed, the infant must receive care in an ongoing and comprehensive medical program that includes oral penicillin given twice a day for the prevention of overwhelming *Streptococcus pneumoniae* infection and parent education about sickle cell disease. The medical program should be staffed by health care professionals who are sensitive to the special needs of infants with sickle cell syndromes and are aware of their propensity to life-threatening infection and death from complications such as acute splenic sequestration and acute chest syndrome.

All infants, of every ethnic group, should be tested to ensure the identification of all affected newborns. Where possible, sickle cell disease screening should be coupled with other newborn screening tests performed to detect hypothyroidism and inborn errors of metabolism. Several screening methodologies are acceptable, including hemoglobin electrophoresis on cellulose acetate and citrate agar, isoelectric focusing, and high-pressure liquid chromatography. Because of the high concentration of Hb F in newborns, solubility tests or sickle cell preparations (sodium metabisulfite) should not be used to confirm the presence of Hb S until the infant has reached 12 months of age and should never be used as a sole diagnostic laboratory procedure. States that test for sickle cell disorders as part of their newborn screening procedures usually confirm the original test result by retesting the child and will also request a repeat specimen if the history indicates that the child was transfused before the blood sample was obtained. It must be emphasized that the responsibility for a final and definitive diagnosis rests with the child's physician.

Red cells of normal newborns contain hemoglobins F and A, "FA," the hemoglobin in highest concentration being listed first. The hemoglobin pattern or phenotype is due to predominance of Hb F at birth. Newborns with sickle cell trait have an

"FAS" phenotype, with more Hb A than Hb S. Infants with SC disease have an "FSC" pattern, those with SS disease, $S\beta^o$ thal, and S HPFH each have an "FS" phenotype on newborn screening. Although infants with $S\beta^+$ thal will generally have an "FSA" pattern on screening, the percentage of Hb A may be so small that these infants will also have an "FS" phenotype. Definitive diagnosis may require testing both parents or deoxyribonucleic acid (DNA) typing of the infant or retesting the infant after 9 months. It is important to remember that newborns with "FA" patterns are not necessarily hematologically normal—they do not have sickle cell disease but may have thalassemia or another disorder of red blood cells. When definitive diagnostic tests cannot be performed in early infancy, it is best to assume that the infant has SS disease, the most common of the FS disorders. When infants are doubly heterozygous for sickle cell and another abnormal hemoglobin other than C, definitive identification by a knowledgeable hematologist is necessary.

In addition to identifying the affected newborn, newborn screening also provides an opportunity to identify couples at risk for having children with sickle cell disorders. Parents of newborns identified with sickle cell trait or hemoglobin C trait should be offered testing for all hemoglobinopathies, including thalassemia, and be appropriately counseled.

Newborn screening may identify variant hemoglobins other than S or C. When these are co-inherited with Hb S, a definitive diagnosis must be made. Hemoglobin S^o_{Arab} disease, for instance, is as serious a condition as SS disease, while the combination of Hb S and Baltimore is as benign as sickle cell trait. If the child has only Hb A and the variant, further diagnostic tests are usually unnecessary, if the child is hematologically normal in other aspects.

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Chapter 6

Infection

Serious bacterial infections are a major cause of morbidity and mortality in patients with sickle cell disease. Severe, overwhelming septicemia/meningitis due to *S. pneumoniae* is the most common cause of death during early childhood, but enteric organisms emerge as important pathogens in older patients. Because of the patient's asplenic condition, and because of disordered humoral immunity, infections in patients with SS disease are more likely to cause morbidity, disseminate, and resist eradication than in individuals unaffected by the disease. Infections also may enhance susceptibility toward vaso-occlusive complications. Prevention and early, aggressive treatment of infection are critical in the management of patients with sickle cell disease.

PREVENTION

Immunization

Children with SS disease have a normal antibody response to vaccines and should receive all immunizations recommended by the American Academy of Pediatrics (these change periodically, and the most current recommendations should be followed (see Table 2)). In addition, children should receive pneumococcal vaccine. Some clinicians recommend that the influenza vaccine be administered according to epidemiologic considerations.

Antibiotic Prophylaxis

Prophylactic penicillin is so effective in reducing the number of life-threatening episodes of pneumococcal sepsis in children with SS disease under age 5 years that most States screen newborns for the disease so they can be placed on the drug by 2 to 3 months of age. Oral penicillin VK (125 mg given twice a day up to age 3 years, then 250 mg given twice a day) is the preferred form of treatment. Prophylaxis should be given to children with SS disease and $S\beta^o$ thal starting at 2 to 3 months of age and continuing until at least age 5 years. Prophylaxis in older children has not been shown to be beneficial and may be unnecessary after pneumococcal immunizations are complete and antibody titers are protective. Some clinicians give prophylaxis to children with SC disease or $S\beta^+$ thal: there is an increased risk of severe infection in such patients, although it is less than in SS disease or $S\beta^o$ thal. Compliance with penicillin prophylaxis can be achieved, provided that a dedicated team of physicians, nurses, and health care educators engage families in intensive educational programs.

Neither the pneumococcal vaccine nor available antibiotics has been shown to eliminate nasopharyngeal colonization with *S. pneumoniae, Neisseria meningitis,* and *H. influenzae* in normal young children or

Table 2

Recommended Immunizations

Birth (or at first visit)	Hepatitis B vaccine #1, hepatitis B immunoglobulin if mother HBsAg†
1 month old (or 4 weeks after first visit)	Hepatitis B vaccine #2
2 months old	DTaP #1, HbcV #1* or Tetrammune, OPV #1
4 months old	DTaP #2, HbcV #2 or Tetrammune, OPV #2
6 months old	DTaP #3, HbcV #3, OPV #3 or Tetrammune, hepatitis B vaccine #3 (or 6 months after second vaccine)
12 to 15 months old	Measles, mumps, rubella (MMR)
5 months old	HbcV booster
15 to 18 months old	DTaP booster #1, OPV #3
24 months old	Pneumococcal vaccine
4 to 6 years old	DTaP booster #2, pneumococcal vaccine booster, OPV #4, MMR (at or before school entry)
14 to 16 years old	TD booster
Annually	Influenza vaccine

*See *MMWR* 1993;42:RR-13, (combination of DPT and HbcV) can be used to replace these vaccines.
†See *Pediatrics* 1994;94:774-5; AAP Committee on infectious disease regarding polio vaccine at 6 months.
DTaP = diphtheria tetanus acellular pertussis vaccine.
DTP = diphtheria tetanus pertussis vaccine.
HbcV = *Haemophilus influenzae* type b conjugate vaccine.
OPV = oral polio virus vaccine.
TD = tetanus diphtheria toxoids vaccine.

those with sickle cell disease. Prophylactic antibiotics prevent bacteremia and tissue invasion, despite continued nasopharyngeal carriage or reexposure. When failure occurs, it may be due to a variety of microbiologic causes as well as a lack of patient compliance. As discussed below, the emergence of penicillin- and cephalosporin-resistant *S. pneumoniae* is a serious evolving problem in many communities and may ultimately undermine the effectiveness of the established prophylactic regimen. Clinicians should be aware that recommendations concerning the use of prophylactic penicillin and the choice of empiric antibiotics in patients with sickle cell disease may well undergo tremendous change during the next few years. At present, the most effective approach is a combination of traditional pneumococcal vaccination and regular penicillin prophylaxis; it is hoped that newer conjugated pneumococcal vaccines will prove protective in infancy.

MANAGEMENT

Pediatric Infection

Fever in a child younger than age 5 years with SS disease often indicates life-threatening bacterial infection. It is estimated that there is a 400-fold increased risk of pneu-

mococcal septicemia/meningitis in this population. Fortunately, *H. influenzae* infections have become exceedingly rare with the advent of the *H. influenzae* vaccine.

Children with sickle cell disease and septicemia generally have fever greater than 102 °F (38.9 °C), but temperatures below 102 °F may also be seen, especially early in the clinical course. In febrile children with sickle cell disease, administration of antibiotics should occur promptly, even for minimal clinical indications such as significant fever, chills, etc. The patient should be evaluated for causes of fever such as otitis media, pneumonia, or urinary tract infection. Chest x-ray, blood, urine, and throat cultures should be obtained without waiting for test results. Lumbar puncture should be performed even if there are only minimal indications of meningitis. An antibiotic effective against *S. pneumoniae* and *H. influenzae* should be promptly administered, preferably intravenously. Because penicillin- and cephalosporin-resistant *S. pneumoniae* are now identified in many regions of the country, antibiotics such as vancomycin have been added to the typical empiric therapy regimen in those areas. It is critical to be aware of the susceptibility patterns of the local flora when selecting empiric therapy. The choice of subsequent antibiotics can be guided by results of cultures and clinical course.

Practice varies widely on indications for admitting febrile SS children to the hospital. There is, however, consensus that *all* SS children with any of the following be admitted for inpatient treatment:

- Temperature greater than 40 °C (> 104 °F).
- Seriously ill appearance.
- Hypotension.
- Poor perfusion, dehydration.
- Pulmonary infiltrate.
- Corrected white blood count greater than 30,000 or less than 5,000/mm^3.
- Platelet count less than 100,000/mm^3.
- Hemoglobin less than 5 g/dL.
- History of *S. pneumoniae* sepsis.

Several centers with expertise in treating large numbers of patients with sickle cell disease in an ambulatory setting have successfully used long-acting parenteral cephalosporins (e.g., ceftriaxone sodium) to treat febrile children as outpatients. This approach is appropriate only when the following conditions apply:

- The patient is clinically at low risk for sepsis (i.e., none of the above factors is present).
- The patient, family, and clinic are capable of impeccable followup, and the patient has immediate emergency access to the hospital.
- The endemic flora have been *demonstrated* to be sensitive to cephalosporins.
- A successful followup program has been established.

If septicemia is confirmed by a positive blood culture, the child should be hospitalized, and therapy should be continued for a minimum of 5 to 7 days. Bacterial meningitis should be treated for 10 days or at least 7 days after cerebrospinal fluid sterilization has occurred. On the other hand, if blood, urine, and throat cultures are negative after 3 days and the patient is well, antibiotic therapy can be discontinued and

the diagnosis presumed to be a viral illness. If fever persists and cultures are negative, the patient should be reevaluated.

Infections in Older Children and Adults

Because pneumococcal infections become less frequent after the first decade of life and infections due to other pathogens found in the general population become more common, a systematic bacteriologic evaluation should be used before administering antibiotics. A persistent fever higher than 101 °F should not be assumed to be due to vaso-occlusive crisis. Infections tend to occur in already damaged areas such as lungs, kidneys, and bones.

Urinary Tract Infections

Pyelonephritis in patients with SS disease is difficult to treat, recurs regularly, and is often associated with septicemia. This is particularly serious during pregnancy. Urine cultures are essential before therapy and should be repeated 1 to 2 weeks after cessation of therapy. Treatment consists of antibiotics and hydration. Urologic evaluation and chronic suppressive antibiotic therapy may be appropriate for patients with repetitive infection.

Osteomyelitis

Osteomyelitis must be differentiated from the more common (~50:1) diaphyseal bone infarction because the two conditions present with similar clinical and imaging findings but are treated differently. Similarly, septic arthritis must be distinguished from the more common joint effusion associated with acute painful episodes. It is essential to establish a bacterial diagnosis (from blood or aspirated joint or subperiosteal fluid) before long-term antibiotics are started to treat osteomyelitis or septic arthritis. Blood cultures may be particularly helpful in the setting where infarcted bone is seeded during an episode of bacteremia.

Increasing antibiotic resistance among *Salmonella* isolates is a major problem. Even if in vitro susceptibility tests suggest efficacy for tetracyclines, cephalosporins, and aminoglycosides, these antibiotics often fail. Ampicillin, quinolines, and trimethoprim-sulfamethoxazole have been demonstrated to be effective (when indicated by in vitro sensitivity tests). Chloramphenicol can also be effective, but its potential for bone marrow suppression requires frequent monitoring of the reticulocyte count. The tendency of *Salmonella* to establish chronic, intracellular infection requires prolonged treatment—typically 1 month of intravenous antibiotic therapy, followed by months of oral treatment. Public health procedures should be implemented to prevent spread of infection to family members.

Bacteriologically proven staphylococcal osteomyelitis requires high-dose penicillinase-resistant penicillin (e.g., nafcillin) for several weeks. If adequate blood levels of the antibiotic can be achieved, a regimen such as 2 weeks of intravenous therapy followed by 4 to 6 weeks of oral therapy can be given. The necessity for surgical incision and drainage or débridement in osteomyelitis of any cause should be based on clinical judgment.

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Chapter 7
Painful Events

Painful crises in sickle cell disease are believed to be caused by ischemic tissue injury resulting from the obstruction of blood flow produced by sickled erythrocytes. The reduced blood flow causes regional hypoxia and acidosis, which further increases the sickling process and may increase the ischemic injury. Painful crises vary in intensity and duration, usually lasting 4 to 6 days but sometimes persisting for weeks. They may vary in intensity from time to time during the course of a single episode. Hypoxia, infection, fever, acidosis, dehydration, menstruation, sleep apnea, obstructive snoring, and exposure to cold may precipitate such events. In addition, patients often cite anxiety, depression, and physical exhaustion as precipitators. In many instances, no precipitating event can be identified.

The frequency and severity of repeated painful crises vary widely among patients. A few patients state that they are always "in pain" and repeatedly request hospitalization. Conversely, approximately one-third of patients rarely seek hospital-based treatment. Many patients can manage painful events at home.

In general, painful crises are a measure of disease severity and have been reported to correlate with early death in adult patients, but we are unable to predict which individuals will be so adversely affected. High hemoglobin levels, low fetal hemoglobin, and a baseline white blood cell (WBC) count of 15,000 are factors that place individuals at greatest risk. A painful crises is one of the most common settings in which death occurs in adult patients. Acute chest syndrome, central nervous system events, bone marrow embolism, and acute multiorgan failure syndrome may suddenly occur during a severe painful crises. In a patient in pain, overtreatment with narcotic drugs or intravenous fluids and other iatrogenic events increase the morbidity of therapy. Pain management requires ongoing assessment of the patient for sites of pain, degree of pain, and effects of pain and pain relief on at least a daily basis.

Pain should be treated as early as possible because undertreatment or persistent pain can debilitate the patient both physically and psychologically. Some of the recognized physical sequelae of unrelieved pain such as stress and dehydration are also precipitating events for acute painful episodes and may account for the not uncommon finding of a patient who initially presents with focal pain but develops diffuse pain within hours of the onset of the crises.

ASSESSMENT OF PATIENTS

There is no clinical or laboratory finding that is pathognomonic of painful episodes in sickle cell disease. The diagnosis of a painful episode is often made solely on the

basis of the medical history and physical examination. The possibility that pain is precipitated by a concurrent medical condition such as infection should be considered, and the physician should search for a precipitating illness in every instance.

Bones are the most common site of pain. Dactylitis, or the hand-foot syndrome (acute, painful swelling of the hands and feet), is the first manifestation of sickle cell disease in many infants. Irritability and refusal to walk are other common symptoms. After infancy, musculoskeletal pain can be symmetrical, asymmetrical, or migratory, and it may or may not be associated with swelling, low-grade fever, redness, or warmth. In both children and adults, sickle vaso-occlusive episodes are difficult to distinguish from osteomyelitis, septic arthritis, synovitis, rheumatic fever, or even gout.

When abdominal or visceral pain is present, care should be taken to exclude sequestration syndromes (spleen, liver) or the possibility of an acute condition such as appendicitis, pancreatitis, cholecystitis, urinary tract infection, pelvic inflammatory disease, or malignancy. Pneumonia ("chest syndrome," see Chapter 8) develops during the course of 20 percent of painful events and can present as abdominal pain. In adults, chest pain may be due to vaso-occlusion in ribs and often precedes a pulmonary event. The lower back is also a site for painful crises in adults.

Patients should be seen by a physician immediately if any of the following high-risk factors exist:

- Fever greater than 101 °F, lethargy, dehydration, or pallor.
- Severe abdominal pain.
- Acute pulmonary symptoms.
- Neurologic symptoms or pain associated with extremity weakness or loss of function.
- Acute joint swelling.
- Recurrent vomiting.
- Pain not relieved by conservative measures.
- Priapism.

LABORATORY TESTS

- Painful events are not commonly associated with changes in the patient's usual hemoglobin level. Concurrent reticulocytopenia is occasionally present. The WBC may be similar to the patient's baseline value; a higher value with an elevated band count suggests that infection is present.
- If a fever greater than 101 °F is present, an aggressive evaluation should be done to find the source (see Chapter 6, Infection).
- If pulmonary symptoms are present, a chest x-ray should be obtained, and measurement of arterial blood gases should be considered (see Chapter 8, Lung).
- If osteomyelitis or septic arthritis is suspected, direct aspiration of the bone or joint and cultures of the aspirates should be obtained. Radiographs and radioisotope or MRI scans may help separate infarction from infection, but they are not always reliable.
- Serum electrolytes and blood pH levels should be obtained for severely ill patients. There is a relatively high incidence of electrolyte disorders in patients

with sickle cell disease, and a decreased weight may be an important sign of dehydration.

GENERAL PRINCIPLES OF THERAPY

In general, the management of acute painful episodes has five essential elements, including health care provider-patient relationships, identification and treatment of any precipitating or associated events, pain assessment, hydration, and analgesics.

Health Care Provider-Patient Relationships

Patients with sickle cell disease have repeated episodes of sudden unexpected pain that often result in fear of a life-threatening event or fear of how they will be treated by health care providers. The health care provider should work to alleviate that fear by providing consistent empathetic treatment. Ideally, continuity of care should be provided. If the patient must be seen by someone unfamiliar with his or her clinical course and previous painful episodes, the new physician should discuss the patient's care with a health care provider who is familiar with the patient. Because this may not always be possible, a consistent approach to pain discussed in advance with the family and outlined in the patient's record is essential. Making a card available to the family and health care providers that describes the patient's steady-state laboratory test results (Hb, reticulocyte count, alloantibodies, bilirubin), clinical problems, and pain medication treatment can decrease certain problems and foster patient trust. In addition, health care facilities should develop a general protocol for the management of pain in sickle cell disease so that patients can be treated in the absence of individualized data.

Identification and Treatment of Any Precipitating or Associated Events

The patient must be thoroughly evaluated with an accurate history, physical examination, and assessment at each presentation for a painful crisis to be certain that no other illness requiring specific treatment is present. It is essential that a painful episode be considered a manifestation of an underlying illness other than sickle cell disease until proved otherwise. These underlying illnesses are often infections or inflammatory conditions that require additional testing.

Pain Assessment

A comprehensive approach to pain assessment requires an evaluation of the patient's perception of pain, physiological responses, and behavioral responses. However, the mainstay of pain assessment must be patient self-reporting. Neither behavior nor physiological responses replace the patient's self-report. Patients in severe pain may use smiling, laughter, and singing as coping mechanisms, and such actions should not be misunderstood. The goal of therapy is pain relief, and when it is achieved, the patient may temporarily exhibit normal behavior (walking about, visiting). Such behavior does not necessarily indicate that the episode is completely resolved.

Each patient should be evaluated by a measurement tool that includes pain intensity and distress scales and an anatomic pain distribution assessment chart. The course of the painful episode should be

accurately assessed using these tools at regular intervals (every 3 to 4 hours), particularly before changes in medication are made. Because patients often manage pain at home and do not report pain to their physician, home pain diaries are helpful in understanding and managing such pain.

Hydration

Dehydration, which causes red cell dehydration and promotes sickling, frequently occurs in patients with sickle cell disease because of reduced fluid intake, increased insensible water loss, and a high incidence of hyposthenuria. Because of hyposthenuria, measurement of urine-specific gravity cannot be relied on to reflect the patient's hydration status. For mild pain, liberal oral hydration is sufficient. For patients with more severe pain, oral hydration should always be attempted if there are sufficient personnel to evaluate and encourage fluid intake. Intravenous hydration is recommended in all other situations. The basic objectives of fluid therapy include correction of fluid and electrolyte deficits, maintenance of normal serum electrolyte concentrations, and administration of fluid volumes (IV + P.O.) to equal 1-1/2 times the daily requirement. The choice of initial parenteral fluid is dictated by the patient's hydration status and electrolyte values. For uncomplicated painful crises, 5 percent glucose in 0.25-0.5 percent normal saline is recommended as the initial fluid replacement. The amount for adult patients is approximately 3 L/day if cardiac status is normal, while that for children is based on the patient's weight.

Parenteral hydration should be monitored closely to avoid iatrogenic congestive heart failure or electrolyte imbalance. Because excessive renal sodium losses occur in some patients, serum electrolytes should be monitored at least every other day. In general, serum sodium concentrations between 130 and 135 mg/dL do not need correction. Elevated sodium concentrations should be avoided. Physical examinations, including daily weight and records of intake and output, are essential. The presence of cardiomegaly on physical examination or chest x-ray usually does not indicate cardiac failure, and brisk parenteral rehydration usually can be safely accomplished. Patients should be monitored closely, however, for tachycardia, tachypnea, rales, gallop rhythm, hepatomegaly, or excessive weight gain.

Analgesics

The goal of analgesic therapy is to provide prompt pain relief. Often, this is not achieved because of inadequate understanding of the clinical pharmacology of analgesics, excessive concern about narcotic addiction, or well-meaning but misguided use of placebos. There is no role for the use of placebos in the evaluation or treatment of the pain of sickle cell disease. The choice of therapy is based on potency, mode of action, and side effects of analgesics (see Table 3). Medication should be administered on a fixed-time schedule, with a dosing interval that does not extend beyond the duration of the desired pharmacological effect. Meperidine is contraindicated in patients with renal dysfunction or central nervous system disease, because its metabolite *normeperidine* (which is excreted by the kidney) can cause seizures.

Patient-controlled programs for severe pain, either dose titration methods or patient-

controlled analgesia (PCA) devices, are the preferred treatment methods. This approach maintains pain control, decreases anxiety, and addresses individual pain relief needs within an acceptable level of adverse effects.

Dose titration without PCAs may be done using a number of techniques. **It is essential in any titration program that frequent, accurate, and timely assessment of the patient's condition by a physician and nurse be done. If this is not possible in the institution, consideration should be given to transferring the patient to an institution that can provide them.** In all cases, a written plan must be developed and implemented at the beginning of therapy; the results of the assessment must be recorded, preferably on a flowsheet. Use the simplest dosing schedule and least invasive pain relief method first. The following are three regimens that can be used. In each titration method, the first (loading) dose is based on prior analgesic history and the patient's condition, including intensity and sites of pain:

(1) After the loading dose, reassess the patient at 30-minute intervals and, based on the assessment, treat with one-quarter to one-half of the loading dose until the patient experiences relief. **This method requires very close observation of the patient and should not be used if this cannot be provided.**

(2) Dose and dosing intervals are prescribed based on the patient's prior history. "Rescue" dosing (for breakthrough pain) is given at one-quarter to one-half the loading dose for recurrent pain between regular doses (e.g., 8 mg of morphine every 3 hours, with 2-4 mg for pain occurring in the interval). Readjust fixed dosing if the patient requires more than three rescue doses in 12 hours.

(3) After the loading dose, increase or decrease the next fixed dose by one-quarter to one-half, depending on the patient's response.

A PCA program usually includes an initial loading dose when a narcotic has not been given recently. The PCA pump delivers intravenous boluses of narcotic on patient demand at a preprogrammed dose and interval. In addition, a lockout may be programmed to prevent further dosing once a maximum dose in a 4-hour period has been reached. Because the patient adjusts his/her own dose, treatment is "titrated to effect." A continuous infusion setting is available and is often used for low-dose infusions, particularly at night. A typical starting PCA program with morphine sulfate could be as outlined below:

1. Loading dose (if needed) 0.05 mg morphine/kg.
2. 1-hour dose limit 0.06-0.1 mg/kg/hr (divided into 4-8 doses).
3. 4-hour lockout limit: 0.2-0.3 mg/kg.
4. A continuous night (10:00 pm-7:00 am) IV infusion rate of 0.02 mg/kg/hr is added without changing the 4-hour lockout limit. Other schemas such as using a formula based on the previous 24 hours of care or treatment can be found in the literature.
5. Standard orders should include:
   a. No other narcotics given.
   b. Close proximity to nursing station.

c. Patient training in PCA.

d. Observations (which must be charted):

- respiratory rate q 1 hr
- blood pressure, heart rate q 2 hr
- pain and sedation scores q 2 hr
- incentive spirometry q 1-2 hr when awake.

Records of the amount of analgesic actually administered and its clinical effect must be carefully preserved, to help in managing future painful crises.

The effect of the route of administration on drug absorption must always be considered. The oral route is generally at least one-half (range one-half to one-sixth) as effective as the parenteral route, depending upon the drug (see equi-analgesic table). Oral administration, however, avoids many of the complications of parenteral therapy. When potent narcotics are used, the physician should remember that side effects include respiratory depression, nausea, vomiting, pruritus, hypotension, constipation, increased secretion of antidiuretic hormone, and changes in the seizure threshold. Synthetic narcotics such as pentazocine, butorphanol, and nalbuphine should be used with caution and should not be used in conjunction with other narcotics because they are agonist-antagonists and may induce withdrawal symptoms or psychotomimetic effects.

Nonnarcotic analgesics are used to treat mild-to-moderate pain. In patients with severe pain, adding these analgesics to narcotic therapy increases analgesia and has a significant narcotic-sparing effect. Therefore, concurrent use of both is recommended. In particular, nonsteroidal anti-inflammatory drugs (NSAIDs) are a helpful adjunct in severe pain in patients who can tolerate their gastrointestinal side effects because while they decrease inflammation at the tissue site, they do not cause sedation, respiratory depression, or bowel or bladder dysfunction. They should not be used in children or for more than 5 days because of the risk of gastrointestinal bleeding and renal disease. Ketorolac tromethamine, an NSAID, is available for parenteral use; preliminary results suggest that it is helpful as an adjunct or primary agent in moderate-to-severe pain. Oral NSAIDs may be useful in patients with chronic pain or arthritis. Care must be taken in patients with compromised renal function because these drugs may cause additional kidney damage. Aspirin, which can cause hyperuricemia, should be avoided in patients with gout. Acetaminophen is the analgesic of choice if the patient is unable to tolerate NSAIDs or aspirin. However, acetaminophen should be used with caution in patients with liver disease because it can cause severe hepatic damage in high doses. Like its parent compound, phenacetin, chronic use can cause renal damage—always a problem in adults with SS disease.

PAIN MANAGEMENT

Prevention

Because all painful episodes cannot be prevented, patients should know how to manage mild pain and should be taught to recognize symptoms suggestive of serious problems. Optimal management of patients with painful events requires adequate education of the patient, family, and health care providers. Conditions that expose the patient to hypoxia, dehydration, and

extreme cold should be avoided. Mountain climbing, flying in unpressurized aircraft, and swimming in frigid water are potentially hazardous. If air travel is necessary, patients should be advised to travel in pressurized aircraft, refrain from alcohol consumption, maintain an increased fluid intake, move about the plane periodically, and stay warm. Fluid intake (juices, soft drinks, and bouillon) should be increased during fevers, high ambient temperatures, and increased physical activity.

Home-Based Management

The majority of painful events can be managed successfully at home, thus fostering patient self-esteem and independence. The success of a home-based program depends on patient education, including not only an explanation of the pathophysiology ("What happened?") but also the expectations and limitations of such treatment ("When should I go to the hospital?"). In addition, the patient should be taught to recognize the more serious complications of sickle cell disease to avoid delay in treatment.

Complete home management programs include specific guidelines for oral fluid intake and effective analgesics. Oral intake, often described in terms of ounces of fluid per day, should be at least 150 cc/kg/day for children and 3 to 4 L/day for adults. Soft drinks, juices, and bouillon are recommended. Fluids devoid of electrolytes should not be the sole source of oral hydration because they can produce an electrolyte imbalance.

NSAIDs, acetaminophen, or aspirin are recommended for mild pain, with the precautions noted above. Codeine is the preferred oral narcotic for more severe pain and should be given with nonnarcotics. More potent oral narcotics such as morphine, hydromorphone, or oxycodone are rarely indicated. Individual patients respond differently to specific analgesics, and open communication between physician and patient is needed. Nausea does not represent allergy to oral narcotics. Patients truly allergic to codeine may be able to use oxycodone. Whenever narcotic agents are given by repeated prescription, it must be established with the patient that such drugs will be obtained from one physician so that the use of the drug may be accurately monitored.

A few patients request excessive amounts of narcotics. Careful records of the number of tablets dispensed should be kept, and records should be reviewed before prescriptions are refilled. The number of tablets to be dispensed should be written in words (e.g., "ten," not "10"), and it is preferable to prescribe doses for a limited period of time (i.e., a week, not a month).

Emergency Department Management

The goals of emergency department management are to assess the clinical problem, treat the pain aggressively in a supportive environment, and make an appropriate diagnosis. High-risk patients should be admitted directly to the hospital. The guidelines for emergency department management are as follows:

- Give appropriate analgesics in a titration regimen to relieve pain and establish a useful regimen. Suggested doses and intervals of administration are based on the severity of the pain (see Table 3).
- Administer IV fluids if necessary (see "Hydration" above); closely monitor fluid intake. The choice of fluids should be

Table 3

Recommended Dose and Interval of Analgesics Necessary To Obtain Adequate Pain Control in Sickle Cell Disease

	DOSE/RATE	COMMENTS
Severe/Moderate Pain		
1. Morphine	**Parenteral:** 0.1-0.15 mg/kg/dose every 3-4 hours. Recommended maximum single dose 10 mg. **P.O.:** 0.3-0.6 mg/kg/dose every 4 hours.	Drug of choice for pain, lower doses in the elderly and infants and in patients with liver failure or impaired ventilation.
2. Meperidine (Demerol®)	**Parenteral:** 0.75-1.5 mg/kg/dose every 2-4 hours. Recommended maximum dose 100 mg. **P.O.:** 1.5 mg/kg/dose every 4 hours.	Increased incidence of seizures. Avoid in patients with renal or neurologic disease or who receive monoamine oxidase inhibitors.
3. Hydromorphone	**Parenteral:** 0.01-0.02 mg/kg/dose every 3-4 hours.	
4. Oxycodone	**P.O.:** 0.04-0.06 mg/kg/dose every 4 hours. **P.O.:** 0.15 mg/kg/dose every 4 hours.	
5. Ketorolac	**Intramuscular:** Adults: 30 or 60 mg initial dose, followed by 15 to 30 mg every 6-8 hours. Children: 1 mg/kg load, followed by 0.5 mg/kg every 6 hours.	Equal efficacy to 6 mg MS, helps narcotic-sparing effect, not to exceed 5 days. Maximum 150 mg first day, 120 mg maximum subsequent days. May cause GI irritation.
6. Butorphanal	**Parenteral:** Adults: 2 mg every 3-4 hours.	Agonist-antagonist. Can precipitate withdrawal if given to patients who are being treated with agonists.
Mild Pain		
1. Codeine	**P.O.:** 0.5-1 mg/kg/dose every 4 hours. Maximum dose 60 mg.	Mild-to-moderate pain not relieved by aspirin or acetaminophen; can cause nausea and vomiting.
2. Aspirin	**P.O.:** Adults: 0.3-0.6 mg/dose every 4-6 hours. Children: 10 mg/kg/dose every 4 hours.	Often given with a narcotic to enhance analgesia. Can cause gastric irritation. Avoid in febrile children.
3. Acetaminophen	**P.O.:** Adults: 0.3-0.6 gm every 4 hours. Children: 10 mg/kg/dose.	Often given with a narcotic to enhance analgesia.
4. Ibuprofen	**P.O.:** Adults: 300-400 mg/dose every 4 hours. Children: 5-10 mg/kg/dose every 6-8 hours.	Can cause gastric irritation.
5. Naproxen	**P.O.:** Adults: 500 mg/dose initially, then 250 every 8-12 hours. Children: 10 mg/kg/day (5 mg/kg every 12 hours).	Long duration of action. Can cause gastric irritation.
6. Indomethacin	**P.O.:** Adults: 25 mg/dose every 8 hours. Children: 1-3 mg/kg/day given 3-4 times.	Contraindicated in psychiatric, neurologic, renal diseases. High incidence of gastric irritation. Useful in gout.

designed to maintain adequate electrolyte balance.

- If the pain is relieved for 3 to 4 hours, administer an oral narcotic and observe for 1 hour. If moderate or severe pain returns, repeat the parenteral narcotic dose and observe. When pain is under control, give an adequate dose of an effective oral narcotic analgesic, if feasible, using equi-analgesic dosing guidelines. If relief is maintained, discharge the patient with a small prescription and follow up within 1 week. If significant pain persists, admit the patient to the hospital. A final dose of parenteral narcotics "for the road" is not recommended.
- Most hospitals have guidelines for the duration of a patient's stay in the emergency department. These may be difficult rules to follow in the case of patients with painful crises. Holding areas for sickle cell disease are recommended to avoid unnecessary hospitalizations. Each patient's management plan should be individually designed.

Patients who require continuing treatment with parenteral narcotics or who cannot take adequate amounts of fluid orally require hospital admission.

INPATIENT MANAGEMENT

A management plan should be developed by the responsible physician, written in the hospital record, and discussed with the patient and other personnel involved in the patient's management. It is important to record this information on a regular basis in the hospital record and to help the patient develop coping skills. A pain measurement and description tool that evaluates pain intensity, mood, distress, and anatomic distribution should be used along with a sedation (level of consciousness) scale.

Fluid intake and urinary output should be monitored carefully, and patients should be weighed daily. Due to the high risk of acute chest syndrome, incentive spirometry and pulse oximetry may be useful. The proper composition of the fluids should maintain adequate electrolyte balance.

Standard pain management with parenteral narcotics should be given by a patient-controlled technique. If a titration technique has not been instituted in the emergency department, it should be initiated when the patient is admitted to the floor and pain is not controlled. If PCAs are not used, narcotics should be given on a fixed schedule (not as needed for pain), with rescue dosing for breakthrough pain as needed. Except when contraindications exist, concomitant use of NSAIDs should be standard treatment. Nurses should be instructed not to give narcotics if the patient is heavily sedated or respirations are depressed. When the patient shows signs of improvement, narcotic drugs should be tapered gradually to prevent a withdrawal syndrome. It is usually advisable to observe the patient on oral pain-relief medications for 12 to 24 hours before discharge from the hospital.

There are several new methods for administering narcotics such as transdermal and epidural administration of morphine. New methods of narcotic administration may be attempted in institutions where there is expertise in their use, where adequate monitoring is available, and appropriate use of standard techniques has not resulted in acceptable pain control.

ALTERNATIVE PAIN MANAGEMENT TECHNIQUES

Behavior modification programs, relaxation therapy, self-hypnosis, and transcutaneous electrical nerve stimulation may be helpful adjuvant therapies for pain management. Simple techniques such as relaxation and distraction are also helpful and can include music, audiotapes, and jaw relaxation exercises. Physical treatment such as massage and heat/cold therapy may be useful. These techniques may supplement but do not replace standard treatments. The success of these approaches may be determined by the patient's commitment, compliance, and trust in the health care provider.

ANXIETY AND SEDATIVE MEDICATION

Diazepam and chlorpromazine do not potentiate the analgesic effect of narcotics, and their use should be avoided. Hydroxyzine may potentiate the analgesic or sedative effect of narcotics and may help selected patients.

OTHER MEASURES

Oxygen Therapy

Oxygen (O_2) therapy does not benefit vaso-occlusive episodes unless hypoxemia is present. In the absence of hypoxemia, prolonged O_2 therapy may induce erythroid hypoplasia.

Sodium Bicarbonate

Sodium bicarbonate therapy has not been shown to improve the clinical course of painful episodes. It should not be used unless acidosis exists.

Vasodilators

Vasodilators such as pentoxyphylline have no proven efficacy in the management of painful episodes.

MANAGEMENT OF CHRONIC PAIN

A few patients almost always complain of pain. It is important to distinguish between acute and chronic pain. Treatment of chronic pain as if it were acute is a dangerous practice that can severely compromise the care of the patient in pain. These individuals may have an underlying medical problem and should be extensively evaluated for a treatable condition such as occult infection or collapsed vertebrae. Regardless of the etiology of pain, chronic depression and anxiety are frequently present in these patients and result in the loss of coping skills. An adequate treatment plan should address these emotional factors and not just the somatic pain. Psychiatric and social problems should be addressed by counseling. In addition, patients should be taught alternative techniques of pain management and encouraged to participate in self-help groups and vocational rehabilitation training programs. Continued transfusion therapy for chronic pain can result in serious morbidity (e.g., iron overload) and should be avoided. Tricyclic antidepressants may be useful in chronic pain syndrome. These drugs have a direct analgesic effect that occurs more quickly and at lower doses than their antidepressant effect. They may also be useful in treating a neuropathic pain component that is refractory to other treatment modalities.

PHYSICAL DEPENDENCE AND ITS CONFUSION WITH DRUG ADDICTION

The fear of addiction is one of the greatest obstacles to adequate pain control in sickle cell disease, a fear that stems from inadequate knowledge of the clinical pharmacology of opioids. This lack of understanding promotes confusion between physical dependence and addiction. Addiction is a socio-psychological state that is characterized by abnormal behavior pattern of drug abuse, by the craving of a drug for other than pain relief, by becoming overwhelmingly involved in the procurement and use of the drug, and by the tendency to relapse after withdrawal. Drug tolerance is not addiction; it indicates that large doses of a narcotic are needed for an analgesic effect, often without expected adverse effects. Physical dependence is a physiologic response to the pharmacologic effects of opioids characterized by the development of withdrawal symptoms when an opioid is abruptly discontinued or if an opioid antagonist is administered. Drug addiction therefore should not be the primary concern of a physician treating patients with sickle cell disease for pain. The physician should focus on providing patients with adequate relief by understanding drug tolerance, physical dependence, and the clinical pharmacology of the drugs. This knowledge should translate into a practice that includes tapering to prevent withdrawal, thereby eliminating physical dependence after treatment for acute pain. Only occasionally does true drug addiction develop in patients with sickle cell disease. Psychological, social, and economic factors are major forces in the patient's addiction rather than the use of prescribed drugs. Addicted patients should be referred to an addiction center, particularly one equipped with comprehensive psychological and social support services. Methadone maintenance without these support services is usually ineffective and should be avoided. It should be remembered that drug-dependent patients can have painful episodes; management of such situations requires compassion, firmness, and most important, knowledge of opiate pharmacology.

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Chapter 8
Lung

ACUTE CHEST SYNDROME

Acute chest syndrome is the second most common cause of hospital admission in patients with sickle cell disease and, in some cases, represents a medical emergency. It is an acute illness characterized by new pulmonary infiltrates on the chest x-ray and varying degrees of chest pain, dyspnea, hypoxemia, fever, and prostration. Because x-ray changes may take several days to appear, the diagnosis is commonly recognized as it evolves and not immediately on presentation. The term "acute chest syndrome" is used because a more precise etiology is rarely documented. In adults, acute chest syndrome usually results from pulmonary infarction etiologies such as bacterial or viral infection, fat/bone marrow embolism, intrapulmonary sickling, and emboli of sickled red cells. In children, it is better to assume an infectious etiology. Appropriate cultures and serological tests should always be obtained. Recent bronchoscopy-bronchial lavage data suggest that pulmonary fat embolism occurs in as many as 44 percent of patients with acute chest syndrome. Although the illness is frequently self-limited, particularly when it involves a small area of pulmonary parenchyma, it can rapidly progress and may be fatal. Frequent chest syndrome episodes indicate severe sickle cell disease and predict early mortality in adults.

CLINICAL DIAGNOSIS

Acute chest syndrome can develop as an isolated event or during the course of a painful vaso-occlusive episode. Pleuritic chest pain is the dominant symptom in adults. Fever, cough, and tachypnea are often the only findings in infants and young children. Involvement of the diaphragmatic pleura can result in abdominal pain. True lung pathology must be differentiated from sternal or rib infarction or cholecystitis. Although the pain of acute chest syndrome can mimic angina or myocardial infarction, coronary artery disease is rare in children and young adult patients. Depending on the extent of the pulmonary involvement, physical examination usually shows tachypnea, and there may be signs of pulmonary consolidation, pleural effusion, or occasionally, a pleural friction rub. Alteration in mental status may reflect hypoxemia and/or narcotic effect, but it may also be seen in patients with systemic fat embolization. In severe cases in adults, the patient is often considered to have adult respiratory distress syndrome.

LABORATORY DIAGNOSIS

The chest radiograph of patients with acute chest syndrome shows infiltrates in one or more lobes (66 percent have single lobe involvement). Pleural effusion occurs in 15 percent of the cases. Radiographic studies

may be normal or nondiagnostic during the first 2 to 3 days, especially if the patient is dehydrated. Cultures of blood, sputum, or pleural fluid occasionally reveal a bacterial pathogen. Measurement of arterial blood gases rather than ear or pulse oximetry may be necessary for initial assessment of the severity of the illness and for subsequent clinical management. Initial samples should be taken while the patient is breathing room air. Because patients with sickle cell disease may have a low arterial oxygen pressure (p_AO_2) during the steady state, the interpretation of low oxygen tension can be difficult unless arterial gas measurements have been previously obtained. However, severe hypoxemia (p_AO_2 below 60 mmHg in an adult or below 70 mmHg in a child) indicates potentially life-threatening disease, particularly if it does not improve with oxygen administration. In patients receiving oxygen by face mask, the severity of the pulmonary process can be assessed by calculating the A-a O_2 gradient. If noninvasive oximetry is used to monitor trends, it is most helpful in conjunction with periodic arterial blood gas measurements.

Complete blood counts, including reticulocyte counts and leukocyte differential counts, should be obtained serially. An increased neutrophil count above baseline level and a shift to the left suggests a bacterial infection. A falling hematocrit, with or without reticulocytosis, is commonly seen as the syndrome evolves and may contribute to tissue hypoxia.

In children, *S. pneumoniae* is less common as a cause of this syndrome than it was before prophylactic penicillin and the pneumococcal vaccine were used. In most adult cases, no pathogen is isolated. Isolation of mycoplasma or viruses or a rise in antibody titers may help suggest the etiology. A viral etiology is more likely in winter, but mycoplasma are more common in the fall. If sputum or bronchial lavage specimens are obtained, they should be stained for fat. A positive result suggests fat embolism. Lung scans generally are not useful in diagnosing the etiology of acute chest syndrome or in making a therapeutic decision. Due to the hypertonicity of most contrast dyes, pulmonary angiography carries the theoretical risk of increased sickling; therefore, the procedure is rarely indicated.

CAUSES OF "CHEST SYNDROME"

1. Hemoglobin S related
   - a. Direct consequence
     - i. Pulmonary infarction - *in situ* sickling
       - aa. etiology unknown
       - bb. hypoventilation 2º to
         - (i) rib/sternal infarction
         - (ii) narcotic administration
         - (iii) postoperative atelectasis.
     - ii. Embolism infarction
       - aa. necrotic bone marrow/fat
       - bb. sickled cells from distal site (i.e., liver sinuoids).
     - iii. Pulmonary edema 2º to fluid overload.
   - b. Indirect consequence-infection
     - i. Bacterial
     - ii. Viral
     - iii. Fungal
     - iv. Protozoan

2. Unrelated to Hb S
    a. Thromboembolism (from thrombosed vein)
    b. Opportunistic infection related to HIV infection
    c. Bronchial obstruction 2º to foreign body or neoplasm
    d. Acute sarcoidosis
    e. Other: aspiration, trauma, etc.

Treatment

All patients with acute chest syndrome must be admitted to the hospital. Depending on the extent of lung involvement and respiratory distress, the intensive care unit may be required for appropriate monitoring of a rapidly changing clinical state. Analgesics should be administered; however, narcotic-induced hypoventilation must be avoided. A delicate balance must be found to provide pain relief and eliminate splinting without causing hypoventilation. Overhydration may be as dangerous as dehydration, and intravenous fluids must be cautiously administered. Oxygen therapy is indicated for hypoxemia, tachycardia, and tachypnea, and it should be monitored by frequent measurement of arterial blood gases. Patients may become profoundly hypoxic if they remove their oxygen masks for eating or bathing. Nasal prongs may be used in these instances, but the amount of oxygen actually inspired will be lower than with a face mask.

It is often impossible to make a reliable *a priori* differentiation between pulmonary infarction and bacterial pneumonia. In 2 to 5 percent of the cases, acute chest syndrome is associated with a positive blood culture; the most common isolates are *S. pneumoniae* and *H. influenzae*. Depending on the local susceptibility pattern of these organisms, and whether the patient was on prophylactic penicillin, an appropriate combination of penicillin, cephalosporin, or vancomycin should be used. Oral erythromycin should be added if *Mycoplasma pneumonia* is suspected. Adjustment of the antibiotic regimen will depend on the results of the bacterial cultures.

Exchange transfusions should be performed if the patient develops multiple lobe involvement, rapidly progressing disease, or signs of respiratory insufficiency (p_AO_2 below 60 mmHg in an adult or below 70 mmHg in a child while breathing oxygen) (see Chapter 10, Transfusion). Patients with chronic hypoxemia, as determined by baseline studies, should be considered for exchange transfusions when there is a drop greater than 25 percent from the steady-state p_AO_2. If progressive severe anemia develops in a patient with borderline abnormal pulmonary function, a simple transfusion of packed red blood cells may be required. Unless thromboembolism is proved, anticoagulant therapy is not recommended.

SYSTEMIC FAT EMBOLIZATION SYNDROME

Systemic fat embolization syndrome is a rare, but often fatal, complication that is due to widespread embolization of liquified necrotic bone marrow fat into the pulmonary vessels and then to the systemic circulation (see Stroke, Chapter 9). Patients with sickle cell disease can develop the syndrome during a severe vaso-occlusive episode. Symptoms include bone pain, fever, chest pain, dyspnea, confusion, agitation, and coma, with or without acute renal

failure. In some cases, disseminated intravascular coagulation with severe microangiopathic hemolytic anemia and multiorgan failure can occur.

A high index of suspicion is essential for early diagnosis. Pulmonary fat embolization can be detected by the finding of intracellular lipid in secretions obtained by bronchial lavage. Demonstration of necrosis on marrow aspirates, presence of refractile bodies on fundoscopic examination, head and neck petechiae, and fat globules in the urine can be helpful in establishing the diagnosis. If the diagnosis is suspected, early institution of exchange transfusions accompanied by supportive treatment may be lifesaving.

ASTHMA

Asthma and chronic asthmatic bronchitis pose a potential therapeutic problem in sickle cell disease patients. Epinephrine use is associated with increasing heart rate and can compromise cardiac stroke output. The diuretic action of some bronchodilators may dehydrate the patient, but these agents are usually required. Hydration is essential, and intravenous fluids should be administered early during an asthma attack that does not quickly resolve. Long-term management is not different from that for individuals without sickle cell disease.

CHRONIC RESTRICTIVE LUNG DISEASE

Chronic restrictive lung disease, with pulmonary hypertension and cor pulmonale in late stages, is a consequence of previous vaso-occlusive episodes and has a poor prognosis. Diagnosis before the clinical onset of cor pulmonale is based on abnormal pulmonary function tests, chest radiograph demonstrating increased parenchymal markings or fibrosis, and chronic hypoxia. Repeated episodes of midline, severe, crushing chest pain signal myocardial ischemia (without coronary artery disease). With recurrent episodes of acute chest syndrome, the patient develops pulmonary hypertension and heart failure. A chronic transfusion program may reduce the frequency of recurrent attacks of chest syndrome, and nocturnal oxygen therapy may be helpful in selected patients.

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Chapter 9
Stroke

Clinically evident stroke is a devastating complication of SS disease that affects from 6 to 12 percent of patients. Strokes are very rare in persons with Hb SC disease. In children under age 10 years, the most common cause of stroke is cerebral infarction. Ischemic stroke typically presents with signs and symptoms of hemiparesis or monoparesis, hemianesthesia, visual field deficits, aphasia, cranial nerve palsies, or acute change in behavior. Although recovery occasionally is complete, intellectual, motor, and sensory impairments are typical sequelae. Intracranial hemorrhage becomes increasingly more common with advancing age. In hemorrhagic stroke, more generalized phenomena such as coma, headache, and seizures occur. Recurrent stroke causes progressively greater impairment and increased likelihood of mortality. A "completed stroke" signifies a fixed neurologic deficit, whereas "stroke in progression" implies worsening of the neurologic deficit or appearance of new focal abnormalities while the patient is under observation. Nonfocal complaints such as dizziness, headache, or fainting are not in themselves representative of cerebral vascular disease but should be investigated carefully.

A transient ischemic attack (TIA) is a focal neurologic deficit persisting for less than 48 hours (24 hours for internal carotid, anterior, or middle cerebral arteries and 48 hours for vertebral or basilar arteries) that follows a vascular distribution. Typically, there is no clinically apparent residual deficit from a TIA, though newer imaging modalities such as MRI and positron emission tomography (PET) have identified ischemic brain lesions in both the gray and white matter in some patients. TIA often is a harbinger of subsequent stroke.

PATHOPHYSIOLOGY

Infarction usually occurs in a segmental pattern that suggests damage to the large cerebral arteries. The most common abnormalities found on arteriography or magnetic resonance angiography (MRA) are marked narrowing or complete occlusion of the anterior cerebral arteries (ACA) and/or middle cerebral arteries (MCA). Multiple, bilateral vessel involvement is usual, even in patients who have unilateral neurologic signs. Vessel narrowing is the consequence of intimal and medial proliferation that is thought to be caused by endothelial damage from sickled red blood cells. The damaged, irregular endothelium can serve as a nidus for the adhesion of platelets and sickle cells, thereby resulting in thrombus formation. The stroke event occurs when narrowing is severe enough to compromise distal flow or the thrombus dislodges and causes distal embolization. Transient neurologic symptoms can result from vessel spasm.

Intracranial hemorrhage can be intracerebral or subarachnoid and can result from rupture of an aneurysm of the circle of Willis. Intracerebral hemorrhage may also occur years later in patients who had prior cerebral infarction as a result of a rupture of fragile collateral vessels (moyamoya).

DIAGNOSIS

A high-resolution, computerized tomographic (CT) scan performed as an emergency diagnostic procedure without contrast may be normal at the onset in cerebral infarction but is helpful in ruling out bleeding, abscess, tumor, or other abnormalities. The CT scan 2 to 7 days later typically is able to demonstrate the area of infarction. MRI is a sensitive technique for detecting intracranial hemorrhage or infarction. MRA permits visualization of major intracerebral vessels without the potential hazards of hypertonic contrast materials. However, MRI/MRA scanning requires more time at the imaging center than CT scanning, and high-resolution equipment (1.5 tesla or more) is required. Lumbar puncture, which should be done only if a CT scan or MRI reveals no evidence of increased intracranial pressure, is occasionally necessary to eliminate infection or subarachnoid hemorrhage as the cause of the stroke.

Arteriography is not necessary to confirm cerebral infarction demonstrated by CT scan, MRI, or MRA, but it can be helpful in clarifying the diagnosis in the rare symptomatic (hemiparesis) patient with normal CT or MRI scans. Use of hyperosmolar contrast material makes arteriography potentially hazardous in patients with sickle cell disease. Adequate hydration, reduction of the Hb S level to less than 30 percent by transfusion, and close supervision decrease the risk. In emergency situations, partial or total exchange transfusion can be used to lower the level of Hb S rapidly (see Chapter 10, Transfusion). It is uncertain whether CT scanning with intravenous infusion of the new contrast agents with reduced osmolarity is less hazardous in untransfused patients.

CT scan or MRI/MRA should be performed on patients who experience a TIA. Patients with persistent or severe headaches, syncopal episodes, or seizures deserve thorough evaluations, often by a neurologist, and may need neurologic imaging. Transcranial Doppler studies or ultrasonography of the large cerebral vessels may reliably predict the patient who is at risk for stroke when narrowing of the MCA or ACA is identified. The prognostic value of newer techniques such as PET or metabolic MRI are under intensive investigation. Data suggest that abnormalities on metabolic MRI scans or PET scans in SS patients, who do not have overt neurologic deficits, may be useful in identifying patients at risk for progression of the cerebral vasculopathy and future strokes. A schema for evaluating neurological events is displayed in figures 1 and 2.

TREATMENT OF ACUTE VASO-OCCLUSIVE STROKE

For the patient with acute occlusive stroke, rapid evaluation and careful monitoring are essential. Patients should be admitted to an intensive care unit. Raised intracranial pressure should be treated promptly with pharmacological agents. Assisted ventilation may be necessary. Hyperventilation therapy, however, should be avoided. The involvement of a neurologist and/or neurosurgeon is essential. Seizures are common during acute infarction and hemorrhage and require anticonvulsant therapy.

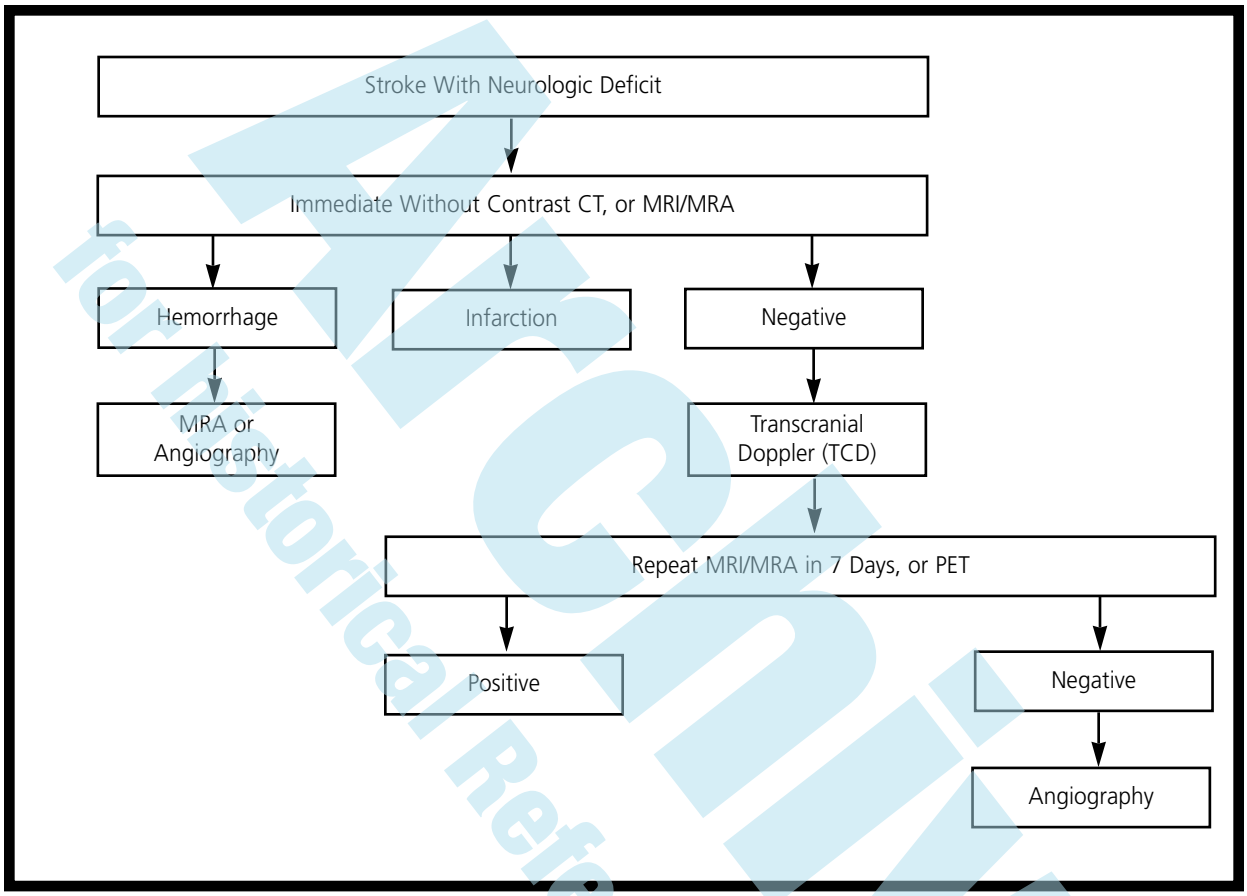

Figure 1

Algorithm for evaluating clinical stroke.

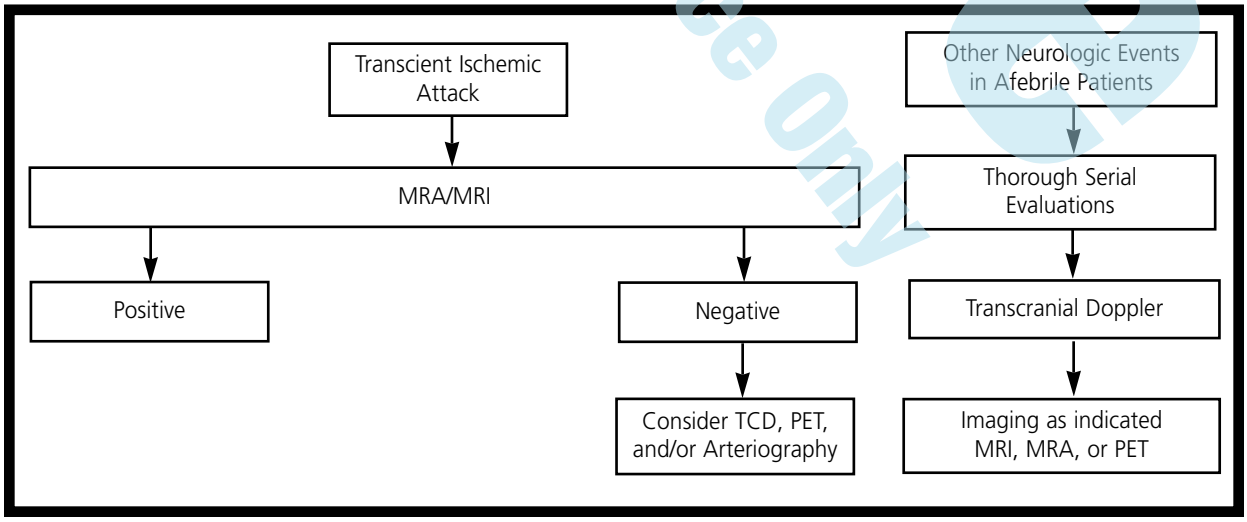

Figure 2

Algorithm for evaluating transcient ischemic attacks and repeat afebrile seizures.

Exchange transfusion to decrease the level of Hb S to less than 30 percent may help to prevent progression of the acute stroke.

In addition to transfusions, it is important to provide rehabilitation services to the patient. Although many children may exhibit remarkable recovery from a stroke, a detailed assessment of intellectual function should be done to determine if the child would benefit from special assistance with academic work because acquired learning difficulties may be the consequence of the stroke.

PREVENTION OF RECURRENT OCCLUSIVE STROKE

Vaso-occlusive strokes will recur in at least two-thirds of patients, unless they are placed on a chronic program. Transfusions of packed red blood cells given at regular intervals to keep the level of Hb S below 30 percent are effective in minimizing a recurrence of cerebral infarction in children. A transfusion program should be maintained for a minimum of 5 years. Should neurologic symptoms develop in adequately transfused patients, repeat imaging studies are warranted. The optimal duration of transfusion therapy is not known. The risk of recurrence in untransfused children is greatest in the first 3 years after the initial event. Many centers transfuse patients for years but modify the intensity of transfusions to reduce the rate of iron accumulation. Centers that transfuse patients for long periods use iron-chelating agents (deferoxamine mesylate) to decrease iron overload. Prognosis for long-term neurologic function and independent self-sufficient adult life is guarded. The role of bone marrow transplantation as an alternative therapy for these patients is unclear at present.

Inadequate transfusion therapy, as defined by a failure to suppress Hb S below 30 percent, may be due to inadequate frequency of transfusions, poor compliance, development of alloimmune or autoimmune antibodies, or blood loss.

Although aspirin or coumadin therapy has been effective in decreasing the risk of recurrent stroke in adult patients with normal hemoglobin (AA), or in those who have had prior TIA, the efficacy of such therapy in central nervous system disease in patients with sickle cell disease has not been established.

HEMORRHAGIC STROKE

Patients with intracranial hemorrhage (IH) may present with focal neurological deficits, severe headache, increased intracranial pressure, or coma. Immediate mortality is as high as 50 percent. This is a frequent cause of sudden unexpected death at home. In patients with end-stage renal failure from sickle cell disease, IH is a common cause of death. Immediate CT or MRI scanning should demonstrate the hemorrhage. Lumbar puncture may be necessary to demonstrate the subarachnoid hemorrhage (blood in cerebrospinal fluid) in some patients. Because vasospasm in the area of hemorrhage can produce secondary cerebral infarction, immediate exchange transfusion is recommended. There are no data regarding the efficacy of long-term transfusion therapy for patients with IH. In those patients who are not uremic, arteriography is necessary to determine if a surgically correctable lesion (aneurysm) is present.

IDENTIFICATION OF PATIENTS AT RISK FOR STROKE

Abnormal cerebral blood flow assessed by transcranial Doppler ultrasonography has been shown to be predictive of stroke in patients with sickle cell disease. Increased flow rates in the intracerebral arteries is secondary to stenosis and is associated with an increased risk for infarctive stroke. Current studies are evaluating the role of routine MRIs in asymptomatic children to identify those with cerebrovascular changes (see Chapter 23).

ACUTE COMA DUE TO GENERALIZED ARTERIAL HYPOXEMIA

Uncommonly, patients with Hb SS and its variants may exhibit a multiorgan dysfunction syndrome following arterial hypoxia that is usually induced by acute and progressive pulmonary disease. The syndrome (often caused by "fat embolism" or bone marrow necrosis) apparently arises from the sickling of erythrocytes in the arterioles of the bone marrow, causing fat and bone marrow embolism. In the brain, there is sufficient resultant hypoxia to cause neuronal dysfunction but not necrosis; hence, the process can be reversible. Multiorgan failure is characterized by the following:

- Often preceded by the most excruciating pain that the patient has ever experienced.
- High mortality rate within the first week.
- Upper extremity and facial petechia (often missed).
- A rapid progressive, generalized neurological deterioration, generally without focal neurological signs, that can progress to coma. The patients may exhibit decorticate, or even decerebrate, posturing.
- Signs of acute tissue injury such as necrosis of the bone marrow, acute centrilobular necrosis of the liver, renal dysfunction, and severe acute chest syndrome (see Chapter 8).
- Elevated serum lipase and fat globules in urine during early stages.
- Normalization of the signs of acute tissue injury and the neurological examination over a period of 1 to 3 weeks.

This syndrome must be treated rapidly and aggressively. Complete exchange transfusion is thought to be useful. Aggressive treatment of hypoxia, including the use of positive end-expiratory pressure (PEEP) or oscillating ventilatory devices if necessary, is essential as well as management in an intensive care unit.

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CHAPTER 10
TRANSFUSION

Transfusion should be used for specific indications in the treatment of patients with sickle cell disease and should be used as sparingly as possible. Transfusion is indicated for certain acute problems (*not* including acute painful episodes) or for the treatment or prevention of chronic complications and other health-related events. Several methods of transfusion are available (simple transfusion, partial exchange, and chronic exchange); the method used depends on the indication for the transfusion. The recommendations in this discussion are for patients with homozygous SS disease and $S\beta^o$ thal. The role of transfusion in the care of patients with Hb SC disease and Hb $S\beta^+$ thalassemia is controversial.

An important principle in the transfusion of sickle cell patients is the avoidance of excessive blood viscosity. Blood viscosity is a function of the intrinsic viscosity of the red blood cells and of the hematocrit. Because sickle cells are intrinsically less deformable than normal cells, raising the hematocrit without substantially reducing the proportion of sickle cells may raise the blood viscosity to dangerous levels. Therefore, simple transfusions should be used with caution in patients with high hematocrits, and the final posttransfusion hematocrit should be 36 percent or less. Patients with high baseline hemoglobin may be more safely transfused using an exchange technique.

INDICATIONS FOR TRANSFUSIONS

The following are generally considered to be indications for red blood cell transfusions in sickle cell disease:

- In severely anemic patients, transfusions should be *simple* transfusions without exchange, hence, without removal of any blood from the patient. Simple transfusions of this sort should be considered in the following situations:
  - — In patients who are so anemic that they have physiological derangement that is manifest by impending or overt high output cardiac failure, dyspnea, postural hypotension, angina, or cerebral dysfunction.
  - — In patients who have had a sudden diminution in hemoglobin concentration, particularly patients having an acute splenic or hepatic sequestration crisis, manifest by rapid splenic or liver enlargement and rapidly falling hematocrit.
  - — In patients who exhibit fatigue and dyspnea, usually at hemoglobin concentrations less than 5.0 g/dL and a hematocrit less than 15 percent, particularly in association with erythroid hypoplasia or aplasia.
- When there is a need to improve microvascular perfusion by decreasing the proportion of erythrocytes containing

Hb S, an exchange transfusion is indicated unless the patient is severely anemic and has good cardiac function. Such conditions include both acute and chronic conditions:

- — Acute or suspected cerebrovascular accidents and TIA (see Chapter 9, Stroke).
- — Multiorgan failure syndrome, including "fat embolization."
- — Acute chest syndrome or other acute lung disease when arterial oxygen cannot be maintained at near-normal levels with oxygen therapy or when the process progresses, despite antibiotic and other indicated therapy.
- — Acute priapism unresponsive to therapy.
- — Surgery on the posterior segment of the eye, even when done under local anesthesia in a nonanemic patient (see Chapter 12, Eye). Transfusion is not needed for laser surgery.
- — Preparation for general anesthesia (see Chapter 21).

- Chronic transfusion programs, usually initiated by exchange transfusion, are indicated for several conditions. In these programs, an effort is made to maintain the percentage of Hb A above 50 to 70 percent, which usually requires repeated transfusions every 3 to 4 weeks. Indications for a chronic transfusion program include:
  - — Children who have had a cerebral vascular accident for the prevention of further complications.
  - — Chronic congestive heart failure in conjunction with other treatment.

EQUIVOCAL INDICATIONS

Transfusion is sometimes suggested for a number of conditions in which its efficacy is unproved. If transfusion is done in these conditions, it should be an exchange transfusion. These conditions include the following:

- Intractable or frequent painful events.
- Situations in which the patient's condition is deteriorating rapidly, and all other treatments have been unsuccessful.
- Before injection of hypertonic contrast material.
- Adults who have had a cerebrovascular accident.
- Leg ulcers (see Chapter 16, Leg Ulcers).
- Complicated pregnancy.
- Chronic organ failure.
- Extreme diminution in performance status due to recurrent complications of sickle cell disease.

When chronic transfusion programs are stopped, many patients have an exacerbation of symptoms that may last for several weeks to months. If these symptoms become excessive or threatening to a patient's health, the transfusion program may need to be reinstituted and then stopped more gradually, although the physiologic justification may be unclear.

NONINDICATIONS AND CONTRAINDICATIONS

The following are *not* considered appropriate indications for transfusion, and transfusion is not recommended in these clinical settings:

- Chronic steady-state anemia. Most patients with sickle cell disease are relatively asymptomatic from their anemia and do not require transfusions to improve oxygen-carrying capacity.
- Uncomplicated acute painful crises.
- Infections.
- Minor surgery not requiring prolonged general anesthesia (e.g., myringotomy, simple biopsy).
- Aseptic necrosis of the hip or shoulder (except when surgery is required).
- Uncomplicated pregnancy.

TYPES OF BLOOD PRODUCTS TO BE USED

Standard bank blood is appropriate for the patient with sickle cell disease. The "age" of the blood (time since collection) is usually not important as long as it is within limits set by the transfusion service. Exchange transfusion with blood less than 5 days old (less than 3 days old in the small infant) helps in acute situations requiring immediate correction of the oxygen-carrying capacity. All blood should be screened for the presence of sickle hemoglobin and confirmed to be negative. A solubility test is adequate for screening in this situation. This procedure eliminates blood with sickle cell trait, which will confuse later measurements of the proportion of sickle cells or Hb S. The antigenic phenotype of the red cells (at least ABO, Rh, Kell, Duffy, Kidd, Lewis, Lutheran, P, and MNS groups) should be determined in all patients older than 6 months of age. A permanent record of this should be maintained in the Blood Bank, and a copy of the record should be given to the patient or family.

All patients with a history of prior transfusion should be screened for the presence of alloantibodies. The efficacy of a chronic transfusion program should be assessed periodically by determining the proportion of Hb S by quantitative hemoglobin electrophoresis as well as the hemoglobin concentration or hematocrit.

Red blood cell preparations depleted of leukocytes by filtration are recommended because of the reduction in febrile reactions and decreased alloimmunization to leukocyte antigens. Washed red blood cells should be used in patients who have a history of severe allergic reactions (bronchospasm) following prior transfusions.

The use of autologous blood transfusions in sickle cell disease should be avoided. Blood relatives should not be used as blood donors for children who may be candidates for bone marrow transplantation.

TRANSFUSION METHODS

Simple Transfusion

Simple transfusions can be used for acute anemia or hypovolemia or in a chronic transfusion program. Packed red blood cells should not be used when only volume expansion is needed.

Exchange Transfusion

Exchange transfusion is used to alter the hemoglobin level rapidly and to replace sickle cells with normal erythrocytes. This type of transfusion reduces the concentration of sickle cells without substantially increasing the hematocrit or whole blood viscosity. Several methods are available that achieve this purpose.

Rapid Partial Exchange

In some patients, whole blood can be removed from one arm at the same time that donor cells are transfused into the other arm. In adults, this procedure can be performed in 500 mL units. In children, the individual exchange aliquots are adjusted to a safe and practical level.

The total volume of blood to be used is proportional to the patient's body weight and hematocrit; thus, different formulas are needed for different initial hematocrit ranges. Exchange transfusions performed with whole blood (or, more commonly, packed cells reconstituted to the volume and hematocrit of whole blood using saline or other diluents) are more efficient than those using packed cells. They may reduce the number of units needed but take slightly more time. In children, a practical estimate of the volume required for exchange (whole blood or packed cells reconstituted to a hematocrit of 30 to 40 percent) is 50-60 mL/kg. In adults, blood can be removed from the patient in 500 mL aliquots, followed by infusion of 500 mL of reconstituted blood; this may be repeated for six to eight units of transfusion. Alternatively, the following technique can be used:

Step 1.
Bleed one unit (500 mL) of blood from the patient, infuse 500 mL of saline.

Step 2.
Bleed a second unit from the patient, infuse two units of blood.

Step 3.
Repeat steps 1 and 2; if the patient has a large red blood cell mass, repeat once more.

The devices used in plasmapheresis can be used to exchange transfuse patients efficiently; red blood cells are removed at the egress and normal blood is infused at the ingress. Usually six to eight units of blood are needed to exchange an adult; formulae are available to calculate the exact amount needed depending on body size, hematocrit, desired hematocrit, and desired percentage of Hb A. Such devices can be used for pediatric patients if the size of the receptacle is sufficiently small so as not to remove too much blood at one time.

Care must be taken in all cases where exchange transfusion is used to be certain that the final hemoglobin level does not exceed 10-12 g/dL to avoid the problems of hyperviscosity. Careful monitoring of the level of hemoglobin and of the percentage of Hb A is necessary to be certain that the goals of the transfusion have been met.

Chronic Transfusion Programs

Once a sufficient level of transfused normal cells (greater than 50 to 70 percent Hb A) is achieved, it is often useful to maintain this for a period of weeks to years. This proportion of normal cells can be maintained by simple transfusions at intervals of 2 to 4 weeks. The level of Hb A must be monitored by quantitative hemoglobin electrophoresis.

TRANSFUSION COMPLICATIONS

Transfusion complications for sickle cell patients are the same as those for any patient receiving acute or chronic transfusion.

Volume Overload

This occurs when too much volume is transfused too quickly. Congestive heart failure and pulmonary edema are most likely to occur in patients who have cardiac dysfunction or minimal cardiac reserve. Administration of intravenous furosemide and partial removal of red cell preserving-fluid before transfusion and a slow transfusion rate can help in preventing this serious problem.

Iron Overload

The serum ferritin levels should be measured periodically. If the level exceeds 2,000 ng/mL (usually after 1 to 3 years of chronic transfusion) and transfusions are still required, patients should be considered for chronic chelation therapy using Desferal. Complications of deferoxamine therapy may include ototoxicity, ophthalmic toxicity, allergic reactions, growth failure, unusual infections (*Yersinia*, fungi), and pulmonary hypersensitivity. Poor patient compliance, because of repeated subcutaneous infusions of medications, is a significant problem with chronic chelation therapy. Ongoing education and support, often provided by a specially trained nurse, is usually necessary to maintain the patients' cooperation. A subcutaneous infusion port or a Hickman catheter may be used for parenteral access. Desferal therapy should be discontinued during acute bacterial infections. A new oral iron chelator (L-1) is currently being evaluated for safety and efficacy.

Alloimmunization and Delayed Hemolytic Transfusion Reactions

The incidence of alloimmunization to red blood cell antigens in transfused patients with sickle cell anemia is approximately 20 to 25 percent, which is greater than in the general population. This condition causes difficulty in obtaining compatible blood and results in a high incidence of delayed hemolytic transfusion reactions. The delayed transfusion reaction occurs 5 to 20 days after transfusion and is due to antibodies not detectable at the time of compatibility testing. It has been found that 30 percent or more of the antibodies to red blood cell antigens may disappear with time, although the recipient remains capable of mounting an anamnestic response to further stimulation by transfusion. The delayed hemolytic transfusion reaction that can result may cause severe anemia, onset of painful crisis, or even death.

ACUTE HEMOLYTIC TRANSFUSION REACTIONS

Acute hemolytic transfusion reactions in sickle cell patients are not different in cause from those in other patients. Major hemolytic reactions occur primarily with major blood group (ABO) mismatches and must be treated aggressively to maintain blood pressure and glomerular filtration; most can be prevented by avoiding clerical and patient or sample identification errors in the cross-matching and transplantation of units from donor site to the patient. Minor hemolytic reactions occur when the amount of antibody in the serum is limiting, and they are characterized by the disappearance of the transfused blood during a period of several days (with a consequent decrease in the hematocrit) and the appearance of hyperbilirubinemia; no further treatment is necessary except monitoring the hematocrit level to ensure that it does not greatly decrease.

Any of these reactions, particularly the delayed variety, are able to initiate a painful episode in the patient with sickle cell disease. In all cases, the patient's blood should be examined very carefully by immunohematologists in the transfusion service to document the antibody or antibodies responsible for the reaction; the patient must be made aware of the complication and be given a card describing the antibodies found.

Alloimmunization and hemolytic transfusion reactions resulting from it can be reduced by the following:

- Acquiring and maintaining adequate records of previous transfusions and complications arising from them.
- Limiting the number of transfusions administered.
- Screening for newly acquired antibodies 1 to 2 months after each transfusion to detect transient antibodies capable of causing a subsequent delayed reaction.
- Diminishing the opportunities for alloimmunization because of a mismatch in the antigens of donors and patients:
  - — Typing the patient before the transfusion (if this has not already been done) for antigens of the Rh and Kell blood groups and avoiding the transfusion of cells bearing these antigens (particularly E, C, and Kell) if the patient lacks the antigen. More complete antigen matching has been suggested, but it is expensive and the utility of such matching is not clear.
  - — Increasing the use of African-American donors of blood because of the similarity of red blood cell antigenic phenotypes. Family members and community groups can assist in accomplishing this objective.

The patient alloimmunized to one red blood cell antigen is more likely to become alloimmunized to others, and care should be taken in selecting transfusion units. Transfusions should be given only for clearcut indications. These patients should be counseled to advise any new physician of their history of alloimmunization. Carrying a card or an identification bracelet listing the red blood cell phenotype and any identified antibodies is strongly recommended.

Autoimmune Anemia Following Allosensitization

In some highly alloimmunized patients, a syndrome of autoimmune hemolytic anemia may follow allosensitization or a hemolytic transfusion reaction. In this case, the patient may become more anemic than before transfusion, and the direct antiglobulin (Coombs') test remains positive even after the incompatible transfused cells have been destroyed. This syndrome occurs because the body produces antibodies against self-antigens, and it may persist from several weeks to 2 to 3 months before disappearing. Further transfusion is complicated by the autoimmune antibody and requires sophisticated blood-banking techniques to find the "least incompatible" blood for transfusion.

Alloantibodies to White Cells, Platelets, and Serum Proteins

Patients who are transfused may become alloimmunized to antigens present on leukocytes and/or platelets but lacking on red blood cells. Such antibodies may cause

a febrile reaction that can be prevented through the removal of the leukocytes by filtration or washing. These antibodies as well as those against serum proteins can cause allergic reactions that can be prevented by prophylaxis with an antihistamine (Benadryl®), removal of leukocytes or plasma by washing, or use of other measures previously noted.

Infection

Hepatitis and other transfusion-transmitted viral diseases in blood occur with the same frequency in sickle cell patients as in other patients receiving transfusions. The effects may be more severe in sickle cell patients because of the presence of the disease. Patients receiving multiple transfusions should be serially monitored for hepatitis C and other viral infections; alpha interferon may be useful in the treatment of patients with chronic hepatitis B and C.

Posttransfusion human immunodeficiency virus (HIV) infection and AIDS are reported in sickle cell disease, occurring as late as 5 to 8 years after the transfusion with blood not known to be from an infected donor. Thus, patients with sickle cell disease who were transfused before blood products were tested for HIV antibodies (1975-85) as well as those transfused with today's "safe" blood should be considered for counseling on testing for HIV infection.

TRANSFUSION FOR SURGERY

A multi-institutional study recently prospectively compared perioperative complication rates of sickle cell anemia patients randomized to aggressive transfusion (decrease Hb S below 30 percent) and conservative transfusion (Hb S approximately 60 percent, Hb to 10 g/dL). Serious complications occurred in approximately one-third of both groups. The most common complication was acute chest syndrome, which occurred in 10 percent of patients. There were no significant differences between transfusion regimens and any complication except transfusion complications, which occurred in 14 percent of aggressively transfused patients and 7 percent of conservatively managed patients. In addition, preoperative hospitalization days attributed to transfusion preparation were 4 days in the aggressively transfused patients compared with approximately 2 days in conservatively managed patients. In conclusion, present data suggest that routine hemoglobin SS patients undergoing major elective surgery should be conservatively transfused as part of their routine management. Transfusion with limited phenotypic units would most likely eliminate the alloimmunization observed from E, K, C, and Fya. Definitive data to recommend no preoperative transfusion in sickle cell disease are not available. However, the present standard of practice suggests that no preoperative transfusion is a possible alternative in healthy hemoglobin SC patients and for limited surgery in stable hemoglobin SS patients. At present, patients having tonsillectomies and adenoidectomies should be transfused for surgery.

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Chapter 11

Splenic Sequestration and Transient Aplastic Crisis

Acute exacerbation of anemia in the patient with sickle cell disease is a significant cause of morbidity and mortality. The most common processes leading to these "crises" in the United States are splenic sequestration and erythroid aplasia.

SPLENIC SEQUESTRATION

Much of the severe morbidity and mortality of sickle cell anemia in the first few years of life is a consequence of the so-called acute splenic sequestration crisis. This was first described in 1945 in a review of 11 fatal cases of sickle cell anemia where death was caused by "abdominal crises." These catastrophic events were characterized by severe anemia, splenomegaly, hypovolemic shock, and sudden death, and it was suggested that patients had literally "bled into their spleens."

Infants and young children with sickle cell anemia whose spleens have not yet undergone multiple infarctions and subsequent fibrosis, and those individuals with other forms of sickle cell disease whose spleens remain enlarged into adult life, can suddenly have intrasplenic pooling of vast amounts of blood. In SS disease, these events can occur as early as 2 months of age and are unusual after age 3 years. They are often associated with viral or bacterial infections. During severe splenic sequestration, the spleen becomes enormous, filling the abdomen and even reaching into the pelvis. The usual clinical manifestations of this complication are sudden weakness, pallor of the lips and mucous membranes, tachycardia, tachypnea, and abdominal fullness. Anemia can be profound, thrombocytopenia due to splenic entrapment is common, and the reticulocyte count is often markedly elevated. Splenic sequestration is one of the most dangerous events in the life of a patient with sickle cell anemia and must be promptly recognized and treated. Within hours of the first signs of this disturbance, hypovolemic shock and death can occur.

With increasing numbers of children diagnosed at birth with sickle cell disease and carefully followed thereafter, it has become apparent that minor (or "subacute") episodes of splenic sequestration are common. These episodes are characterized by a moderate increase in spleen size associated with a fall in baseline hemoglobin level of 2 to 3 g/dL. The reticulocyte count may increase above usual levels. These episodes may resolve spontaneously or splenomegaly may persist; management consists of careful surveillance. Some patients may ultimately require splenectomy if significant cytopenias occur.

Early diagnosis of sickle cell disease permits training of parents to palpate their infants' abdomens to determine the size of the spleen (see Chapter 1). Parents must be instructed to seek immediate medical

attention if they notice increased pallor, abdominal pain or enlargement, or rapid splenic enlargement. Educating parents is an essential component of newborn screening followup and has resulted in reduced mortality from splenic sequestration.

Splenic sequestration crises can occur in older patients with Hb SC disease and $S\beta^+$ thal whose spleens either remain enlarged or retain the capability to enlarge. Although these episodes are often mild, are associated with decreased hemoglobin levels of 2 to 3 g/dL, and rarely require supportive transfusions, severe and fatal sequestration has occurred in some patients.

In children or adults with splenomegaly (usually patients with Hb SC disease or Hb $S\beta^+$ thal), acute splenic infarction may occur, causing severe left upper quadrant pain that is sometimes accompanied by a "splenic friction rub" audible when the patient inspires. The infarcts may be visualized by CT or MRI scans. Although these episodes often resolve with conservative management, intractable pain may necessitate splenectomy.

Treatment of the acute splenic sequestration is directed toward the prompt correction of hypovolemia with plasma expanders followed by red blood cell transfusion as they become available. A dramatic regression of splenomegaly and rise in hemoglobin level can occur in a short time after transfusion. Because of this phenomenon, the goal of transfusion should be to restore intravascular volume and achieve a posttransfusion hemoglobin level of 6-8 g/dL; although transfusion is usually required, care should be taken not to overtransfuse. Because severe splenic sequestration can result in fatality within a few hours and because of its tendency to recur, splenectomy should be strongly considered if a child has had two or more of these episodes; some would recommend splenectomy after a single severe episode. Because the spleen in SS disease is frequently dysfunctional after 6 to 9 months of age, the risk of postsplenectomy infection is probably not greatly increased. Alternatively, a program of chronic transfusion can be used in infants younger than age 2 years, the age at which immunization with the pneumococcal vaccine is more effective. Chronic transfusion therapy usually reduces spleen size, restores function, and prevents sequestration, thus avoiding splenectomy in the very young child. When transfusions are discontinued, however, the child may again be at risk for sequestration. Educating parents about splenic palpation is particularly important after the child has had an initial episode.

Some patients with sickle cell disease develop chronic massive splenomegaly with associated hypersplenism. Splenectomy is indicated when the degree of anemia, neutropenia, or thrombocytopenia is severe, or when pain or discomfort is associated with the enlarged spleen.

TRANSIENT APLASTIC CRISES

Because the red blood cell lifespan is shortened in sickle cell disease, even transient suppression of erythropoiesis can result in severe anemia; these episodes are called transient aplastic crises. The large majority of episodes of severe reticulocytopenia are due to infection by parvovirus B-19, also the cause of erythema infectiosum ("fifth disease"). Patients may present with increased fatigue, dyspnea, more severe anemia than usual, and few or no reticulocytes. The anemia is often well-compensated, with minimal elevation of pulse or respiratory rate. Although fever

and signs of upper respiratory infection may be present, skin rash is characteristically absent. Concurrent acute chest syndrome may occur. Confirmation of acute parvovirus B-19 infection is possible by a variety of serological and microbiological techniques. Erythroid aplasia terminates spontaneously after 5 to 10 days; leukoerythroblastosis is common in the peripheral blood during recovery. Patients who present in the convalescent phase may be mistakenly assumed to have hyperhemolysis because of severe anemia and high reticulocyte levels.

Treatment for transient aplastic crisis is supportive. Packed red blood cell transfusions are often necessary in those with SS disease and $S\beta^o$ thal because of tachycardia and tachypnea. Transfusions are required less frequently in those with other forms of sickle cell disease. If the patient can be relied on to return for frequent checkups or seek medical help if symptoms worsen, prolonged hospitalization is usually not required.

In addition to erythema infectiosum, parvovirus B-19 has been associated with hydrops fetalis secondary to intrauterine infection and chronic viremia with anemia or pancytopenia in patients with immunodeficiency. Respiratory isolation of patients with transient aplastic crisis should be implemented to prevent exposure of other patients with sickle cell disease, patients with immunodeficiency (e.g., congenital, HIV-related, or chemotherapy-induced), and pregnant females (i.e., nursing staff). Patients should be considered infectious until reticulocytosis occurs.

A marked decrease in the reticulocyte count below what is usual for a given patient can herald aplastic crisis. Therefore, the evaluation of the febrile patient should include measurement of the reticulocyte count; a low reticulocyte count mandates further monitoring of the hemoglobin level. Various viral and bacterial infections can cause transient and less severe hypoplasia. Particularly in adolescents and adults, urinary tract or pulmonary infections, as well as severe and protracted painful crises, should be considered causes of reticulocytopenia.

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Chapter 12
Eye

Sickle cell hemoglobinopathies have the potential to cause ophthalmic complications that affect vision. Unless the ophthalmoscopic evaluation includes a thorough examination of the posterior and peripheral retina through a dilated pupil, these complications can go unnoticed.

Proliferative sickle retinopathy (PSR) can lead to vitreous hemorrhage and retinal detachment. Laser photocoagulation can benefit many patients with proliferative retinopathy. A certain percentage of patients who develop retinal holes or traction can be spared retinal detachment and blindness if they are treated appropriately. Once detachment or nonclearing vitreous hemorrhage is present, surgical intervention is often helpful in restoring vision.

It is recommended that patients with sickle hemoglobinopathies have yearly eye examinations, including indirect ophthalmoscopy. These examinations should begin in childhood (see Chapter 2, Adult Health Care Maintenance). Patients with significant retinopathy should undergo fluorescein angiography and be evaluated and followed by a retinal specialist. Immediate referral to an ophthalmologist is also indicated when there is a sudden change in visual acuity or when there is trauma to the eye. Trauma is often associated with elevated intraocular pressures, and, in a patient with sickle cell disease, even a slight elevation may result in permanent loss of vision (see "sickle cell hyphema" below).

NONPROLIFERATIVE SICKLE RETINOPATHY

Nonproliferative sickle retinopathy includes vascular occlusions, retinal hemorrhages, retinoschisis cavities, iridescent spots, black sunbursts, angioid streaks, and macular changes. These changes usually do not affect visual acuity.

PROLIFERATIVE SICKLE RETINOPATHY

Although peripheral retinal vascular occlusions are often observed in childhood, retinal neovascularization generally occurs in the second and third decade. Retinal neovascularization is most common in Hb SC disease but may also be seen in SS disease and Sβ thal.

The evolution of neovascularization is affected by the patient's age and hemoglobin type. It remains unclear why neovascularization progresses rapidly in some patients with sickling hemoglobinopathies and is virtually absent in others with the same hemoglobin type. The risk of further hemorrhage depends in part on the amount of neovascularization. Untreated sickle cell retinopathy may cause blindness by vitreous hemorrhage or retinal detachment.

Laser photocoagulation is often effective in eradicating proliferative retinopathy with an acceptably low rate of complications.

VITREOUS HEMORRHAGE AND RETINAL DETACHMENT

Proliferative sickle retinopathy causes vitreous hemorrhage. Degeneration and fibrosis of the vitreous cavity can lead to a tractional detachment of the retina or retinal hole formation, sometimes followed by detachment. These are the most common causes of blindness in sickle cell disease. If a vitreous hemorrhage does not clear in 3 to 6 months or if a tractional retinal detachment occurs, vitrectomy (removal of the vitreous), often in combination with a retinal detachment operation (a scleral buckling procedure), is the treatment of choice. Partial exchange transfusion (see Chapter 10, Transfusion) is recommended for all patients with sickle hemoglobinopathies before eye surgery in an effort to improve treatment of potential postoperative complications such as hyphema and ischemic necrosis of the anterior segment of the eye.

SICKLE CELL HYPHEMA

Individuals with sickle cell hemoglobinopathies, including sickle cell trait, who have hyphemas (blood in the anterior chamber) due to trauma or surgery are at risk of developing elevated intraocular pressure even if only small amounts of blood are present. The biochemical and metabolic conditions in the aqueous humor favor erythrocyte sickling, and as a result, sickle erythrocytes can plug the outflow pathways and cause increased intraocular pressure. Moderate elevation of intraocular pressure in eyes of patients with sickle cell disease hemoglobinopathy can produce permanent deterioration of visual function. These patients should be referred immediately to an ophthalmologist for medical or surgical intervention.

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Chapter 13

Contraception and Pregnancy

Pregnancy carries some increased risk for a woman with sickle cell disease and her fetus, but the risks are not so great as to prohibit desired pregnancies. Every woman of childbearing age with sickle cell disease who is sexually active should be advised of the likelihood that her pregnancies will be successful but should also be advised that some risks may be greater than for women without sickle cell disease. Particular attention should be given to ensure that the genetics of sickle cell disease is understood.

CONTRACEPTION

Sickle cell disease is not an indication for sterilization. Contraception, however, offers the option of informed family planning. The methods for contraception include barrier methods, oral contraceptives, long-acting intramuscular contraceptives, intrauterine devices (IUDs), and condoms. There is no evidence that use of the pill is more dangerous for women with sickle cell disease than for those without the disease. Studies in women without sickle cell disease have shown that low-dose estrogen oral contraceptives are the most reliable of the common contraceptive methods. The long-acting intramuscular contraceptives are also effective. Barrier methods such as a diaphragm and gel have a higher rate of failure than oral contraceptives. The IUDs are very reliable but cause a significant risk of bleeding and infection that would present serious problems for women with sickle cell disease. Condoms are less reliable but also provide protection against the spread of AIDS and other sexually transmitted diseases. Adolescents and preteens should receive sex education that includes a discussion of abstinence.

MANAGEMENT OF PREGNANCY

Women should be advised to seek medical care early in pregnancy. Prenatal care should be with either the primary physician or the obstetrician; full responsibility should be in one set of hands, with advice from the other. An obstetrician or high-risk clinic experienced in the management of women with sickle cell disease is best if available. Initial assessment should include a medical history directed to eliciting factors that influence pregnancy outcome such as obstetrical experiences; medical complications such as renal, neurological, or pulmonary difficulties; chemical dependency (either prescription or other); and excessive alcohol or tobacco use. Visits should include close monitoring and should be frequent—ideally, every 2 weeks until the 28th week of pregnancy and weekly thereafter. All pregnant patients should receive 1 mg of folic acid daily in addition to the usual prenatal vitamins, minerals, and iron supplements, unless iron stores are known to be increased. All routine prenatal screening examinations should be performed.

All patients should be screened for the presence of red cell alloantibodies, regardless of their transfusion history. A patient should be told if antibodies are present and given a document with details in case she delivers at a hospital other than the one planned for delivery. Management of the alloimmunized mother should follow meticulous prenatal obstetrical practices that include following Rh or other antibody titers, administering Rh immunoglobulin if indicated, and performing amniocentesis to assess fetal development and bilirubin concentration. If alloantibodies are identified, arrangements with the blood bank should be made early in pregnancy to identify, if possible, sources of compatible blood.

The father should also have his hemoglobin type identified. If he has sickle cell trait or is a carrier of another hemoglobinopathy (including thalassemia), the possibility of prenatal diagnosis to identify sickle cell disease in the fetus should be raised early in pregnancy. Such services are described in Chapter 14, Prenatal Diagnosis.

Intrauterine growth can be gauged by the measurement of fundal height and confirmed by ultrasound. The cervix is examined in the second and third trimester to detect softening and dilatation, which may suggest preterm labor. Monitoring every 2 weeks or weekly after 28 weeks by nonstress test, stress test, biophysical profile, umbilical blood flow, and recording of fetal well-being by the method of Sadovsky and Polishuk are useful and cost efficient. As with any pregnancy in which intrauterine growth retardation becomes evident, bedrest is recommended and early delivery considered if growth fails to accelerate toward the normal rate or if urinary estriol falls. Stress tests should be used if there are questions of uteroplacental insufficiency.

Although some physicians institute prophylactic transfusion in asymptomatic pregnant patients with SS disease, there is no firm evidence that outcomes improve because of such transfusions. However, transfusions continue to play an important role in the management of acute events.

SICKLE-RELATED COMPLICATIONS OF PREGNANCY

The management of painful episodes does not differ during pregnancy (see Chapter 7, Painful Events). Narcotics can be used in conventional doses, and hydration is important. Other complications of sickle cell disease, including acute chest and right upper quadrant syndromes, acute anemic episodes, new onset neurological events, and septicemia, should be managed as they are in nonpregnant patients. Preexisting renal disease and congestive heart failure may worsen during pregnancy.

COMPLICATIONS OF PREGNANCY

Intrauterine growth retardation occurs with greater frequency in patients with SS disease than in SC disease and $S\beta^+$ thal patients. Preterm labor and premature delivery occur with increased frequency; risk factors include severe anemia, increased prostaglandins, abruptio placentae, placenta previa, multiple gestations, urinary tract infection, cigarette smoking, and overuse of narcotics. Toxemia of pregnancy, thrombophlebitis, pyelonephritis, and spontaneous abortions may have increased frequency in patients with sickle cell disease. These should be treated as in the patient who does not have sickle cell disease.

DELIVERY

The hemodynamics of anemia and high cardiac output are accentuated during periods of uterine contraction. Pain should be counteracted by the liberal use of narcotics. If delivery is uncomplicated, local or regional anesthesia is advised. If fetal distress or anatomic considerations prompt cesarean section, general or spinal anesthesia is necessary. Blood loss should be replaced according to the usual obstetrical practice. Cardiac function may be compromised by hypoxemia, anemia-increased fluid loss, and acidosis. Transfusion in relation to anesthesia is discussed in Chapter 10. Oxygen and maintenance hydration should be administered during labor and delivery.

POSTPARTUM CARE

Routine postpartum care should be followed meticulously, and hydration should be maintained. The risk of embolism can be reduced by the use of embolic stockings and early ambulation. Preventing atelectasis in postpartum patients is important, and fevers should be aggressively diagnosed and treated. The newborn baby should be screened for hemoglobinopathies as well as other genetic disorders (see Chapter 5, Newborn Screening).

INTERRUPTION OF PREGNANCY

If interruption of pregnancy is considered at less than 13 weeks, analgesia rather than anesthesia is usually all that is required for suction curettage. Beyond 13 weeks, hypertonic urea solutions are injected into the uterus, and contractions are stimulated with prostaglandin F2. Hypertonic sodium chloride solution should not be injected because it can cause sickling; however, hypertonic urea is safe. At the first followup visit, the patient should be counseled about contraceptive techniques. Rh-negative women should receive Rh immunoglobulin after therapeutic or spontaneous abortion.

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Chapter 14
Prenatal Diagnosis

Each year in the United States there are 4,000 to 5,000 pregnancies at risk for sickle cell disease. As with other genetic diseases, advances in technology have provided safe and accurate methods for performing prenatal diagnosis for sickle cell disease as early as the 10th gestational week. Prenatal diagnosis is best accomplished by a reproductive genetics team familiar with sickle cell disease and experienced in the provision of accurate genetic diagnosis of couples at risk after nondirected genetic counseling. The team must be expert in obtaining a fetal sample for analysis and performance of diagnostic laboratory tests and must be prepared to handle consideration of pregnancy termination. A necessary proviso for prenatal diagnosis of sickle cell disease is that diagnostic methodology not be allowed to exceed our ability to predict clinical severity. The degree of control that ethically can be exerted over the biological makeup of unborn children must be weighed.

COUNSELING

Couples at risk for conceiving a child with homozygous SS disease, Hb SC disease, or Sβ thalassemia should be referred for genetic counseling. This process must be carried out with the realizations that all mothers requesting prenatal diagnosis desire to bear children and that fetal welfare is never enhanced by prenatal diagnosis. Counseling includes an objective description of a patient's life with a particular form of sickle cell disease. It is important that counseling takes into account the clinical differences among the various types of sickle cell disease and the heterogeneity within genotypes. It is also important that discussions of prenatal diagnosis and pregnancy interruption be conducted in a sensitive nondirected manner. Many patients have relatively benign disease; the ability to predict disease severity would be a valuable asset in counseling and prenatal diagnosis, but this is still lacking. Currently, some centers introduce couples at risk to patients with sickle cell disease to provide a better understanding of the disease and a firmer basis for decisions on prenatal diagnosis and possible interruption of pregnancy. The decision regarding use of the results of prenatal diagnosis should always be left to the parents; informed decisionmaking is their prerogative.

Couples who elect to have prenatal diagnosis must be referred to an appropriate center as early in pregnancy as possible because the time-consuming diagnostic processes must be completed before the 24th gestational week, after which pregnancies for genetic diseases are not terminated.

GENETICS

Codominant inheritance of the sickle cell gene means that individuals homozygous for the mutation have clinical disease and that heterozygous individuals, although asymptomatic, are detectable. When an individual with sickle cell trait is considering conceiving a child with a mate who is heterozygous for Hb S, Hb C, or β thalassemia, there is a one-in-four chance for each pregnancy that the offspring will inherit a form of sickle cell disease. When one parent has sickle cell anemia and the other is heterozygous for any of these three disorders, there is a one-in-two chance with each pregnancy of conceiving a child with sickle cell disease.

FETAL TISSUE SAMPLING

Analyses are performed on DNA from fetal cells obtained by chorionic villus sampling (CVS) in the first trimester, perhaps as early as the 10th gestational week. As an alternative approach, amniocentesis can be performed safely in the l6th gestational week, a time when there is sufficient amniotic fluid. These sampling methods result in a far lower rate of fetal demise than the fetal blood sampling method practiced previously, and their use now is nearly universal. It is common practice to initiate tissue culture as a backup source of fetal DNA in case insufficient DNA for analysis is obtained initially. The emphasis on methods of early sampling to safeguard against unacceptable delays in diagnostic testing have encouraged the use of CVS as the method of choice for fetal sampling. However, the use of CVS before 9 weeks' gestation is associated with increased rates of limb reduction anomalies. Moreover, when CVS is used for sampling, confined placental mosaicism may result in mistaken diagnoses of heterozygosity in homozygous fetuses. CVS is not recommended until after 10 weeks' gestation, and diagnoses of heterozygosity must be confirmed by amniocentesis later in pregnancy. The use of preimplantation testing and assaying fetal cells in the maternal circulation offer hope for safer sampling in the future.

The Hb S and Hb C genes can be detected directly in fetal DNA samples. If the specific mutation responsible for thalassemia in a parent is known, that gene can also be detected. In some laboratories, several relatively common mutations are sought, but a negative result is not helpful. The use of genetic linkage analysis for indirect identification of these genes is no longer necessary. Fetal blood sampling is used only in centers where DNA-based testing is unavailable.

DIAGNOSTIC TESTS

Tests using polymerase chain reaction (PCR) provide sensitivity, simplicity, and rapidity to DNA-based methods. PCR provides greater amounts of DNA for analysis, often obviates the wait for tissue culture growth, and shortens the time for diagnosis to days rather than weeks. Several molecular diagnostic laboratories are available with expertise in prenatal diagnosis of hemoglobinopathies.

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Chapter 15
Gallbladder and Liver

GALLBLADDER

Pathophysiology

Because red blood cell hemolysis increases bilirubin production, the total serum bilirubin is increased in hemolytic diseases. This is accentuated in sickle cell disease because red blood cell sequestration in the liver and consequent hepatocellular dysfunction cause decreased bilirubin excretion. The increase in bilirubin is typically most marked in SS disease and $S\beta^0$ thal, is less likely in hemoglobin SC disease, and may be absent or only slightly increased in $S\beta^+$ thal. When the liver is functioning at maximum efficiency, the total serum bilirubin should not exceed 4 mg/dL, and the conjugated fraction should not exceed 10 percent of the total.

Because of the increase in bilirubin production, gallstones are common in SS disease. They are found in approximately 14 percent of children younger than age 10 years, about 30 percent of adolescents, and about 75 percent of adults by age 30 years. Gallstones are almost as common in $S\beta^0$ thal and also occur in about 40 percent of patients with Hb SC disease and 20 percent of patients with $S\beta^+$ thal. Gallstones are frequently multiple. They are composed mainly of desiccated bile, which is radiolucent, but the stones are radiopaque and contain calcium bilirubinate in about 60 percent of patients.

Differential Diagnosis

Gallstones can be totally asymptomatic for many years. Alternatively, they may cause chronic symptoms of fullness after meals, nausea, vomiting, and right upper quadrant pain. Complications of cholelithiasis include acute cholecystitis, common bile duct obstruction, and acute pancreatitis. Biliary colic may cause right upper quadrant or diffuse abdominal pain. This abdominal pain may also be due to peptic ulcer disease in patients with SS disease and should be considered in the history and, if indicated, evaluated by examination of the upper gastrointestinal tract. Although gallstones are often seen on the plain radiograph, a biliary ultrasound investigation not only detects stones more accurately but can also detect biliary sludge (the precursor of stones), a deformed or thickened gallbladder wall, and changes in the caliber of the common bile duct. Ultrasound also provides information about the liver and pancreas and saves the patient multiple x-ray exposures associated with contrast cholecystography. Scanning after the administration of technetium-99m iminodiacetic acid (HIDA) is particularly useful to confirm cystic duct occlusion and to evaluate gallbladder function (after the administration of cholecystokinin). Newer analogues (mebrofenin, for example) can be used at higher serum bilirubin concentrations than HIDA.

Management

In most patients, management does not differ from that used in the general population. Most physicians defer surgery until symptoms occur. However, some physicians recommend cholecystectomy once stones are identified because of frequent difficulty in diagnosing the cause of abdominal pain in children with sickle cell disease. In adult patients, vague right upper quadrant discomfort after meals can be relieved by antispasmodics. Some patients remain symptom free for many years by avoiding dietary excesses and restricting their intake of fried and fatty food. When gallstone symptoms are chronic or recurrent, elective cholecystectomy is indicated. Right upper quadrant pain is not relieved by surgery in all patients.

Acute cholecystitis should be treated conservatively with antibiotics and hydration; electrolyte balance and general supportive measures should be maintained. Elective cholecystectomy should be performed after the acute attack subsides to avoid adhesions around the inflamed gallbladder (usually within 6 weeks). Emergency surgery should be avoided, unless there is evidence of common bile duct obstruction. If obstruction is suspected or if liver function tests are significantly more abnormal than before the attack, endoscopic retrograde cholangiography (ERCP) may be quite helpful and, occasionally, therapeutic. For elective procedures, laparoscopic surgery, done by experienced providers, has been safe and convenient and has been associated with low postoperative morbidity. Both ERCP and laparoscopic cholecystectomy may be necessary if common duct and gallbladder stones are present.

Preparation for Cholecystectomy

The question of whether preoperative transfusion is necessary before major abdominal surgery is discussed in Chapter 10, Transfusion. Currently, most patients undergoing laparoscopic cholecystectomy are not transfused preoperatively if their hemoglobin level is above 7.0 g/dL. As for all patients, anesthesia for sickle cell disease patients requires maintenance of good hydration, normal body temperature, and effective ventilation (see Chapter 21, Surgery and Anesthesia). An intraoperative cholangiogram is recommended to rule out intrahepatic or common duct stones.

Postoperative Care

Postoperative complications may be more common in sickle cell anemia patients than in the general population and include atelectasis, pneumonitis, and pulmonary infarction. Preoperative and postoperative physiotherapy using an incentive spirometer, plus early ambulation, may reduce the frequency of these complications. Most patients have an uneventful recovery from surgery. There is no evidence that surgical wound healing is delayed in patients with sickle cell disease.

ACUTE LIVER DISEASE

The patient who presents with right upper quadrant abdominal pain, increased jaundice, and fever needs careful evaluation and management. The symptoms may be caused by acute cholecystitis, viral hepatitis, intrahepatic vaso-occlusive common bile duct obstruction, or drug-induced hepatotoxicity. Episodes of hyperbilirubinemia may occur in the absence of abdominal pain or other symptoms and may have

a benign self-limited course resolving in 1 to 2 weeks. In other cases, liver dysfunction is associated with fever, leukocytosis, and a clinical presentation similar to that seen in drug-induced cholestasis.

In children and adults, the liver may be the site of red blood cell sequestration during a vaso-occlusive crisis, with increased jaundice, an acutely enlarged tender liver, and a fall in hemoglobin and hematocrit. Acute liver disease rarely progresses rapidly to liver failure with an increase in serum levels of hepatic enzymes, multiple coagulation defects, uncontrollable hemorrhage, and death.

Increased levels of serum alkaline phosphatase, lactic dehydrogenase, and SGOT (AST) do not necessarily indicate liver disease because they may arise from bone and/or hemolyzed red blood cells. Intermittent elevations of serum liver enzymes may be seen in the absence of symptoms, but in acutely ill patients, viral hepatitis should be considered. These patients may become deeply jaundiced and show marked abnormalities of serum aminotransferases and coagulation function tests. These patients also should be treated like other patients with liver failure.

CHRONIC LIVER DISEASE

Transfused patients are at risk for viral hepatitis, and some will develop chronic active hepatitis and progress to cirrhosis. In the chronically transfused patient, liver enlargement and fibrosis may result from hemosiderosis, but the incidence of frank hemochromatosis is lower than in thalassemia major. Studies of liver biopsy materials suggest that continued hemolysis and Kupffer cells engorgement, which could cause intrahepatic hypoxia, may not be as important a cause of chronic liver dysfunction as previously thought. In the older patient, chronic congestive heart failure, especially when associated with pulmonary hypertension, may be an important additional factor in producing cirrhosis. Careful evaluation of patients with hepatic complications, including judicious use of liver biopsy, has shown that a substantial proportion can be explained by disorders unrelated to sickle cell disease. Chronic active hepatitis seen on biopsy may be due to the hepatitis B or C virus; if that diagnosis is confirmed by measurement of antibody titers or detection of the viral genome by use of PCR, therapy with interferon should be considered.

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Chapter 16
Leg Ulcers

Between 10 and 20 percent of patients with SS disease develop debilitating leg ulcers. The ulcers usually appear between the ages of 10 and 50 years and are seen more frequently in males than in females. Leg ulcers are rare in individuals with Hb SC disease and Sβ thal as well as in patients younger than age 10 years.

PATHOPHYSIOLOGY

Sickle cell ulcers usually begin as small, elevated, crusting sores on the lower third of the leg, above the ankle and over and around the medial or lateral malleolus. Occasionally, ulcers are seen over the tibial area or the dorsum of the foot. They can be single or multiple. Some heal rapidly, others persist for years, and others heal only to recur in the area of scarred tissue. In the early phase, the neighboring skin appears to be healthy, but as the ulcer persists, the surrounding skin shows hyperpigmentation with a loss of subcutaneous fat and hair follicles. These ulcers can be very painful and often are accompanied by reactive cellulitis and regional (inguinal) adenitis. Warmer temperatures, lower steady-state hemoglobin, and lower fetal hemoglobin appear to enhance ulcer formation. Once an ulcer forms, recurrence is common.

DIAGNOSIS AND LABORATORY TESTS

A general physical examination should search for other causes of leg ulcers such as varicose veins, diabetes mellitus, and collagen vascular disease. Before therapy, a radiograph of the leg is needed to establish the presence or absence of chronic changes in the underlying bone. Periosteal thickening below the ulcer is not uncommon, but underlying osteomyelitis is rare. Quantitative cultures can be taken from the base of the ulcer with the use of a dermal punch biopsy. The aim of treatment is to reduce the colony count by local cleansing or topical antibiotics.

SUGGESTED TREATMENT

Leg ulcers are very difficult to treat. There are many treatment modalities described. None of them has been proved to give consistently beneficial results. Active patient participation in the care of leg ulcers is essential because of the ulcers' chronicity. Nursing staff members can be particularly helpful in assisting patients. Patients should be encouraged to wash their legs and feet daily and to wear proper shoes and support stockings. Leg ulcer management is difficult and can be frustrating to both patient and medical and nursing

staff members because therapy is often unsatisfactory. Patients should be encouraged to promptly report to the physician when they develop an ulcer. Ulcers less than 2-3 cm have a greater chance of healing. Once ulcers are persistent for more than 6 months, they become chronic, and treatment is difficult.

Ulcer Care

- Wash the leg with mild soap or diluted solutions of liquid household bleach (1 tablespoon in 1 gallon of water). Then gently use gauze or a cotton swab to remove slough from the ulcer base.
- Wet-to-dry dressings will help debride necrotic tissue to achieve a clean(er) base. The dressing is applied after soaking it in saline (or diluted household vinegar if a *Pseudomonas* infection is suspected) and allowed to dry on the ulcer. It is then removed (without moistening if possible) to debride the ulcer, and the process is repeated at intervals of 3 to 4 hours. Rest and elevation of the leg are desirable.
- Alternately, the patient can be instructed to have complete bedrest for 7 to 10 days. During the day, wet saline dressings are applied frequently. At night, dry nonstick adhesive dressing is applied and the leg is wrapped with Kerlix dressing.
- Apply cocoa butter or oil over the skin around the ulcer and massage.
- Apply topical antibiotics or antibacterial agents to help reduce local infections and to enhance the development of granulation tissue. Once granulation tissue appears, saline dressings can be used and healing slowly ensues.

Unna's Boot (Zinc Oxide-Impregnated Bandage)

If healing fails to occur and the ulcer is not acutely infected, 2 to 3 weeks of Unna's boot application is recommended. The zinc oxide-impregnated bandage should be applied after cleansing (as previously described) to cover the ankle, the ulcer area, and up to about 3 inches below the knee joint. The boot should be left in place for 1 week. It provides support, protects the ulcer from trauma, and contributes to effective débridement on removal. Three or four applications may be required before there is definite evidence of healing, at which time the use of saline dressings can be continued. Antibiotics or other ointments should not be applied under the Unna's boot bandage because they may react with zinc to produce an allergic reaction.

RGD Peptide Matrix (Argidene Gel™)

A topical viscous gel can enhance healing, providing the extracellular matrix for physical support, the macromolecular scaffold to facilitate the migration of fibroblasts, and endothelial cells and keratinocytes to the wound sites. The gel is applied to cover the wound once a week, and an Unna boot is applied. The procedure is repeated until healing begins.

Transfusions

Blood transfusions can be used when the ulcer does not heal or it progresses with persistent hyperpigmentation and induration of the surrounding skin. Transfusions should be given to raise the hemoglobin to at least 10 g/dL and to reduce Hb S to less than 30 percent. If the ulcer does not heal after 6 months, transfusions should be

discontinued. If healing does occur, transfusions should be gradually discontinued.

Skin Grafts

Skin grafts may be tried for nonhealing recalcitrant leg ulcers and for the patient who does not comply with prolonged medical management. Before plastic surgery, it is necessary to reduce the colony count of bacteria in the ulcer base to less than 10^5/g of tissue by both débridement and the use of local antibiotics.

The patient should be hospitalized and prepared for anesthesia with transfusions (see Chapter 10, Transfusion). Skin grafting can be performed under general or spinal anesthesia. A split thickness graft from the thigh area is recommended. The leg should be immobilized. The patient may be hospitalized for 1 to 2 weeks following surgery.

Free Flaps (Free Tissue Transfer)

Free flaps can be used for patients with chronic leg ulcers that persist for several years. With the advent of microsurgery, free flap grafts may become the procedure of choice for providing sufficient soft tissue for coverage of large recalcitrant ulcers. Flaps include the use of latissimus dorsi muscle, temporoparietal fascia, and split omentum.

These procedures are a method of primary treatment. Patients need meticulous preoperative preparation, aggressive blood transfusion, and continued transfusion in the postoperative period of 3 to 4 months to maintain Hb S at less than 30 percent. In the postoperative period, the leg should be protected from external trauma and edema. Leg elevation, bedrest, and the use of elastic stockings are encouraged. The patient should protect the free flap area with proper shoes such as soft boots to avoid scratching the area. The area around the flap should be well lubricated with baby oil and massaged at least once a day.

CONCLUSIONS

If the patient is unwilling to wait the long periods required for the trials of medical treatment, skin grafting may be the procedure of choice for chronic ulcers. If a breakdown of the graft occurs, a repeat procedure is encouraged. When ulcers heal, the scarred tissue is easily injured. Foot exercise and elevation of the foot are important to improve circulation. Continued cooperation among the patient, the surgeon, and the primary physician is necessary for successful results.

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Chapter 17
Bones and Joints

The bones and joints are frequently involved in sickle cell disease and are the major sites of pain in vaso-occlusive crises. Bone marrow hyperplasia occurs as a result of chronic hemolytic anemia, which can cause bone distortion in childhood, leading to such deformities as tower skull, bossing of the forehead, and gnathopathy (distortion of the maxilla resulting in protrusion of the upper incisors and overlapping of the upper jaw). Probably because the hyperplastic marrow is more vascular than fatty, bone marrow infarction is more common in SS disease than in other forms of sickle cell disease.

In cancellous bones such as the vertebrae, infarction of bone trabeculae in the central part of the vertebral body, supplied by the nutrient artery, causes a collapse of the vertebral plates leading to compression and the classical radiographic appearance of "fish mouth" disc spaces and the "step" sign (a depression in the central part of the vertebral body). Back pain, a common symptom in sickle cell disease, probably indicates a continuation of this process. Occasionally, other cancellous bones are involved such as the metaphysis and epiphysis of long bones involving the adjacent joint, the os calcis causing pain in the heel, and the bones of the face with resulting pain and swelling.

In the long bones, because of the anatomic arrangement of the fine branches of the nutrient artery that penetrate the inner layers of bone to anastomose with vessels that form the periosteum, infarction frequently causes swelling and edema in the overlying soft tissues. This can mimic acute osteomyelitis. The earliest example of this is the hand-foot syndrome in infants that is discussed later in this chapter. Multiple long-bone infarcts occur frequently in sickle cell crises in older children and adults and can be demonstrated by bone scans. When long-bone infarcts heal, they can cause new layers of bone to be laid down in the central cavity, which in radiographs give the appearance of "a bone within a bone." Most patients with SS disease show these changes. An approach to management of a patient with pain in a long bone is outlined (see Chapter 7, Painful Events).

Perhaps the most difficult problem caused by acute pain and swelling of a long bone in sickle cell disease is the differential diagnosis from acute osteomyelitis. Although uncommon, infection must always be considered, but it can usually be ruled out by close clinical observation, blood cultures, and occasionally, aspiration of the affected area (see Chapter 6, Infection). Plain radiographs are not helpful in the early stages and should not be taken routinely. Bone scans are not usually helpful in differentiating a simple infarct from osteomyelitis.

OSTEONECROSIS OF THE FEMORAL AND HUMERAL HEADS (ASEPTIC NECROSIS)

This condition affects patients with all types of sickle cell disease. The hips and shoulder joints are about equally affected, although weight bearing makes femoral head necrosis more likely to cause severe disability. Although osteonecrosis can occur at any age (the earliest reported case was in a child age 3 years), a recent prospective study of a large number of patients by the Cooperative Study of Sickle Cell Disease showed a peak incidence in Hb SS patients between ages 25 and 35 years and at a slightly older age in patients with Hb SC disease and $S\beta^+$ thal. The natural history of osteonecrosis in sickle cell disease has yet to be studied in a prospective fashion; it is clear that when the disease occurs before closure of the epiphyses, considerable healing can occur. However, patients in their late teens and early twenties presenting with the early development of a crescent sign (a fracture line within the necrotic femoral head beneath the cartilage) may have total collapse and destruction of the head, with persistent pain and difficulty in walking within a few months. In older patients, sclerosis and even some considerable deformity of the femoral head apparent on the radiograph may persist with little change for many years without causing much discomfort or disability.

The diagnosis of aseptic necrosis of the femoral head is usually made when the patient complains of intermittent or persistent pain in the groin or buttock. Occasionally, there may be an acute synovitis mimicking a septic arthritis. Any attempt to move the joint through its range of movement is resisted because of acute pain. Radiographs should be taken in the AP and "frog leg" positions and examined for evidence of changes in the bone density of the femoral head. In the early stages, however, the radiographs may appear normal. The earliest changes associated with pain can be detected by MRI and radionuclide imaging. If there is bilateral disease, however, the radionuclide scans may be difficult to interpret. MRI is very sensitive and can detect small areas of necrosis several months before symptoms occur; it frequently reveals bilateral disease when symptoms are still unilateral.

Total hip replacement has no place in the management of early osteonecrosis. Presently, initial treatment consists mainly of avoidance of weight bearing and judicious use of local heat and analgesics for pain relief up to 6 months. This is particularly important in children and teenagers for whom a considerable healing potential exists. In children, osteotomy with rotation to change the area of the head subjected to weight has been used in the past with variable results. For older patients with persistent hip pain and a positive MRI but without radiological evidence of collapse, core decompression of the femoral head performed by an orthopedic surgeon experienced in this technique can sometimes result in immediate pain relief.

For an individual beyond adolescence who is severely incapacitated by hip pain and who cannot carry out activities of daily life and requires relief, surgical replacement of the entire joint must be considered, even when the patient is in his or her early twenties. The patient should be made aware that hip replacement is not always successful in eliminating symptoms and in restoring function in sickle cell disease patients; also, loosening and other complications may necessitate revision (removal

and insertion of a new prostheses) at a later date. Infection is uncommon, but if removal of the prosthesis later becomes necessary because of infection, reinsertion is unlikely to be successful and is rarely considered.

Aseptic necrosis of the shoulder may be quite disabling, especially in a person who needs to use both arms continuously at work. Although most painful shoulders settle down with NSAIDs, surgical intervention is occasionally warranted and can result in pain relief and improved range of movement.

HAND-FOOT SYNDROME

The hand-foot syndrome is a fairly common phenomenon that is seen almost exclusively in the infant and young child. It presents with pain, low-grade fever, and diffuse nonpitting edema of the dorsum of the hands and feet, which extends to the fingers and toes. One to four extremities may be affected at one time.

Radiographic changes of elevation of the periosteum and necrosis are seen in the metacarpals and phalanges or metatarsals but may not appear for 1 week or more. The syndrome is best treated with analgesia, hydration, and parental reassurance. In spite of the often striking radiographic changes and swelling that may persist for several weeks, the syndrome is almost always self-limited, and bones usually heal without permanent deformity. Transfusions, antibiotics, and other measures are not necessary, but it should be noted that early osteomyelitis can have a similar presentation. Therefore, it is recommended that in the presence of fever and marked inflammation, or if there is no clinical improvement in 2 to 3 days, the patient should be evaluated for osteomyelitis with appropriate blood cultures and direct aspiration of the area involved.

OTHER BONE AND JOINT SYNDROMES

The differential diagnosis of joint effusions in patients with sickle cell disease is difficult because of a variety of possible etiologies. Effusions and periarticular swelling can occur secondary to synovial infarction or infarction in the end of the adjacent long bone. The knee is a common site. Gout, septic arthritis, osteoarthritis, or rheumatic or collagen vascular disease should be considered and ruled out by appropriate tests. Because treatments for these disorders differ, it is important to aspirate the joint for culture, protein, and microscopic analysis if the patient is febrile or there are signs of marked inflammation. Such a tap should be performed in the hospital by an experienced physician. If evidence for a coexistent disease is obtained, it should be treated as in other patients.

In the absence of clear diagnostic findings (bacteria or uric acid crystals), simple supportive measures, including analgesia, local heat, hydration, and bedrest for 5 to 7 days, are indicated. NSAIDs are often very effective for 4 to 6 days and may be tried in teenagers or adults with normal renal function. Other anti-inflammatory agents may also be useful, but proper precautions should be taken to avoid gastric irritation. If signs of effusion persist, radiographic studies should be obtained, and joint fluid analysis may have to be repeated.

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Chapter 18
Renal

Clinical and pathologic data indicate that intravascular sickling occurs more readily in the kidney than in any other organ. A series of progressive and random pathologic events involving the kidney begins early in the first decade of life in a patient with sickle cell disease and continues throughout life. The distribution of blood flow in the kidney and the hypertonicity of the renal medulla create a situation where red blood cells containing sickle hemoglobin undergo deoxygenation in an acidic and hyperosmolar environment that causes them to sickle more easily. The combination of hypoxia, hypertonicity, and acidosis in the renal medulla leads to stasis in the vasa recta and to ischemia of the renal medulla and papillary tip. Distortion of regional blood flow, focal interstitial nephritis and fibrosis, tubular dysfunction and atrophy, and papillary necrosis result. Table 4 indicates the progressive renal events that can occur in each decade of life in association with sickle cell disease.

HYPOSTHENURIA

The earliest and most common renal defect in sickle cell disease is hyposthenuria, which is expressed as an inability of the kidney to maximally concentrate the urine. It is almost universally evident by the time the patient with SS disease reaches age 3 years. This condition results in an obligatory urinary output of greater than 2,000 ml/day—in effect, a form of nephrogenic diabetes insipidus. The resultant increased fluid requirement renders the patient much more susceptible than the normal individual to dehydration, which is a precipitating cause of vaso-occlusive crises. A liberal fluid intake should be ensured, to provide for both the obligatory urinary water loss and normal daily fluid requirement. The abnormality of the renal medulla may render the patient hyporesponsive to "loop" or osmotic diuretic agents such as furosemide or mannitol, respectively. Hyposthenuria also frequently gives rise to nocturia (enuresis in the child). When the latter occurs, other causes should also be considered. Hyposthenuria is also seen in individuals with Hb AS (see Chapter 22, Sickle Cell Trait.)

RENAL TUBULAR DYSFUNCTION

Patients with sickle cell disease are unable to acidify their urine maximally when they are subjected to acid loading, and this can sometimes lead to significant systemic acidosis. If metabolic acidosis is found in a patient with sickle cell disease, renal hydrogen ion excretion should be evaluated to determine whether it plays a role in the process. If it is present, it should be corrected by judicious therapy with sodium bicarbonate. Impaired renal tubular potassium excretion has also been described in sickle cell disease and, in some cases, can

Table 4

Progressive Renal Events in Sickle Cell Disease

First Decade	Second Decade
Decreased medullary blood flow	Microscopic papillary necrosis
Nocturia	Loss of vasa recta
Enuresis	Renal tubular siderosis
Hyposthenuria	Renal tubular acidosis
	Irreversible hyposthenuria
Hyperfiltration	Potassium excretion defect
	Proteinuria
	Bacteruria
	Hematuria

Third Decade	Fourth Decade and Beyond
Macroscopic papillary necrosis	Renal failure
Interstitial nephritis	
Membranoproliferative glomerulonephritis	
Decreased renal blood flow, glomerular filtration rate (GFR)	
Nephrotic syndrome	
Pyelonephritis	
Decreased urate clearance	
Hypertension	

SOURCE: Thompson A, Lessin L, Antonovych T. The sickle cell nephropathies. In: Fried W (ed). *Comparative clinical aspects of sickle cell disease*. New York: Elsevier, 1982.

result in a tendency toward modest hyperkalemia, which is hyporesponsive to kaliuretic agents such as furosemide. Hyperkalemia can increase as patients age. When the amount is significant (K ≥ 5.5 meq), other causes should be sought. Spurious hyperkalemia may result from hemolysis and/or thrombocytosis.

HYPERURICEMIA

About 15 percent of children and 40 percent of adults with SS disease have high-normal or elevated serum uric acid levels. This condition is due to the increase in urate production associated with accelerated erythropoiesis coupled with a decreased renal clearance of urate. Hyperuricemia in SS disease responds poorly to uricosuric agents, but the uric acid level can be lowered with the use of allopurinol. Uric acid nephropathy is rare, but if recurrent uric acid stone formation occurs, urinary alkalinization with oral sodium bicarbonate is recommended. Clinical gout is uncommon in sickle cell disease. When it is demonstrated by the presence of intracellular uric

acid crystals in joint fluid, it is treated with NSAIDs and allopurinol.

GROSS HEMATURIA

Gross hematuria occurs commonly in sickle cell disease. Less commonly, it also occurs in sickle cell trait (although the larger number of AS persons make them more frequent visitors to medical facilities). The bleeding is usually painless, although clot formation in the renal pelvis or ureter can produce renal colic. It is frequently unilateral, with the left kidney being involved in 80 percent of the cases. It can show a pattern of intermittency, lowgrade chronicity, or persistence. The pathogenic mechanism is thought to be sickling in the vasa recta, which leads to stasis and ischemia, with extravasation of blood into the renal parenchyma and collecting system, or in some cases to micropapillary or macropapillary necrosis. As with all patients who have hematuria, the differential diagnosis in patients with sickle cell disease includes papillary necrosis, glomerulonephritis, tuberculosis, tumor, stones, and urinary tract infection. Bleeding disorders should also be considered. Evaluation can require renal ultrasonography, intravenous pyelography (with adequate prehydration), cystoscopy, urine culture, and measurements of coagulation and hemostatic function.

Good hydration should be maintained with a urine flow in excess of 2 to 3 ml/kg/hr to decrease the tendency to clot in the renal pelvis and ureter. In the presence of refractory hematuria, patients should be treated with epsilon aminocaproic acid (EACA) at an oral dosage of 2 to 8 g/day. The principal danger of this therapy is the formation of clots in the renal pelvis and ureter. Therefore, when EACA is used, the patient should be hospitalized and placed at bedrest, and high urine flow (> 3 ml/kg/hr) should be maintained. Ferrous sulfate should be given to correct documented iron deficiency.

Transfusion can be indicated both for a falling hematocrit and for reducing the propensity for occlusion of the medullary vessels. When hematuria is chronic and severe, patients should have bedrest with high fluid intake, and exchange transfusion should be considered with or without EACA therapy. Every measure should be taken to avoid nephrectomy for hematuria in patients with sickling disorders because the contralateral kidney remains at risk for sickle cell-related complications. Nephrectomy is warranted only for a life-threatening exsanguinating hemorrhage.

RENAL PAPILLARY NECROSIS

Renal papillary necrosis is a relatively common finding in patients with sickle cell disease. It can be asymptomatic or accompanied by hematuria or proteinuria. Irregularities or "pseudodiverticuli" of the renal papillary tips seen on intravenous pyelograms (IVP) have been reported in about 50 percent of adults with sickling disorders. The etiology is identical to that described for hematuria. The disorder is usually asymptomatic and is most commonly diagnosed at the time of an IVP. It is believed that the ischemia or necrosis of the renal papillary tip as well as the associated interstitial nephritis, which can also be caused by heavy ingestion of certain analgesics (e.g., aspirin, acetaminophen, and NSAIDs), may cause increased susceptibility of patients with sickle cell disease to pyelonephritis.

URINARY TRACT INFECTION

Asymptomatic bacteriuria and symptomatic urinary tract infections are common in sickle cell disease patients. Radiologic changes are often difficult to differentiate from interstitial nephritis due to ischemia or analgesic nephropathy.

Because women with sickle cell disease may be at greater risk for pyelonephritis, frequent urinalyses and periodic urine cultures with colony counts may be useful as a routine surveillance measure. Significant bacteriuria (> 10^5/mL) and documented pyelonephritis should be treated with appropriate antibiotic therapy, and repeat cultures should be obtained to confirm "sterilization" of the urine. Initiation of antibiotic therapy with trimethoprim-sulfa or ampicillin is recommended; on the basis of culture and sensitivity data, therapy should then be modified. Blood cultures should be obtained on febrile patients with suspected pyelonephritis. Individuals who have had a single bout of pyelonephritis should have careful long-term monitoring, including repeat urinalyses, cultures, and renal function studies. With an initial bout of pyelonephritis or with recurrence in a previously unstudied patient, an IVP should be done, possibly in consultation with a urologist, to exclude a predisposing or resultant anatomic defect in the urinary tract. In children, a voiding cystourethrogram may be indicated. Patients with persistent or recurrent pyelonephritis should be considered for long-term antibiotic therapy (see Chapter 6, Infection).

PROTEINURIA AND NEPHROTIC SYNDROME

Approximately 25 percent of adult patients with SS disease have chronic proteinuria due to hyperfiltration, glomerulopathy, and glomerular capillary hypertension. Nephrotic syndrome associated with a membranoproliferative glomerulonephritis has been described in patients with SS disease. If proteinuria persists for more than 4 weeks, it should be evaluated with 24-hour urinary protein quantitation and creatinine clearance. In the presence of prenephrosis (24-hour urine protein > 2.0 g/24 hrs or nephrotic syndrome (protein > 3.0/24 hrs, hypoalbuminemia, hyperlipidemia, and edema), the patient should be referred to a nephrologist for evaluation and possible renal biopsy. When biopsies are done, pathologic examination should include immunohistology (IgG, C^1, IgM, and anti-renal tubular epithelial antigen) and electron microscopy to establish the histologic diagnosis.

HYPERTENSION

Persistent elevation of diastolic blood pressure in patients with sickle cell disease usually signals underlying renal disease. It occurs in fewer than 5 percent of individuals with sickling disorders and increases with advancing age. Although the hypertension appears to be renoprival in nature, plasma renin levels are variable. Evaluation of hypertension in the patient with sickle cell disease is the same as in other individuals. Transient hypertension may occur during painful episodes and following red blood cell transfusions.

Therapy for hypertension in patients with sickling disorders differs from that used for other individuals. Diuretics generally are to be used with caution, particularly in younger patients because dehydration may provoke a vaso-occlusive crisis. The natriuretic response to loop diuretics is

decreased, particularly in older patients. Initial therapy with beta-adrenergic blockers or calcium channel inhibitors is preferred, and the dosage must be individualized. In hypertensive patients with significant proteinuria, angiotensin-converting enzyme inhibitors may both control hypertension and reduce proteinuria by decreasing glomerular capillary hypertension.

Due to the compensatory alterations of cardiovascular function in sickle cell disease patients, the deleterious effects of hypertension on the heart and vascular system are likely to be amplified. When congestive heart failure is present in the hypertensive sickle cell patient, afterload reduction therapy is indicated. Because the risk of stroke is increased in sickle cell disease and arterial aneurysms of the circle of Willis may appear as early as the second decade, effective control of blood pressure is imperative.

CHRONIC RENAL FAILURE

Chronic renal failure in sickle cell disease is associated with end-stage renal disease due to one or a combination of the sickle cell nephropathies discussed above. Chronic renal failure occurs in a small percentage of patients with sickling disorders, and its prevalence in sickle cell disease appears to be greater than among the general African-American population. When it is associated with metabolic acidosis without significant hyperkalemia and with BUN levels less than 80.0 mg/mL and creatinine less than 4.0 mg/mL, patients can usually be managed with conservative measures, including oral sodium bicarbonate, oral phosphate binders such as Amphojel®, and a low-protein diet. In this instance, BUN, creatinine, electrolytes, and acid-base balance should be carefully monitored. Drugs with altered pharmacokinetics in the presence of renal failure should either be avoided or have dosages appropriately modified. As renal failure progresses, the patient should be referred for dialysis or possible renal transplantation.

Sickle cell disease is not a contraindication for hemodialysis or renal transplantation. Sickle cell disease patients who have received renal homografts may experience more frequent pain crises due to increased hematocrit driven by erythropoietin produced by the graft kidney. Recurrent sickle cell nephropathy in the transplanted kidney has been reported.

In some patients, the increased anemia found with chronic renal failure causes cardiopulmonary complications and necessitates a chronic transfusion program. Treatment with recombinant erythropoietin (EPO) improves the anemia of renal failure in nonsickle cell disease patients; however, there are no large studies of the use of EPO in Hb SS patients with renal failure. The experience with a few of these patients so far indicates that large doses of EPO (300 - 350 U/kg three times a week) may be required to induce a significant increase in hematocrit or to alleviate a transfusion requirement.

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Chapter 19

Priapism

Priapism is a persistent, painful penile erection. Three clinical categories are discussed in this chapter, including recurrent acute priapism, acute prolonged priapism, and chronic priapism.

RECURRENT ACUTE PRIAPISM

This is the most common form of priapism in which the patient gets short attacks that subside spontaneously. The patient usually copes with this problem and may not seek medical advice. The natural history is variable. Most patients will continue to get attacks throughout their lives and will maintain some degree of potency. Others will eventually become impotent. A small group will develop an acute attack that will not subside without active and aggressive treatment in a timely fashion.

ACUTE PROLONGED PRIAPISM

The painful erection that does not subside after several hours is an emergency and should be treated aggressively. If untreated, the attack will last for several weeks, resulting in total impotence. Even with aggressive treatment, preservation of potency may be compromised. The presenting features are persistent erection, severe pain, and tenderness of the penile shaft. Radionuclear penile scan may show a very low flow, and penile blood gas may have a pO_2 of less than 5.

CHRONIC PRIAPISM

This is a rare form of presentation that may follow an acute episode or may arise de novo. The penis is semierect and there is no pain. Clinically, this results in a progressive increase in the size of the penis, and penile scan shows good blood flow. Penile ultrasound shows dilated deep dorsal arteries in both corporeal bodies, and the patient has difficulty in getting a complete erection. Occasionally these patients may develop an acute episode. Suddenly for no apparent reason the penis becomes rigid and painful. These episodes may affect only a part of the penile shaft.

PATHOPHYSIOLOGY

The specific mechanisms that precipitate attacks of acute priapism in patients with sickle cell disease are unknown. Acute attacks often start during sleep, occasionally following sexual activity, but frequently no identifiable event is noted. An unusually full bladder is commonly associated with the onset of nocturnal attacks. Some episodes appear to be triggered or exacerbated by dehydration.

Some patients with priapism have preservation of flow to the glans and spongiosal tissue. Venous outflow from the corpora cavernosa is not always totally occluded as had been earlier postulated. These facts establish the rationale for transfusing

normal red cells because these cells can be expected to gradually reach areas of poor circulation. Alternatively some patients may have tricorporal priapism, which is more severe.

Presumably, a viscous mass of deoxygenated and damaged red cells develops that further impairs or occludes outflow. Edema and inflammation can result. Evacuation of this material can delay irreversible damage to the corpora cavernosa. Hemoglobin electrophoresis of penile blood in transfused patients occasionally shows that no Hb A has entered the corpora cavernosa. These observations establish the rationale for aspiration and irrigation and for the temporary corpora spongiosum shunt procedure currently in use (see Winter procedure below).

GENERAL MANAGEMENT

The goals of management are to assist with emptying the corpora cavernosa, relieve the patient's pain, and, if possible, prevent impotence. As with other inflammatory events in sickle cell disease, fever and leukocytosis can occur in the absence of infection. Nevertheless, infectious etiologies should be ruled out.

Recurrent Acute Priapism

Patients often manage this condition at home. Emptying the bladder, warm baths, and exercise are all recommended techniques. The patient should be encouraged to empty the bladder frequently once the attack has begun. At the same time, however, the patient should be encouraged to increase oral intake of fluid to offset any possible contribution of systemic dehydration. If the episode does not resolve in 3 hours, the patient should seek medical attention.

Acute Prolonged Priapism

Possible etiologies for this pattern should be sought. These include infection (particularly of the prostate), recent trauma, medications with autonomic effects, alcohol excess, marijuana use, or sexual activity.

Initial treatment of acute, prolonged priapism should include rigorous intravenous hydration, parenteral narcotics to relieve pain, and if necessary, insertion of a Foley catheter to promote bladder emptying. In addition, preparations should be made to reduce the percentage of sickle cells to less than 30 percent while maintaining the hematocrit below 35 percent. This objective can most effectively be accomplished by exchange transfusion. Patients who are likely to respond to transfusion regimens begin detumescence within 1 or 2 days, although complete detumescence may take weeks to months. There are reports of cerebrovascular hemorrhage in children following exchange transfusions for priapism.

Concepts in the surgical treatment of severe priapism in sickle cell disease are currently changing toward a simpler procedure and much earlier intervention. Opinion is not yet uniform, but recent studies suggest that if detumescence has not begun within 24 hours following completion of transfusion therapy, a significant response to transfusion alone is unlikely. In this case, a penile aspiration should be tried first; if this is not successful, a Winter procedure (spongiosum-cavernosum shunt) or a Hashmat shunt are recommended under local anesthesia in adults or, preferably, general anesthesia in children. A saphenous shunt is no longer recommended.

Despite interventions, impotence remains a frequent complication of priapism. For incapacitating recurrent priapism, a trial of

chronic transfusions for 3 to 6 months is often successful.

MANAGEMENT OF IMPOTENCE

Although the patient is not suffering with pain, erectile function is often absent or impaired. Management of impotence by implantation of a prosthesis has been performed by some urologists. Other patients, however, are able to adjust to the altered sexual function, usually with the support of an accommodating partner, because ejaculation, orgasm, and fertility remain intact. Surgical intervention is rarely needed in prepubertal boys.

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Chapter 20
Heart

The anemia of SS disease is usually well tolerated by the cardiovascular system for long periods. However, like other moderately severe anemias, cardiac function is ultimately affected. Physicians caring for patients with SS disease should be aware of cardiovascular involvement in these patients because the physician may be confronted with a variety of symptoms and physical findings similar to ventricular abnormalities, valvular dysfunction, and myocardial ischemia, which pose diagnostic and therapeutic difficulties.

CARDIAC FUNCTION

The reduced oxygen-carrying capacity due to anemia increases demand on the heart with an increased cardiac output. This chronic volume overload initiates compensatory responses, primarily cardiac enlargement. Although both dilation and hypertrophy frequently occur, systolic and diastolic performance of the left ventricle in the resting state is usually preserved. However, with radionuclide imaging studies and echocardiographic-derived indices, abnormalities in contraction and relaxation may be identified. In patients with these abnormalities, reduced peripheral vascular resistance maintains normal left ventricular systolic performance (as measured by ejection fraction).

In the absence of coexistent cardiovascular disease, overt left ventricular failure is unusual in patients with sickle cell disease. However, symptoms such as dyspnea, palpitations, and easy fatigability frequently seen in these patients may lead to clinical misdiagnosis of heart failure. Without documented evidence of failure, treatment of symptoms with digitalis and diuretics is not indicated, and transfusion should be considered if the hemoglobin concentration is quite low. Right ventricular enlargement is less common and usually occurs in patients with pulmonary hypertension, which is a consequence of recurrent pulmonary artery thrombosis.

CHILDREN

Insights into the adaptation of children and adolescents to chronic anemia have been gleaned primarily from echocardiographic studies. Children with SS disease and hemoglobin levels in the range of 6 to 8 g/dl increase cardiac output at rest by 50 percent to meet the need for oxygen delivery to the tissues. This increase is achieved primarily through larger stroke volume, which results in the clinical findings of hyperdynamic circulation, heart murmur, and cardiomegaly. Cardiomegaly is a healthy adaptation to anemia and should not by itself be considered pathologic. Few children develop congestive heart failure in the absence of a sudden and profound decrease in hemoglobin concentration. Correction of severe anemia may require

exchange blood transfusion (see Chapter 10, Transfusion). Most children and adolescents with sickle cell anemia successfully adapt to the increased cardiac demands posed by chronic anemia and usually have a reduced exercise capacity of 50 to 75 percent of that of unaffected children. Unlike adults, they are less likely to admit to exercise intolerance.

Because there is no evidence that exercise is harmful, and the beneficial effects of exercise are well known, children with sickle cell disease are encouraged to participate in physical activities and to set their own limits. If exercise-related symptoms occur, they should be evaluated with exercise electrocardiography. Fifteen percent of adolescents performing exercise stress tests develop S-T depression on electrocardiogram due to subendocardial ischemia.

It is important to remember that children with SS disease are subject to the same medical conditions as other children, and findings that might suggest congenital, rheumatic, or other underlying heart disease should be investigated. In such cases, heart function is most reliably assessed by echocardiography and a cardiology consultation.

ADULTS

Exercise Performance

Exercise capacity is reduced in most patients with SS disease. Most are able to achieve less than 50 percent of maximum predicted workloads. The cause for this decreased physical performance is likely multifactorial, and the role of cardiac dysfunction in this reduced work capacity is unclear. A significant number of these patients undergoing symptom-limited exercise testing develop S-T-segment depression on EKG, which appears to relate to older age, low level of hemoglobin, and the product of heart rate and systolic blood pressure. As described in children, these changes are due to subendocardial ischemia but are not associated with pain. Atherosclerotic coronary obstruction is unlikely to be the cause.

For patients seeking advice on exercise, participation in noncompetitive recreational activities should not be discouraged. However, exercise should not be performed to the point of exhaustion. The same general principle applies to work; that is, employment requiring a modest but not an exhausting degree of exertion is acceptable. Specific recommendations for conditioning exercise or training cannot be made at this time because of lack of available data. Exercise under adverse conditions, for example, cold weather, high altitude, or cold water exposure, should be avoided.

Valvular

Systolic murmurs are common in patients with SS disease, are usually best heard in the second and third intercostal spaces, and are a consequence of the increased cardiac output. However, basal diastolic murmurs are rare and should be considered pathologic when present. Structural valvular deformities do not appear to be increased in this disease. The prevalence of mitral valve prolapse has been reported to be high in patients with SS disease; however, this finding was not confirmed by the Special Cardiac Study of the Cooperative Study of the Clinical Course of Sickle Cell Disease.

Diagnostic Testing

- *Doppler echocardiography* is recommended to assess a cardiac murmur suspected to be pathologic in origin.
- *Resting and stress cardiac imaging studies (radionuclide or echocardiographic)* are useful in determining cardiac chamber dimensions and global systolic function of both right and left ventricles.
- The utility of *exercise testing* in patients with exercise-induced chest pain is limited because exercise-induced EKG changes may not represent coronary obstructive disease. In individuals suspected of having coronary artery disease, this procedure should be supplemented with *thallium myocardial perfusion scanning* or *dobutamine stress echocardiography.*
- *Cardiac catheterization* using contrast media has been performed safely in small numbers of patients with SS disease after partial exchange transfusion. Experience with this invasive procedure in sickle cell disease is limited and should be reserved for those patients in whom there is a high index of suspicion for the diagnosis of significant epicardial coronary artery disease and whose cardiac status cannot be satisfactorily evaluated by noninvasive testing. Dehydration resulting from the diuretic effect of the hypertonic contrast media must be avoided. Use of *nonionic* contrast material may prevent this complication.

Myocardial Infarction

Clinical and autopsy studies in adult patients demonstrate the infrequent occurrence of myocardial infarction in individuals with SS disease. Coronary anatomy in these patients is remarkable for the absence of significant atherosclerosis. However, a postmortem study of 70 patients with SS disease revealed that 17 percent had myocardial infarction or fibrosis despite normal coronary arteries. Recently, a group of patients with acute chest pain during sickle cell pain crisis was described with clinical evidence of myocardial ischemia or infarction. The role of red cell sickling in the pathogenesis of this phenomenon is unclear. Coronary spasm, as a secondary event of sickling, has been suggested as a mechanism. Although coronary insufficiency is rare in patients with sickle cell disease, an electrocardiogram and cardiac enzymes should be obtained on all adult patients hospitalized with vaso-occlusive episodes and chest pain suggestive of myocardial ischemia or infarction. Sickle cell anemia is normally associated with dilated coronary arteries free of atherosclerotic plaque; however, newer diagnostic tests suggest that this does not preclude the development of myocardial ischemia or infarction.

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Chapter 21

Surgery and Anesthesia

Patients with sickle cell disease who undergo surgery have an increased risk of perioperative complications. Careful preoperative preparation of the patient by a team consisting of a surgeon, hematologist, and anesthesiologist will minimize or eliminate these complications.

PREEXISTING HEALTH OF THE PATIENT

Patients with organ damage and/or coexistent disease must be identified because they are at increased risk for perioperative complications.

In particular, older patients, those with a history of pulmonary or CNS disease, recurrent hospitalizations, and/or those who have been previously heavily transfused are at high risk for perioperative complications, especially acute chest syndrome and vaso-occlusive events. A physical examination and chart review should be supplemented by the following tests:

- Arterial oxygen pressure or oxygen saturation measured by pulse oximetry.
- Pulmonary function tests with bronchodilator response analysis for patients who have acute chest syndrome, asthma, or other pulmonary complications.
- Echocardiogram.
- Renal and liver functions.

TYPES OF SURGERY

Surgical procedures that have an increased probability of ischemia or hypoxia deserve special attention. These include cardiothoracic surgery; techniques associated with hypotension, hypothermia, and hyperventilation; and vascular surgery.

Laparascopic surgery appears to lower the postoperative complications of sickle cell disease and should be used in appropriate settings.

PREOPERATIVE CARE

All patients should be evaluated by the anesthesiologist the day before surgery. Patients requiring general anesthesia should receive maintenance fluids at least 12 hours before surgery, with strict attention paid to urinary output and weight. Preoperative assessment of the patient should include checking for signs of vaso-occlusion, fever, infection, and dehydration. The laboratory and physical examination results should be reviewed to identify abnormalities in the heart, liver, kidneys, brain, and lungs.

INTRAOPERATIVE MANAGEMENT

All patients should be monitored with at least an EKG and have a determination of inspired oxygen concentration by pulse oximetry or blood gas testing. Measurements of electrolyte and urine output and invasive hemodynamic monitors

may be required, depending on the patient's clinical status and the type of surgery. A warm temperature should be maintained in the operating room. General anesthesia should aim for a mild respiratory alkalosis (pH about 7.45) and a normothermic, well-hydrated patient. The patient should receive a minimum of 50 percent oxygen in combination with the anesthetic agent. Blood replacement for significant intraoperative blood loss is recommended. Intraoperative blood salvage techniques (cell savers) are not recommended.

Postoperatively, oxygen should be administered until the effects of anesthesia have worn off. Patients who have surgical wounds that interfere with respiration may require an extended use of oxygen. Continued monitoring by oximetry is recommended in the recovery room and/or intensive care unit. Postoperative parenteral hydration should keep the patient at 1 to 1½ times maintenance. Aggressive respiratory care is necessary in sickle cell disease to minimize pulmonary complications.

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Chapter 22
Sickle Cell Trait

Sickle cell trait is not a disease. It is not a cause for abnormalities in the blood count and does not produce vaso-occlusive symptoms under physiologic conditions. Sickle cell trait does not adversely affect the individual's life expectancy.

Sickle cell trait (AS) is a heterozygous condition in which the individual has one beta^S gene and one beta^A globin gene, resulting in the production of both Hb S and Hb A with a predominance of Hb A. Sickle cell trait is found in 8 percent of the American Black population. The diagnosis should be established by hemoglobin electrophoresis. Persons who have more Hb S than Hb A on electrophoresis (and have not been transfused) have Hb Sβ^+ thal and not sickle cell trait.

Hemoglobin electrophoresis is used to screen persons for sickle cell trait and will also detect persons with sickle cell disease and heterozygotes (carriers) for other hemoglobin disorders such as Hb C. Like sickle cell trait, hemoglobin C trait produces no hematologic abnormalities aside from a few target cells on blood smears. Hemoglobin C trait is not detected by solubility testing or by a sickle cell preparation.

Sickle cell trait has been associated with several clinical conditions, including hyposthenuria, painless hematuria, and an increased risk of urinary tract infection during pregnancy. Hematuria in persons with sickle cell trait must be evaluated thoroughly to exclude other causes, as in other patients. Traumatic hyphema in individuals with sickle cell trait requires special management (see Chapter 12, Eye).

When individuals with sickle cell trait become hypoxic, they rarely develop symptoms related to vaso-occlusion. A recent retrospective study of military recruits showed an increased risk of sudden death following extreme exertion during basic training in soldiers with sickle cell trait compared with individuals with only Hb A. The magnitude of the increased risk was very small (32 per 100,000 compared with 1 per 100,000 for recruits with Black parents who had normal hemoglobin) and appeared to be related to the recruit's age. No increased risk of sudden death has been reported in civilians, including those who participate in athletics. Changes in training programs for recruits seem to have reduced the problem of sudden death during basic military training. There appears to be no increased risk for individuals with sickle cell trait who undergo general anesthesia. However, splenic infarction has been reported as a result of flying above 15,000 feet in unpressurized aircraft.

Individuals with sickle cell trait should receive informative and nondirective genetic counseling. Before counseling couples, it is important to perform hemoglobin

electrophoresis and Hb A_2 and Hb F measurements on both prospective parents. In parents who are not carriers of an abnormal hemoglobin, measurements of Hb A2 and Hb F are needed to identify thalassemic conditions. When both parents have sickle cell trait, they have a 25 percent chance with each pregnancy of having a child with SS disease. If one parent has sickle cell trait and the other has a beta thalassemic disorder, they are at the same risk for having a child with a sickle beta thalassemia syndrome. In couples where one individual has sickle cell trait and one has hemoglobin C trait, the chance of having a child with Hb SC disease is also 25 percent with each pregnancy. If one parent has SS disease and the other has sickle cell trait, the risk of having a child with SS disease is 50 percent with each pregnancy (see Chapter 14, Prenatal Diagnosis, for further discussion).

In rare cases, individuals thought to have sickle cell trait subsequently were shown to have sickle hemoglobin plus another hemoglobin variant. In at least one instance (Hb S-Antilles), the "S" molecule actually had two amino acid substitutes in the same β chain. Thus, in cases where symptoms occur in an individual thought to have sickle cell trait, careful confirmation of laboratory diagnosis is essential.

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Chapter 23

Experimental Therapy

The lifespan of patients with SS disease has increased significantly in the past 30 to 40 years, partly because of improvements in the general health of all citizens and therapeutic approaches described in earlier chapters. Today, the median survival of Hb SS patients is about 45 years. Further improvements in the quality of life and of the lifespan will come from treatments such as penicillin prophylaxis and others that must be considered experimental at the present time. Faced with severely ill patients who have the most to gain and the least to lose from experimental therapy, health providers and patients must consider the options available. Patients should be involved in a therapeutic trial whenever possible. In all cases, patients must be carefully informed of potential risks and benefits of the proposed therapy. Treatment should be carried out by physicians with experience in sickle cell disease, the use of the therapy involved, and in the conduct of experimental therapeutic trials.

HYDROXYUREA

Fetal hemoglobin (Hb F) interferes with the polymerization of Hb S in solution and with the sickling of Hb SS red blood cells. Hydroxyurea, a cytotoxic chemotherapeutic agent, was shown to augment Hb F production in SS patients in a preliminary trial, without serious toxicity. To date, no trials have been carried out in patients with SC disease or Sβ thal. The mechanism of action is still unclear but probably involves altered proliferation of early red blood cell precursors capable of increased Hb F synthesis. A double-blind multicenter trial has recently concluded that use of the drug can reduce the frequency of painful episodes by almost 50 percent. With long-term risks poorly understood, the caveats described above should be followed. Other drugs such as erythropoietin and butyrate derivatives may be capable of augmenting Hb F production by other means. Their role in therapy, alone or combined with hydroxyurea, is still unclear.

BONE MARROW TRANSPLANTATION

Successful bone marrow transplantation can cure sickle cell anemia, and initial reports from Europe suggest that transplantation can be carried out with relatively low morbidity and mortality. Most investigators agree that transplantation should be considered for severely affected children; the dilemma is that severely affected patients are poor risks for an arduous procedure. At present, unrelated donors should not be used, and the availability of compatible sibling donors is limited. A national collaborative study of transplantation in pediatric patients in the United States, with strictly defined criteria for eligibility, is currently under way; preliminary

results are somewhat encouraging. Umbilical cord blood may prove to be an important resource for stem cell transplantation in sickle cell disease.

It is hoped that such studies will permit a definition of risk factors and improved eligibility criteria for bone marrow transplantation in Hb SS patients just as risk factors and eligibility criteria for bone marrow transplantation have been defined for patients with thalassemia major. Cost-benefit analyses, in terms of health and well-being of patients and financial outlays for individual patients and for society as a whole, also will emerge from this ongoing research.

PROPHYLACTIC TRANSFUSION TO PREVENT STROKE

Transcranial Doppler studies can demonstrate arterial narrowing in SS patients who subsequently have strokes. A randomized trial is currently under way to determine whether chronic transfusion therapy can prevent first strokes in children with abnormal Doppler studies.

GENETIC ENGINEERING

Once fanciful, gene therapy now seems a very possible future development. Basic laboratory studies are under way, but it appears unlikely that application to patients will be possible for a number of years.

IMPORTANCE OF ONGOING CLINICAL RESEARCH

The foregoing chapters reaffirm that our current therapy provides patients with sickle cell disease some solace but not enough to prevent an uncertain future. Most of our patients and their families know the current therapeutic limitations; however, knowledge that new treatments are under active investigation may make that burden somewhat lighter and provide them with reason to hope.

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U.S. DEPARTMENT OF HEALTH AND
HUMAN SERVICES

Public Health Service
National Institutes of Health

NIH Publication No. 95-2117
December 1995