THE MANAGEMENT OF SICKLE CELL DISEASE

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Contents

SPECIAL TOPICS

Preface

Enclosed is the fourth edition of a book that is dedicated to the medical and social issues of individuals with sickle cell disease. This publication, which was developed by physicians, nurses, psychologists, and social workers who specialize in the care of children and adults with sickle cell disease, describes the current approach to counseling and also to management of many of the medical complications of sickle cell disease.

Each chapter was prepared by one or more experts and then reviewed by several others in the field. Additional experts reviewed the entire volume. This book is not the result of a formalized consensus process but rather represents the efforts of those who have dedicated their professional careers to the care of individuals with sickle cell disease. The names of the authors, their affiliations, and their e-mail addresses are listed in the front of the book.

Multiple new therapies are now available for children and adults with sickle cell disease, and often the options to be chosen present a dilemma for both patients and physicians. This book does not provide answers to many of these newer questions but rather explains the choices available. The book, which focuses primarily on the basic management of indiv-

iduals with sickle cell disease and provides relevant online resources at the end of the chapters, is to serve as an adjunct to recent textbooks that delve more deeply into all aspects of the disorder.

The authors hope that this book will be used by medical students, house staff, general practitioners, specialists, nurses, social workers, psychologists, and other professionals as well as the families and patients who are coping with the complexities of sickle cell disease on a daily basis. The book, any part of which can be copied freely, will be placed on the National Heart, Lung, and Blood Institute (NHLBI) Web site and will be updated as needed.

Research is essential to provide the knowledge required to improve the care of individuals with sickle cell disease, but it is the physicians and other health care personnel who must ensure that the very best care is actually delivered to each child and adult who has this disorder. We hope that this book will help to achieve this goal.

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INTRODUCTION

This edition of *The Management of Sickle Cell Disease* (SCD) is organized into four parts: Diagnosis and Counseling, Health Maintenance, Treatment of Acute and Chronic Complications, and Special Topics. The original intent was to incorporate evidence-based medicine into each chapter, but there was variation among evidence-level scales, and some authors felt recommendations could be made, based on accepted practice, without formal trials in this rare disorder.

The best evidence still is represented by randomized, controlled trials (RCTs), but variations exist in their design, conduct, endpoints, and analyses. It should be emphasized that selected people enter a trial, and results should apply in practice specifically to populations with the same characteristics as those in the trial. Randomization is used to reduce imbalances between groups, but unexpected factors sometimes may confound analysis or interpretation. In addition, a trial may last only a short period of time, but long-term clinical implications may exist. Another issue is treatment variation, for example, a new

pneumococcal vaccine developed after the trial, which has not been tested formally in a sickle cell population. Earlier trial results may be accepted, based on the assumption that the change is small.

In some cases, RCTs cannot be done satisfactorily (e.g., for ethical reasons, an insufficient number of patients, or a lack of objective measures for sickle cell "crises"). Thus the bulk of clinical experience in SCD still remains in the moderately strong and weaker categories of evidence.

Not everyone has an efficacious outcome in a clinical trial, and the frequency of adverse events, such as with long-term transfusion programs or hematopoietic transplants, might not be considered. Thus, an assessment of benefit-to-risk ratio should enter into translation of evidence levels into practice recommendations. A final issue is that there may be two alternative approaches that are competitive (e.g., transfusions and hydroxyurea). In this case the pros and cons of each course of treatment should be discussed with the patient.

The practice guidelines best supported by scientific evidence are:

- Penicillin prophylaxis prevents pneumococcal sepsis in children [evidence from Prophylactic Penicillin Studies I and II (PROPS I & II)].

- Pneumococcal vaccine prevents pneumococcal infection in children.

- In surgical settings, simple transfusions to increase hemoglobin (Hb) levels to 10 g/dL are as good as or safer than aggressive transfusions to reduce sickle hemoglobin (Hb S) levels to below 30 percent.

- Transfusions to maintain a hematocrit of more than 36 percent do not reduce complications of pregnancy.

- Transfusions to reduce Hb S levels to below 30 percent prevent strokes in children with high central nervous system blood flow [evidence from the Stroke Prevention Trial in Sickle Cell Anemia (STOP I)].

- Hydroxyurea decreases crises in patients with severe sickle cell disease [evidence from the Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH) trial].

The following nomenclature, derived from the Council of Regional Networks for Genetic Services (CORN) guidelines for the U.S. newborn screening system [Pass KA, Lane PA, Fernhoff PM, et al. U.S. newborn screening system guidelines II: Follow-up of children, diagnosis, management, and evaluation. Statement of the Council of Regional Networks for Genetic Services (CORN). *J Pediatr* 2000;(4 Suppl):S1-46], is used throughout this book:

Genotype	Full Name	Abbreviation
β^s / β^s	Sickle cell disease-SS	SCD-SS
β^s / β^c	Sickle cell disease-SC	SCD-SC
β^s / β^o thalassemia	Sickle cell disease-S β^o thalassemia	SCD-S β^o thal
β^s / β^+ thalassemia	Sickle cell disease-S β^+ thalassemia	SCD-S β^+ thal

DIAGNOSIS AND COUNSELING

WORLD WIDE WEB RESOURCES

SICKLE CELL AND GENETIC WEB SITES

Sickle Cell Disease Association of America (SCDAA)
http://www.sicklecelldisease.org
A patient advocacy site with information for the public.

Center for Disease Control and Prevention: Hemoglobin S Allele and Sickle Cell Disease
http://www.cdc.gov/genomics/hugenet/reviews/sickle.htm
An excellent article about sickle cell genetics and epidemiology.

The Comprehensive Sickle Cell Centers
http://www.rhofed.com/sickle
A description of a major clinical research program supported by the NHLBI.

Harvard Sickle Cell Program
http://sickle.bwh.harvard.edu
A comprehensive source for information for patients and health care providers.

The Sickle Cell Information Center
http://www.emory.edu/PEDS/SICKLE
A broad range of information for the public and professionals.

National Organization for Rare Disorders, Inc.
http://www.rarediseases.org
A portal for all rare diseases.

ClinicalTrials.gov—Linking Patients to Medical Research
http://www.clinicaltrials.gov
A search engine for clinical trials in different diseases.

The National Newborn Screening and Genetics Resource Center (NNSGRC)
http://genes-r-us.uthscsa.edu
Information and resources for health professionals, the public health community, consumers and government officials.

Genetic Alliance
http://www.geneticalliance.org
A support organization for different genetic problems.

REGIONAL GENETIC NETWORKS

Mid-Atlantic Regional Human Genetics Network (MARHGN)
http://www.pitt.edu/~marhgn/
Genetic services for Delaware, Maryland, New Jersey, Pennsylvania, Virginia, West Virginia, and the District of Columbia.

Mountain States Genetics Network
http://www.mostgene.org
Genetic services for Arizona, Colorado, Montana, New Mexico, Utah, and Wyoming.

Pacific Northwest Regional Genetics Group (PacNoRGG)
http://mchneighborhood.ichp.edu/pacnorgg/
Genetic services for Alaska, Idaho, Oregon, and Washington.

Southeastern Regional Genetics Group (SERGG)
http://www.emory.edu/PEDIATRICS/sergg/index.html
Genetic services for the Southeastern region: Alabama, Florida, Georgia, Kentucky, Louisiana, Mississippi, North Carolina, South Carolina, and Tennessee.

Texas Genetics Network (TEXGENE)
http://www.tdh.state.tx.us/genetics/home.htm
Genetic services for Texas.

NEONATAL SCREENING

The demonstration in 1986 that prophylactic penicillin markedly reduces the incidence of pneumococcal sepsis (1) provided a powerful incentive for the widespread implementation of neonatal screening for sickle cell disease (SCD) (2). Neonatal screening, when linked to timely diagnostic testing, parental education, and comprehensive care, markedly reduces morbidity and mortality from SCD in infancy and early childhood (2-11). Approximately 2,000 infants with SCD are identified annually by U.S. neonatal screening programs (12,13). Screening also identifies infants with other hemoglobinopathies, hemoglobinopathy carriers, and in some states, infants with α-thalassemia syndromes.

METHODS

Forty-four states, the District of Columbia, Puerto Rico, and the Virgin Islands currently provide universal screening for SCD. Screening is available by request in the other six states. The majority of screening programs use isoelectric focusing (IEF) of an eluate from the dried blood spots that also are used to screen for hypothyroidism, phenylketonuria, and other disorders (13-15). A few programs use high-performance liquid chromatography (HPLC) or cellulose acetate electrophoresis as the initial screening method. Most programs retest abnormal screening specimens using a second, complementary electrophoretic technique, HPLC, immunologic tests, or DNA-based assays (13-15).

The sensitivity and specificity of current screening methodology are excellent (11), but neonatal screening systems are not foolproof. A few infants, even in states with universal screening, may not be screened. Other infants with SCD may go undiscovered because of extreme prematurity, blood transfusion prior to screening, mislabeled specimens, clerical errors in the laboratory, or the inability to locate affected infants after discharge from the nursery (5,14,16-20). It is imperative that all infants, including those born at home, be screened and that the initial screening test always be obtained prior to any blood transfusion, regardless of gestational or postnatal age. Information requested on screening forms should be recorded accurately and completely to facilitate the followup of positive screening tests and interpretation of results. In states that have not yet implemented universal screening, neonatal screening for SCD should be requested for all high-risk infants (those of African, Mediterranean, Middle Eastern, Indian, Caribbean, and South and Central American ancestry). Any high-risk infant not screened at birth, or for whom neonatal screening results cannot be documented, should be screened for hemoglobinopathies prior to 2 months of age.

Hemoglobins (Hb) identified by neonatal screening are generally reported in order of quantity. Because more fetal hemoglobin (Hb F) than normal adult hemoglobin (Hb A) is present at birth, most normal infants show Hb FA. Infants with hemoglobinopathies also

show a predominance of Hb F at birth. Those with SCD show Hb S in absence of Hb A (FS), Hb S with another hemoglobin variant (e.g., FSC, FSD$_{Punjab}$), or a quantity of Hb S greater then Hb A (FSA). Hundreds of other Hb variants may also be identified. Most of these variants are associated with few or no clinical consequences, but some are associated with significant anemia or other problems. Many screening programs also detect and report Hb Bart's, indicative of α-thalassemia.

SICKLE CELL DISEASE

As shown in table 1, a number of different neonatal screening results may be indicative of sickle cell disease (14,21). Hb FS in infancy is associated with a variety of genotypes with a wide range of clinical severity. Most infants with screening results that show Hb FS have SCD-SS, but other possible conditions include sickle β°-thalassemia, sickle δβ-thalassemia, and sickle HPFH. Some infants with sickle β⁺-thalassemia also show FS screening results when the quantity of Hb A at birth is insufficient for detection (22). The coinheritance of α-thalassemia may complicate differentiation of genotypes in some infants (23). For infants with positive screening tests, confirmatory testing of a second blood sample should be accomplished by 2 months of age so that parental education, prophylactic penicillin, and comprehensive care can be promptly implemented (11,14). In many states, confirmatory testing is provided by the screening program using hemoglobin electrophoresis (cellulose acetate and citrate agar), IEF, HPLC, and/or DNA-based methods. Solubility tests to detect Hb S are inappropriate screening or confirmatory tests, in part because high levels of fetal hemoglobin (i.e., low concentrations of Hb S) give false-negative results in infants with SCD.

Hemolytic anemia and clinical signs and symptoms of SCD are rare before 2 months of age and develop variably thereafter as Hb F levels decline (table 1). Thus for infants with an FS phenotype, serial complete blood counts (CBCs) and reticulocyte counts may not clarify the diagnosis during early infancy, and testing of parents or DNA analysis may be helpful in selected cases (14). In all cases, infants with Hb FS should be started on prophylactic penicillin by 2 months of age, and parents should be educated about the importance of urgent medical evaluation and treatment for febrile illness and for signs and symptoms indicative of splenic sequestration (11,14).

Achieving an optimal outcome for each affected infant is a significant public health challenge. State public health agencies should have a responsibility to ensure the availability, quality, and integration of all five components of the neonatal screening system: screening, follow-up, diagnostic testing, disease management and treatment, and evaluation of the entire system (12-15). To be beneficial, screening, follow-up, and diagnosis of sickle cell disease must be followed by prompt referral to knowledgeable providers of comprehensive care (2,11). Comprehensive care includes ongoing patient and family education about disease complications and treatment, disease-specific health maintenance services including pneumococcal immunizations and prophylactic penicillin, access to timely and appropriate treatment of acute illness, nondirective genetic counseling, and psychosocial support (14). The extent to which these services are provided directly by public health agencies or by other clinics and providers will vary among states and communities. However, all states should have the responsibility to ensure that each infant and family with SCD receive appropriate services and to conduct

Table 1. Sickle Hemoglobinopathies: Neonatal Screening and Diagnostic Test Results

Disorder	Approx. % of U.S. patients	Neonatal screening results[1]	Hb separation by 2 months of age[1]	Serial CBC, reticulocytes	Hematologic studies by 2 years				DNA dot blot
					MCV[2]	Hb A_2[3] (%)	Hb F (%)	Hb F distribution	
SCD-SS	65	FS	FS	Hemolysis and anemia by 6-12 months	N or ↑[4]	<3.6[4]	<25	Heterocellular	β^s
SCD-SC	25	FSC	FSC	Mild or no anemia by 2 years	N or ↓	NA[5]	<15	Not applicable[6]	β^s β^c
SCD-S β^+ thal	8	FSA or FS[7]	FSA	Mild or no anemia by 2 years	N or ↓	>3.6	<25	Not applicable[6]	β^A β^s
SCD-S β^o thal	2	FS	FS	Hemolysis and anemia by 6-12 months	↓	>3.6	<25	Heterocellular	β^A β^s
SCD-S $\delta\beta$ thal	<1	FS	FS	Mild anemia by 2 years	↓	<2.5	<25	Heterocellular	β^s
S HPFH	<1	FS	FS	No hemolysis or anemia	N or ↓	<2.5	<25	Pancellular	β^s

Hb = hemoglobin, MCV = mean cell volume, thal = thalassemia, N = normal, ↑ = increased, ↓ = decreased, HPFH = hereditary persistance of Hb F.

Table shows typical results—exceptions occur. Some rare genotypes (eg. SD$_{Punjab}$, SO ^{Arab}, SC ^{Harlem}, S Lepore, SE) not included.
1. Hemoglobins reported in order of quantity (e.g. FSA = F>S>A).
2. Normal MCV: >70 at 6-12 months, >72 at 1-2 years.
3. Hb A_2 results vary somewhat depending on laboratory methodology.
4. Hb SS with co-existent α-thalassemia may show ↓MCV and Hb A_2 >3.6 percent; however, neonatal screening results from such infants usually show Hb Bart's.
5. Quantity of Hb A_2 can not be measured by hemoglobin electrophoresis or column chromatography in presence of Hb C.
6. Test not indicated.
7. Quantity of Hb A at birth sometimes insufficient for detection.

a continuing program of long-term followup (12,14,15). Providers may be asked to supply public health agencies with the followup data needed for tracking and outcomes evaluation.

OTHER HEMOGLOBINOPATHIES

As shown in table 2, neonatal screening identifies some infants with non-sickle hemoglobinopathies (14,25-30). Infants with Hb F only may be normal infants who do not yet show Hb A because of prematurity or may have β-thalassemia major or another thalassemia syndrome. Infants without Hb A need repeat testing to identify those with SCD and other hemoglobinopathies. Homozygous β-thalassemia may cause severe transfusion-dependent anemia. Infants with FE [Hb F + hemoglobin E (Hb E)] require family studies, DNA analysis, or repeated hematologic evaluation during the first 1 to 2 years of life to differentiate homozygous Hb E, which is asymptomatic, from Hb E βᵒ-thalassemia, which is variably severe (26-29). It is important to note that most infants with β-thalassemia syndromes (i.e., β-thalassemia minor and β-thalassemia intermediate) are not identified by neonatal screening.

ALPHA-THALASSEMIA SYNDROMES

The red cells of newborns with α-thalassemia contain Hb Bart's, a tetramer of γ-globin. Many, but not all, neonatal screening programs detect and report Hb Bart's (14,25,31,32). As shown in table 3, infants with Hb Bart's at birth may be silent carriers or have α-thalassemia minor, Hb H disease, or Hb H Constant Spring disease. Silent carriers, the largest group with Hb Bart's at birth, have a normal CBC. Persons with α-thalassemia minor generally show a decreased mean cell volume (MCV) with mild or no anemia.

Newborns with more than 10 percent hemoglobin Bart's by IEF or more than 30 percent hemoglobin Bart's by HPLC or those who develop more severe anemia need extensive diagnostic testing and consultation with a pediatric hematologist to accurately diagnose and appropriately treat more serious forms of α-thalassemia such as Hb H disease or Hb H Constant Spring disease (33). The identification of Hb Bart's in Asian infants may have important genetic implications because subsequent family testing may identify couples at risk for pregnancies complicated by hydrops fetalis (14,25,34).

CARRIERS OF HEMOGLOBIN VARIANTS

Approximately fifty infants who are carriers of hemoglobin variants (i.e., hemoglobin traits) are identified for every one with SCD (14). The screening laboratory can usually confirm the carrier state by using a complementary methodology. Some programs recommend confirmation of carriers by testing a second specimen from the infant.

Carriers are generally asymptomatic (table 4), and thus identification is of no immediate benefit to the infant. However, parents are entitled to the information and can benefit from knowing the child's carrier status, in part because the information may influence their reproductive decision-making. Therefore, parents of infants who are detected to be carriers through neonatal screening should be offered education and testing for themselves and their extended family (2,11,14). Such testing may raise concerns about mistaken paternity and should not be performed without prior discussion with the mother. Testing of potential carriers requires a CBC and hemoglobin separation by hemoglobin electrophoresis, IEF, or HPLC. To identify those with β-thalassemia,

Table 2. Non-Sickle Hemoglobinopathies Identified by Neonatal Screening*

Screening Results	Possible Condition	Clinical Manifestations
F only	Premature Infant	Repeat screening necessary
	Homozygous β^o-thalassemia	Severe thalassemia
FE	EE	Microcytosis with mild or no anemia
	E β^o-thalassemia	Mild to severe anemia
FC	CC	Mild microcytic hemolytic anemia
	C β^o-thalassemia	Mild microcytic hemolytic anemia
FCA	C β^+-thalassemia	Mild microcytic hemolytic anemia

*Other, less common hemoglobins, also may be identified.

Table 3. Alpha-Thalassemia Syndromes Identified by Neonatal Screening

Screening Results	Possible Condition	Clinical Manifestations
FA+Bart's	α-thalassemia silent carrier	Normal CBC
	α-thalassemia minor	Microcytosis with mild or no anemia
	Hb H disease	Mild to moderately severe microcytic hemolytic anemia
	Hb H Constant Spring	Moderately severe hemolytic anemia
FAS+Bart's, FAC+Bart's, FAE+Bart's, FE+Bart's	α-thalassemia with structural Hb variant	Clinical manifestations, if any, depend on the structural variant (e.g., Hb E) and severity of α-thalassemia

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Table 4. Hemoglobinopathy Carriers Identified by Neonatal Screening

Screening Results	Possible Condition	Clinical Manifestations
FAS	Sickle cell trait	Normal CBC Generally asymptomatic (see chapter 3)
FAC	Hb C carrier	No anemia Asymptomatic
FAE	Hb E carrier	Normal or slightly ↓ MCV without anemia Asymptomatic
FA Other	Other Hb variant carrier	Depends on variant; most without clinical or hematologic manifestations

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accurate quantitation of Hb A_2 by column chromatography or HPLC and of Hb F by alkali denaturation, radial immune diffusion, or HPLC is also needed if the MCV is borderline or decreased.

UNIDENTIFIED HEMOGLOBIN VARIANTS

Many of the more than 600 known hemoglobin variants are detected by current neonatal screening methods. Many are rare, and most are not identifiable by neonatal screening or clinical laboratories. Each year more than 10,000 infants with unidentified hemoglobin variants are detected by U.S. neonatal screening programs (13,35). The definitive identification of these variants is accomplished for fewer than 500 of these infants, in part because of limited reference laboratory capacity. Most infants are heterozygotes, and most will have no clinical or hematologic manifestations. However, some variants, particularly unstable hemoglobins or those with altered oxygen affinity, may be associated with clinical manifestations even in heterozygotes. Other variants have no clinical consequences in

heterozygous or homozygous individuals, but may cause SCD when coinherited with Hb S, and thus have potential clinical and genetic implications (21).

Followup of these infants is problematic, in part because uncertainty may cause frustration and anxiety for parents and health care providers. No national consensus has yet been produced to guide neonatal screening programs and clinicians in the followup of infants with unidentified hemoglobin variants. The following approaches may be considered. If the infant is a heterozygote (i.e., the quantity of Hb A is equal to or greater than the quantity of the unidentified hemoglobin), the infant is well (without anemia or neonatal jaundice), and the family history is negative for anemia or hemolysis, then no further hematologic evaluation may be necessary.

Alternatively, some recommend repeat IEF, HPLC or hemoglobin electrophoresis and/or obtaining a CBC, reticulocyte count, and peripheral smear for red cell morphology between 6 and 12 months of age. Fetal hemoglobin (γ–globin) variants disappear by 1 year of age, and the absence of anemia or hemolysis

may be reassuring for parents of infants with hemoglobin variants that persist (α- or β-globin variants). For some families, it may be appropriate to offer hemoglobin electrophoresis, IEF, or HPLC and/or CBC, blood smear, and reticulocyte counts on parents. Infants with clinical or laboratory evidence of hemolysis or abnormal oxygen affinity and those without Hb A, especially compound heterozygotes with Hb S, require definitive hemoglobin identification (21,36,37). This may require protein sequencing, DNA analysis, or HPLC combined with electrospray mass spectrometry in a specialized reference laboratory (38). Identification of the hemoglobin variant to clarify genetic risks should also be considered for families in which another hemoglobin variant (e.g., Hb S) is present.

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Sickle Cell Trait

Individuals who have sickle cell trait (SCT) do not have vaso-occlusive symptoms under physiologic conditions and have a normal life expectancy. The inheritance of SCT should have no impact on career choices or lifestyle. SCT is found in 8 percent of African Americans and is also prevalent in persons of Mediterranean, Middle Eastern, Indian, Caribbean, and Central and South American descent. Neonatal screening (chapter 2) will provide early detection of SCT. This chapter will discuss clinical syndromes associated with SCT, some of which occur only under conditions of extreme physiologic stress.

EYE

TRAUMATIC HYPHEMA

The presence of SCT significantly alters the management of traumatic hyphema, which is discussed more fully in chapter 14, Sickle Cell Eye Disease.

RENAL AND GENITOURINARY TRACT

HYPOSTHENURIA

Individuals with SCT can develop microscopic infarction of the renal medulla, resulting in loss of maximal urine concentrating ability; this condition is present in most adults with SCT (1). Maximum urine osmolality following fluid deprivation or intranasal DDAVP may be as low as 400 to 500 mOsm/kg. Coexistent α-thalassemia provides partial protection against this urine-concentrating defect (2).

HEMATURIA
(ALSO SEE CHAPTER 19, RENAL ABNORMALITIES IN SICKLE CELL DISEASE)

Necrosis of the renal papillae can result in hematuria, which is usually microscopic. Gross hematuria is occasionally provoked by heavy exercise or occurs spontaneously. Individuals with hematuria should be evaluated by a urologist, who will perform imaging studies as needed to exclude neoplasms (3-5) or renal stones or any related problems with flow of urine from the calyces to the urethra.

Individuals with acute episodes of gross hematuria are cautioned to avoid exercise but are encouraged to continue to perform sedentary work. They are encouraged to take fluids (equivalent to half-normal saline) and may also receive sodium bicarbonate 650 to 1,200 mg per day. If bleeding persists, an antifibrinolytic agent such as epsilon aminocaproic acid (EACA) can be prescribed (6). In a controlled trial of individuals with SCT who had hematuria, administration of EACA at an oral dose of 6 to 8 grams daily in four to six divided doses caused resolution of hematuria at a mean of 2.2±0.3 days, compared with 4.5±1.9 days for those individuals not receiving the

drug (6). The authors reported a high incidence of ureteral obstruction by clots accompanied by flank pain (in 15 of 38 episodes with an intravenous pyelogram [IVP]), which resolved without specific therapy over 2 to 37 days. However, ureteral obstruction by clot also occurred at the same frequency in the absence of EACA. Although the best dose and duration for use of EACA in treatment of hematuria related to SCT has not been adequately investigated, one effective regimen is administration of 3 grams 3 or 4 times per day for 1 week; in most patients, hematuria will resolve after 2 to 3 days (7). In some individuals, iron replacement and even transfusions may be required.

Occasionally, bleeding is so brisk or persistent that it is necessary to perform invasive surgery to visualize bleeding sites, identify the pathology at those sites, and stop the bleeding by local measures in order to save the kidney.

URINARY TRACT INFECTION

The frequency of urinary tract infection is higher in women with SCT than in racially matched controls, especially during pregnancy, when the frequency is about double (8). The presence of SCT in men was not associated with increased frequency of urinary tract infection in a large study of patients in U.S. Department of Veterans Affairs' hospitals (9).

AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

The incidence of end-stage renal failure from this disorder is identical for Caucasians and African Americans; however, the onset of end-stage renal failure occurs at an earlier age for individuals with SCT than for African Americans without SCT (38 years versus 48 years [p<0.003]) (10).

COMPLICATIONS OF STRENUOUS EXERCISE

Risk factors for exercise-related death of young adults with SCT include environmental heat stress during the preceding 24 hours (11), incomplete heat acclimation, wearing heat-retaining clothing, dehydration, delay in recognition or treatment of exertional heat illness, obesity with poor exercise fitness (12), sustained heroic effort above customary activity, and inadequate sleep. Many of these factors were present in military recruits under extreme conditions of 8 weeks of physical training, where the excess mortality rate for those with SCT was 1 per 3300 in the late 1970's (13). The higher risk of exercise-related death is attributed mainly to the intensity of new exercises or to sustained duration for which the individual is unprepared. This higher risk is eliminated by measures to prevent exertional heat illness, which should be incorporated into all intensive exercise programs and made available to all participants.

SCT does not contraindicate participation in competitive sports. In fact, many reports show no increased morbidity or mortality for professional athletes with the trait (1) who stay fit during the off-season. Prevention of exertional heat illness requires hydration or similar measures for distance runners and military recruits (1,14,15). Individuals should increase performance levels gradually, and training should cease and restart slowly if myalgia occurs. There is no requirement to screen for SCT before participation in athletic programs.

SPLENIC INFARCTION

Splenic infarction usually presents as severe abdominal pain localized within a few hours to the left upper quadrant. It is best seen on a computerized tomography (CT) scan, which may show a region of hemorrhage. An episode

of splenic infarction with SCT usually resolves in 10 to 21 days and rarely requires surgical intervention. Splenic infarction associated with SCT may occur with hypoxemia from systemic disease or from exercise at sea level or at high altitude (1). Splenic infarction is associated with flights in unpressurized aircraft at 15,000 feet or more but may occur rarely at mountain altitudes higher than 6,000 feet above sea level. The frequency seems to be disproportionately greater in phenotypically non-African American individuals (16), an observation that may be due to reporting bias. Nevertheless, numerous individuals with SCT have participated successfully in long-distance races in the Cameroon and in high-altitude sports, including the Olympics in Mexico City. Thus, the majority of people with SCT can travel safely to mountain altitudes for recreational activities; however, rare individuals who have had splenic complications may risk recurrence.

SURGERY AND OTHER MEDICAL CONDITIONS

Surgery is not likely to be complicated by the fact that an individual has SCT (17). Individuals with SCT are not at increased risk for an adverse outcome from anesthesia, and they are not limited in their choice of anesthetic agents. There is no convincing evidence that SCT is associated with increased frequency or severity of diabetic retinopathy, stroke, myocardial infarction, leg ulcers, avascular necrosis and arthritis, or the bends due to diving. Some case reports of possible associations of SCT with increased medical morbidity may represent situations in which other variants of β- or α-globin chains produced undiagnosed SCD (18). Rare cases may be due to increased 2,3-DPG or altered oxygen affinity, which might increase polymerization of Hb S sufficiently to cause a phenotype of SCT to behave like SCD (18,19).

EDUCATION AND GENETIC COUNSELING

All persons with SCT should be educated about the inheritance of SCD and about the availability of partner testing, genetic counseling, and prenatal diagnosis (see chapter 4).

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GENETIC COUNSELING

Sickle cell trait (SCT) is not considered to be a health problem, but individuals who test positive should be informed about the implications for their health and family planning. Thus, the primary issues addressed in this chapter are what information should individuals receive, and who should provide it (1-8).

Despite mandatory newborn screening programs implemented in most states by 1991, children with SCT may not recall or understand the implications by the time they reach childbearing age. Currently, there are two major circumstances in which adults will learn that they have SCT, leading to two groups of counselees:

1. Parents of a child with SCT. When a newborn with SCT is identified through screening, at least one of the parents will have SCT.

2. Pregnant women. During prenatal care, women from racial groups with a high prevalence of the sickle cell gene frequently are tested for the gene.

SCT counseling has two components—education and decision-making—but the emphasis differs in the two cases above. For the first group, the focus is on education, that is, to enable individuals to make informed decisions, in their own interest, about future family planning. For the second group, the focus is on education and informed decisions, in their best interest, about the current pregnancy.

CONTENT AND APPROACHES

Although there is basic information that all counselees should receive, the goals are sufficiently different for the two groups, so that there should be substantive differences in the content and the approaches of the respective counselors. An essential principle for each counseling group is that advice, personal opinions, and societal positions must not be given or implied. This admonition must be obeyed strictly because, in each case, self-determination is the desired outcome. Counselors must not influence decisions inappropriately—overtly through statements or covertly through facial expressions, tone of voice, body language, etc.—particularly if asked, "What should I do?"

Since counseling goals are based entirely upon the principle of self-determination, and are not intended to be preventive, the counselor's success is not determined by a decline in the incidence of sickle cell disease (SCD) but the extent to which informed self-interest decisions are made.

BASIC CONTENT FOR ALL SESSIONS
- Purpose and goal of the session
- How sickle cell conditions are acquired—genetic basis
- Difference between SCT and SCD
- Health problems that can occur in SCD

- Variability of and inability to predict occurrence and frequency of health problems in SCD

- Potential outcome of each pregnancy if one or both partners has SCT

- Family planning options

- Racial groups who have SCD and the percent of individuals in the counselee's racial group who have SCT and SCD

- Average life span of individuals with SCT and SCD

ADDITIONAL CONTENT FOR PREGNANCY OUTCOME DECISIONMAKING SESSIONS

There are several noncognitive factors that pregnant women (and the fathers) may wish to consider in order to reach a decision consistent with the goal. These factors include:

- Coping skills relative to a child with a serious illness

- Personal and cultural values relative to childbearing

- Religious beliefs

- The need and desire to have children

- Feelings and attitudes about abortion

- Belief about self-determination versus fate as determinants of adverse events

INSTRUCTIONAL/EDUCATIONAL TECHNIQUES

- Use lay language whenever possible.

- Translate scientific terms into common everyday usage whenever possible.

- Use graphics to illustrate key points.

- Establish a dialogue rather than using a strict lecture format or information-giving format.

- Implement a pre- and postassessment.

- Use the postassessment as an opportunity to clarify misinterpretation or uncertainties that the genetic test revealed.

- Provide literature written in lay language covering the essential facts.

- Make available sources of more detailed information for those who are interested.

- Communicate the availability of the provider for followup questions.

- Follow a structured protocol to ensure that the essential features are covered. This should not prevent interaction.

WHO SHOULD COUNSEL

Ideally, the first group should be counseled by geneticists and genetic counselors with master's degrees who have been certified by the American Board of Medical Genetics or the American Board of Genetic Counselors. However, the number to be counseled far exceeds the supply and the availability of these professionals. Thus, there has been a need to train others to provide this service. This can be achieved with laypersons and paraprofessionals (2,4). Individuals selected for this task must possess certain personal qualities, including good communication skills, an engaging personality, and the discipline to limit information transmission to what has been approved for them to provide. Several training programs offer certification for all comers; however, there is no statewide or national requirement for certification.

It is not sufficient to have trained and certified counselors. Since certification simply means that individuals are qualified, they should be periodically monitored to see if they consistently follow the protocol. In one program this is achieved by audiotaping all sessions and

randomly selecting tapes for review and critique (4). Other procedures are to conduct postsession interviews with counseled individuals, or to periodically schedule sessions with a trained, knowledgeable, simulated counselee (preferably without the counselor's awareness).

Ideally, individuals who are trained to provide services for the first group should be titled "sickle cell educators" rather than "sickle cell counselors" because the term counseling implies assisting individuals to make decisions, which is not their role. The individuals who are trained to provide services for the second group are indeed counselors. The use of the title counselors for the first group is so traditional that changing the title will not occur, but the distinction is worth noting. The second group should be counseled only by individuals specifically trained to assist individuals to make psychosocial decisions. This includes geneticists, master's degree genetic counselors, social workers, and psychologists. The latter two, of course, would have to be "sickle cell educated."

MINIMAL ACCEPTABLE ACHIEVEMENTS

For the first group, the interest in being counseled and the information of personal value is so highly variable it is desirable to have a minimal acceptable achievement level in a basic counseling session. For example, the counselee should understand:

- The family planning options open to persons with SCT.

- SCT is not an illness, so no restrictions need to be placed on his or her activities.

- The variability in severity of SCD.

- Both parents must have the trait for the child to have SCD.

- The 25 percent chance that each pregnancy will result in a child with SCD if both parents have the trait.

- Some of the reasons couples might decide to have or not have children if both have the trait.

SCT COUNSELOR TRAINING PROGRAMS

University of South Alabama
1433 Springhill Avenue
Mobile, Alabama 36604
Contact Person: Linda Jones
(334) 432-0301

Texas Department of Health
1100 West 49th
Austin, Texas 78756
Contact Person: Mae Wilborn
(512) 458-7111 x2071

Cincinnati Comprehensive Sickle Cell Center
3333 Burnet Avenue
Cincinnati, Ohio 45229
Contact Person: Lisa McDonald
(513) 636-4541

Genetic Disease Branch
State Department of Health Services Branch
Berkeley, California 94704
Contact Person: Kathleen Valesquez
(510) 540-3035

Sickle Cell Disease Association of America, Michigan Chapter
18516 James Couzens Highway
Detroit, Michigan 48235
Contact Person: Jetohn Thomas
(313) 864-4406

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HEALTH MAINTENANCE

Child Health Care Maintenance

For decades, complications of sickle cell disease (SCD) produced the highest mortality rate in the first 3 years of life (1). However, public health programs and comprehensive care for children who have SCD reduced early childhood mortality in countries such as the United States, United Kingdom, France, Jamaica, and Saudi Arabia. Unfortunately, childhood mortality is high in other parts of the world, especially sub-Saharan Africa where SCD is prevalent but organized SCD programs are rare. These guidelines are directed to health care workers mainly in the United States, but the approaches may be modified as other conditions and situations permit.

PATHOLOGIC MECHANISMS

Sickle cells can obstruct blood flow to the spleen, which results in functional asplenia within the first few years of life. In addition to a filtration function, the spleen has B-cells for antibody production, and when the organ suffers infarcts and shrinks, this capacity is lost. Asplenia causes susceptibility to bacterial infections, particularly with pneumococcus.

CLINICAL FINDINGS

Neonatal Diagnosis

Newborn screening may be performed on blood from the umbilical cord or a heel-prick. Abnormal results should be confirmed with a second sample, using a different method (2). Sickling and solubility tests generally are not useful because they give negative results when the fetal hemoglobin (Hb F) level is high, and do not distinguish between sickle trait (Hb AS) and different forms of SCD. Tests on the parents may help to confirm the hemoglobin (Hb) genotype of the baby but can be incorrect in cases of single parenthood or nonpaternity. "Deductive" methods based on blood counts, red cell indices, and relative levels of Hb F and A_2 cannot distinguish between conditions such as SCD-SS with α-thalassemia and SCD-S β°-thalassemia, nor are they useful in children younger than 6 months of age where the relative levels of hemoglobins have not stabilized (3). These problems are avoided if DNA-based methods are applied to detect specific mutations. The determinations of $β^s$ haplotypes and α-thalassemia contribute to the definitive diagnosis of SCD but play a minor role clinically.

Once a definitive diagnosis is made, the parents should start an educational program with practical information about the specific type of SCD that affects their child (4-6). The initial counseling session sets the tone for how the parents regard their child's condition and the new health care team. Parents often ask about the expected course and capabilities of the child with SCD. A person experienced in the care of children with SCD should be available to answer these questions without medical jargon and should allow time for other questions. It is important to tell parents not to raise children with SCD as sick children, since they are not ill most of their lives.

Parental education about SCD cannot be accomplished in one counseling session. Providers who do not have the resources to provide this important service should refer the family to an appropriate facility. Future sessions should be planned to provide information appropriate for the child's age, diagnosis, and clinical course.

SPECIAL EVALUATIONS

Specific physical, laboratory, and other evaluations are needed to monitor children with SCD (7).

Physical Examination

SCD in young children has a variable presentation. The earliest physical sign may be jaundice in the first few weeks of life. If hemolysis is not significant clinically, parents and other family members should be reassured about eye color changes so that they do not become overly anxious. Hepatomegaly is a common finding in children with SCD; the cause is unknown, but it does not signify liver dysfunction. Spleen size should be measured,

and parents should be made aware of it. Organomegaly leads many children with SCD to have a protuberant abdomen, often with an umbilical hernia. Almost all SCD patients with moderate-to-severe anemia have a cardiac systolic flow murmur that does not require further evaluation. Parents should be reassured about the murmur so that they will not be alarmed when other doctors and nurses notice it. Bone marrow expansion often causes maxillary hypertrophy with overbite; orthodontics are recommended to prevent or correct this problem. Growth and development should be followed closely in children with SCD, and nutrition should be optimized. Children and parents should be counseled about potential social problems related to short stature and delayed sexual development, which greatly affects adolescents.

Laboratory Evaluation

It is useful to collect a series of baseline values on each patient to compare with those at times of acute illness. Table 1 shows a typical schedule of routine clinical laboratory evaluations.

Table 1. Suggested Routine Clinical Laboratory Evaluations

Tests	Age	Frequency
CBC with WBC differential, reticulocyte count	3 mo – 24 mo >24 mo	every 3 mo every 6 mo
Percent Hb F	6 mo – 24 mo >24 mo	every 6 mo annually*
Renal function (creatinine, BUN, urinalysis)	≥12 mo	annually
Hepatobiliary function (ALT, fractionated bilirubin)	≥12 mo	annually
Pulmonary function (transcutaneous O_2 saturation)	≥12 mo	every 6 mo*

* Frequency may vary based on patient's clinical course.

Special Studies

The brain and lungs are among the organs susceptible to serious damage in SCD. Early detection of dysfunction may allow intervention to reduce risk of further damage.

Brain. Transcranial Doppler ultrasonography (TCD), magnetic resonance imaging (MRI) with or without angiography, and neuropsychometric (NPM) studies have been used extensively to evaluate children with SCD. An abnormally high blood flow velocity by TCD in the middle cerebral or internal carotid arteries is associated with an increased risk of stroke; however, blood flow results should be interpreted cautiously because they are dependent on the technique employed. TCD screening of children with SCD-SS is recommended to start at 2 years of age and continue annually if TCD is normal and every 4 months if TCD is marginal. Children who have abnormal results should be retested within 2 to 4 weeks. The STOP trial (Stroke Prevention Trial in Sickle Cell Anemia) in 1997 showed that a transfusion program reduces the risk of strokes in patients with abnormal TCDs (see chapter 13, Stroke and Central Nervous System Disease).

Children with SCD who have "silent" cerebral infarcts detected by MRI have a higher rate of abnormal NPM studies and a higher risk for overt strokes. Stroke prevention strategies based on abnormal MRI results have not been tested, but children with abnormal MRI or NPM studies could be evaluated more frequently and carefully and considered for therapeutic measures.

Lungs. Children with SCD frequently have abnormal pulmonary function tests (PFT). PFT should be done regularly in those with history of recurrent acute chest episodes or low oxygen saturation. Lung function declines with age, so it is important to identify those who need close monitoring and treatment.

MANAGEMENT

The major complications of SCD are discussed in other chapters, so only topics of special relevance to children and parents are mentioned below.

PARENT EDUCATION

Home caregivers have a crucial role in the successful management of children with SCD, and this should be emphasized at each counseling session. Parents should be taught physical assessment skills (e.g., palpation of spleen), how to avoid vaso-occlusive complications and treat pain, and when to administer prophylactic antibiotics. Educational materials and methods should be matched to the literacy level of the caregiver. Instruction should be provided on how to navigate the medical system. Information about physical findings, laboratory values, and medications should be retained by the caregiver in case it is needed in an emergency.

FEVER

The constant danger of overwhelming infection is one of the most difficult concepts to impart to caregivers (8). Fever is one of the most common signs of illness in children, and most parents are unaware that their child could die from infection. Pneumococcal vaccination and penicillin prophylaxis have reduced the risk of mortality for SCD children, and because of vigilance of parents and health care providers, death from pneumococcal infection is rare at major sickle cell centers in the United States. Current recommendations for vaccinating children, providing prophylactic therapies, and educating parents about the signs and dangers of infection should not be relaxed.

Parents should be discouraged from giving antipyretics at home at the first sign of fever. Advice that the febrile child deserves further evaluation only after recurrence or persistence

of fever (following antipyretic therapy) is wrong and potentially dangerous. A history of fever should be taken seriously, and health care workers, particularly those in emergency rooms, should not challenge parents whose children may have no or only low-grade fever on presentation. At a minimum, the well-looking, nonfebrile child should be observed in the emergency room for a few hours to determine whether fever or other signs of infection develop.

All children with SCD who have fever (>38.5°C or 101°F) and other signs of infection (chills, lethargy, irritability, poor feeding, vomiting) should be evaluated promptly. The younger the child, the higher should be the index of suspicion. In a child with no obvious source of infection, a minimum evaluation should include blood culture, complete blood count, reticulocyte count, and chest x rays (for those younger than 3 years of age). Immediately after the blood is taken, the child should be given broad-spectrum antibiotics, preferably intravenously. Broad-spectrum antibiotics should be given even if these tests cannot be performed. In areas of the world where malaria is endemic, antimalarial treatment should be added to the antibiotic coverage. Further management protocols vary by locality.

While bacterial infection is the major reason for concern about the febrile child with SCD, other complications should not be overlooked (9). Both acute splenic sequestration and erythroid aplasia ("aplastic crisis") are commonly associated with fever. Early acute chest syndrome in young children may show no pulmonary signs.

PAIN EPISODES

Painful events are common in children with SCD. The earliest complication observed clinically is often dactylitis ("hand-foot syndrome"), which starts at less than 1 year of age. Typical vaso-occlusive pain may involve limbs, abdominal viscera, ribs, sternum, vertebrae, and sometimes skull bones. Pain episodes can start suddenly, or they may follow an illness along with decreased activity, loss of appetite, and increased jaundice. Parents should be assured that most pain episodes have no identifiable precipitating factors, so that they do not blame themselves or their children. Likewise, health care providers should not assume that the pain is due to the fault of the parent.

Children with pain should be evaluated. Parents should be taught to localize the exact site of pain, to ensure that a limp is due to pain and not weakness, and to assess the degree of pain for appropriate treatment.

The object of pain management is relief, even in the youngest children. Parents should be taught proper analgesic use in order to manage most pain episodes at home. Medications given for mild and moderate pain include acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, and mild opioids, such as codeine, for young children. Stronger NSAIDs and opioids are reserved for older children with severe pain. Parents should be educated about the side effects of these drugs and reassured about the risk of drug addiction when they are used properly. If home management fails, parents are encouraged to call for consultation or a hospital visit.

CLINICAL SEVERITY

A report from the Cooperative Study of Sickle Cell Disease (CSSCD) identified early predictors of clinical severity such as dactylitis before 12 months of age, average Hb level of less than 7 g/dL in the second year of life, and elevated leukocyte count (>13,700/μL) before 10 years of age (10). Further studies will be required to identify those at high risk in order to consider therapies such as hydroxyurea, chronic transfusions, or bone marrow transplants.

COMPREHENSIVE MANAGEMENT

Comprehensive management of SCD often requires a team that comprises doctors, nurses, health educators, and medical social workers. Often emergency room physicians, radiologists, anesthesiologists, surgeons, and critical care specialists also become involved. Facilities generally should have medical consultants, hematology and microbiology laboratories, a radiology service, and blood bank available 24 hours a day. On occasion, patients may need TCD, computerized axial tomography, MRI, and MRI with angiography, which are available at major medical centers.

After the diagnosis of SCD, the comprehensive care team must initiate and coordinate medical and psychosocial care for the child and family. These activities should include education, genetic counseling, and preparation for independent living.

SUMMARY

Survival of children with SCD has been improved largely through prevention of overwhelming bacterial infections. Preventive measures include newborn screening, protective vaccinations, teaching caregivers to recognize early signs of illness, and prompt treatment of suspected infections.

RECOMMENDATIONS

GENERAL HEALTH MAINTENANCE FOR CHILDREN

Frequent Visits

Children with SCD should receive the same general health care as children without the disease. Well-child visits for growth monitoring, immunizations, and counseling on preventive health measures should be supplemented with specific information about SCD. The schedule of visits in the first 2 years of life should be every 2 to 3 months, planned to coincide with the immunization schedule. After the age of 2, the frequency of visits depends on patient/family needs and access to medical consultation, but it should be at least every 6 months.

Immunizations

In addition to routine immunizations against hepatitis B, polio, diphtheria, pertussis, tetanus, *Haemophilus influenzae* type b, measles, mumps, and rubella, children with SCD require additional immunizations. The recent introduction of the pneumococcal-conjugated vaccine (PCV) for children in the United States is important for those with SCD. Prevnar (Wyeth-Lederle), the 7-valent PCV (PCV7) licensed in the United States, covers pneumococcal serotypes 4, 9V, 14, 19F, 23F, 18C, and 6B, and has possible cross-reactivity with serotypes 6A, 9A, 9L, 18B, and 18F. Together these serotypes account for 87 percent of bacteremia and 83 percent of meningitis due to pneumococcus in the United States. The American Academy of Pediatrics (AAP) recommends Prevnar for children with SCD up to 59 months of age. However, there is no reason why older SCD patients should not receive the vaccine. The 23-valent pneumococcal polysaccharide vaccine (PPV23, also known as 23PS), previously recommended at 2 years of age with a booster at age 5, still should be used in addition to the

conjugated vaccine. The recommended schedules of vaccination for the prevention of pneumococcal infection in U.S. children with SCD are shown in tables 2 and 3 [modified from (11,12)].

Meningococcal vaccination has not been recommended routinely for children at most U.S. sickle cell centers, probably due to infrequent meningococcal infections reported. If children live in or travel to areas with a high prevalence of meningococcal infection, this vaccine should be given. In addition, influenza vaccination is recommended seasonally for patients with SCD.

Penicillin Prophylaxis
The most important intervention in the routine management of children with SCD is penicillin prophylaxis to prevent pneumococcal infection (13), which justifies newborn screening. Penicillin is given twice daily from as early as 2 months of age, a treatment supported by the hallmark Penicillin Prophylaxis Studies of the 1980s. It was recommended that children with SCD-SS be given penicillin VK: 125 mg by mouth twice daily for those under 3 years of age, and 250 mg twice daily for those 3 and older. Penicillin may be given as a liquid or tablet; finely crushed pills may be given to young children. Pills have an important advantage because they are stable for years, compared to liquid forms of penicillin that must be discarded after 2 weeks. An alternative to oral penicillin is an injection of 1.2 million units of long-acting Bicillin™ every 3 weeks.

A study in children older than 5 years of age, found no clinical benefit of penicillin prophylaxis compared with placebo, indicating that treatment may be stopped at that age (14). Patients on penicillin had no increased infections with

penicillin-resistant organisms or other adverse effects. Since splenic function is still absent in patients with SCD older than 5 years of age, parents should be given the option to continue penicillin if desired. For patients allergic to penicillin, erythromycin ethyl succinate (20 mg/kg) divided into 2 daily doses can provide adequate prophylaxis. The importance of prophylactic antibiotics should be emphasized at all visits because parents may become noncompliant with this essential treatment.

Although the data that support these recommendations were generated in SCD-SS patients, they are assumed to be valid for SCD-S β^o-thalassemia. The CSSCD showed a higher-than-expected incidence of bacteremia in children younger than 3 years of age with SCD-SC. Pneumococcal infection has been reported in SCD-SC in the first two decades of life, although less frequently than in SCD-SS. Protection of SCD-SC patients with prophylactic penicillin and antipneumococcal vaccine is probably wise even without experimental data. It is difficult to recommend prophylaxis for children with SCD-S β^+-thalassemia.

Nutrition
Nutrition counseling is an important part of routine health care. Mothers should be encouraged to breastfeed their infants; iron-fortified formulas are an alternative. However, additional iron should not be given unless the patient is proved iron-deficient, since people with SCD accumulate iron faster than normal. Microcytosis in children with SCD could be due to α- or β-thalassemia trait rather than iron deficiency. Folic acid (1 mg orally) is given daily to patients with chronic hemolysis, such as those with SCD, to reduce the risk of bone marrow aplasia.

Table 2. Recommended Schedule of Pneumococcal Immunization in
Previously Unvaccinated Children with Sickle Cell Disease

Product Type	Age at 1st dose	Primary series	Additional doses
PCV7 (Prevnar)	2-6 mo	3 doses 6-8 wk apart	1 dose at 12 to <16 mo
	7-11 mo	2 doses 6-8 wk apart	1 dose at 12 to <16 mo
	≥12 mo	2 doses 6-8 wk apart	—
PPV23 (Pneumovax)	≥24 mo	1 dose at least 6-8 wk after last PCV7 dose	1 dose, 3-5 yr after 1st PPV23 dose

Table 3. Recommended Schedule for Catch-up Pneumococcal Immunization
for Previously Vaccinated Children with Sickle Cell Disease

Age	Previous doses	Recommended
12-23 mo	Incomplete primary PCV7	2 doses PCV7, 6-8 wk apart
≥24 mo	4 doses PCV7	1st dose PPV23, 6-8 wk after PCV7; 2nd PPV23 dose, 3-5 yr after 1st PPV23
	1-3 doses PPV7 (before 24 mo of age)	1 dose PCV7; 1st dose PPV23, 6-8 wk after PCV7; 2nd PPV23 dose, 3-5 yr after 1st PPV23
	1 dose PPV23	2 doses PCV7, 6-8 wk apart, 1st dose given at least 8 wk after PPV23 dose; 2nd PPV23 dose, 3-5 yr after 1st PPV23

Current U.S. Food and Drug Administration indications are for administration of PCV7 only to children younger than 24 months of age.

Deficiencies in nutrients (e.g., zinc) should be corrected if they occur. Fluoride, given in vitamins or in drinking water, will prevent dental caries. Standard antibiotic prophylaxis should be used to cover dental procedures such as extractions and root canal therapy.

Counseling

In addition to genetic counseling, children and teens with SCD and their families may need academic and vocational guidance, as well as advice on recreational activities and travel. The basic premise is that parents should treat their affected child as normally as possible, and they should encourage activities that foster self-esteem and self-reliance. These feelings will help children and adolescents to cope more effectively with their illness.

Academic and Vocational Counseling

Educational materials should be provided to teachers and other school officials who interact regularly with children with SCD. School personnel should meet with the parents to set realistic educational goals. Illness often interrupts schooling and extracurricular activities, so tutoring or other assistance may be needed. Unless impaired by cerebrovascular disease, children with SCD have normal intelligence and should be encouraged to reach their full potential.

Vocational counseling is important for adolescents and adults with SCD. The long-term goal is to prepare the child with SCD for independent living. Introducing children and adolescents to adults with SCD who have coped successfully with their illness has a positive effect.

Recreation and Travel

Patients should be encouraged to exercise regularly on a self-limited basis. School-age children should participate in physical education, but they should be allowed to rest if they tire and encouraged to drink fluids after exercise. The potential risks of strenuous exertion should be discussed with the patient. Children and adolescents may engage in competitive athletics with caution because signs of fatigue may be overlooked in the heat of competition. Coaches are advised against blanket exclusion from participation or excessive demands for athletic excellence. Patients with SCD should dress warmly in cold weather and avoid swimming in cold water.

Children with SCD may benefit from attendance at a summer camp, either an appropriate regular camp or a special one for children with SCD. If the staff members are knowledgeable about the disease and comfortable with the care of these children, the campers can learn self-reliance and share experiences about SCD while having fun. Health care providers have found such camps to be a valuable experience for children with SCD.

Patients or families often seek advice on the best modes of travel. Flying in pressurized aircraft usually poses no problems for sickle cell patients; however, they should dress warmly to adjust for the cool temperature inside, drink plenty of fluids, and move about frequently when possible. On the other hand, travel above 15,000 feet in nonpressurized vehicles can induce vaso-occlusive complications. Ordinary travel by car, bus, or train is not associated with an increased risk of complications, although frequent rest and refreshment

stops should be taken. Patients are encouraged to consult their physicians before travel, and they are advised to carry with them specific medical information about their diagnosis, baseline hematologic values, a list of current medications, and the name and telephone number of their physicians. Providers should give patients the names of physicians or health care facilities to contact in case of emergencies.

TRANSITION TO ADOLESCENCE

Adolescence is a difficult time of life for youngsters with chronic diseases. While their peers become independent, teenagers with SCD may need frequent help due to illness. They can become frustrated and have trouble expressing their feelings. Concern about issues such as body size, sexual function, pain management, and death often is expressed as rebellion, depression, or refusal to heed treatment plans and medical advice.

Adolescents should be advised not to use tobacco, alcohol, and illegal drugs. Postpubertal adolescents should be educated about sexuality, safe sex practices, and the use of condoms to prevent sexually transmitted diseases. Girls should be counseled about the risks of pregnancy in women with SCD, safe birth control practices, and the merits of pregnancy at the right age and social circumstances.

Adolescents may view their long-time pediatric health care providers as too close to their parents and not speak frankly to them. In this case, families could be referred to adolescent medicine specialists to discuss sensitive issues and preparation for adulthood. Alternatively, adolescents may be able to express their concerns through "teen support groups."

The change from a pediatric to an adult care setting is often difficult, and adolescents should be given help to access adult care facilities. In some centers, this transition is eased by concurrent pediatric/adolescent/adult sickle cell clinic sessions. Chapter 6 provides more information about how to facilitate the patient's transfer from pediatric to adult health care specialists.

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Adolescents with sickle cell disease (SCD) face the same challenges as their healthy counterparts. They desire acceptance by their peers but, at the same time, wish to become more independent. Additional help is needed to transition to new health care providers and facilities (1). In a prospective study of over 3,500 patients (2), the course of SCD varied as patients matured, but the frequency of pain episodes correlated with disease severity. Patients older than age 20 with frequent painful events had the greatest risk of early death, indicating that continuity of care is important to minimize morbidity and mortality. Communication with the patient, family, and multiple providers is needed, but coordination may be difficult between different departments, such as pediatric and adult clinics.

ISSUES

Several factors conspire to make transition difficult. Young people with SCD become familiar with the pediatric environment and providers to whom they may literally owe their lives. Adolescent bravado may result in a tendency to deny illness and a reluctance to go to a strange adult care facility. Adolescents desire independence as adults but may not be ready to face new responsibilities for appointments and medications. For example, although young patients with SCD feel healthy, they must have routine ophthalmology exams to forestall blindness. They also need support to deal with issues such as contraception, sexually transmitted diseases, and family planning.

Moreover, the current health care environment tends to neglect the needs of patients with chronic disorders. Insurers seek groups of young and healthy people to reduce costs. Patients with chronic illnesses such as SCD frequently lose medical coverage when they become legally independent of their parents. To reduce expensive hospitalizations, integrated transition programs can provide age-appropriate treatment and continuity of care from pediatric to adult facilities.

CLINICAL FINDINGS

Studies from the Duke Comprehensive Sickle Cell Center show that a patient's coping style significantly predicts the extent of health care contact, activity, and psychological distress (3). Patients with *active coping styles* (use of multiple cognitive and behavioral strategies) had fewer emergency room visits. Those using *passive adherence* coping styles (reliance on concrete, passive approaches to pain, such as resting, without resourcefulness when initial efforts fail) had more emergency room visits and participated in fewer activities at home and in school. Another study found that *negative thinking* (expression of fear and anger) correlates with psychological distress (4). Nine months after the initial assessment, these studies showed that the coping strategies of younger children and adults are relatively stable, but those of adolescents are in flux. For individuals who rely on less adaptive strategies (passive adherence or negative thinking), adolescence may be

a period when these maladaptive styles predominate. This stress complicates transition.

The unpredictability and stress of SCD pain episodes affects the entire family, but the extent of the psychological impact varies among studies. Some show little psychological variation between adjustment in siblings and patients, and little difference from population norms (5), while others show significant stress on siblings (6). Parents' coping styles also affect children's activity levels, distress, and coping strategies. Kramer (7) found 49 percent of the parents of SCD patients in their sample to be clinically depressed according to the Center for Epidemiological Studies Depression scale (CES-D). Programs exist to improve the education and coping of family members, reduce daily strain, and teach stress management techniques (8,9).

IMPLEMENTATION OF TRANSITION

ASSESSMENT

The members of a transition team include physicians, mid-level practitioners (e.g., nurses or physician assistants), and social service workers—from both pediatric and adult facilities. Each of these providers views patients from a different perspective, so they must meet together often to assess readiness of patients and their families for transition. Written medical records may not contain enough details of a patient's history, so verbal discussion of "group" knowledge helps. New providers can miss problems when presented with just a discharge summary and list of medications. The meetings also give providers who treat adults a chance to ask questions and to assure pediatricians that patient needs will be met.

Physicians and nurses are the primary health care providers for most people with SCD, but

pediatric and adult teams are organized differently, which creates problems with transition. General pediatricians often are the focus of care for children with SCD, and hematologists are usually consultants. This structure was established because all children need to see pediatricians for development checks and routine immunizations. Since many children with SCD have few other problems, general pediatricians are the main contacts, and pediatric hematologists advise about additional interventions such as pneumococcal vaccination and penicillin prophylaxis.

By contrast, most adolescents and young adults ages 18–30 are healthy, so few see health care providers for preventive measures. The result is that hematologists become the primary providers for young people with SCD. Because patients must take the initiative for health maintenance, their readiness to accept this responsibility should be assessed.

A patient's chronologic age should not automatically trigger transition. Some 18-year-old youths are not ready to go from pediatric to adult care, so developmental age is a more appropriate guide. For instance, delayed neurocognitive development from cerebrovascular injury may hamper a patient's ability to adjust to adult health care until age 20 or 21. Similarly, a patient who has just experienced a serious complication, such as acute chest syndrome, is unprepared psychologically for transition to new providers.

Social service workers play a major role in assessment, since they have more contact with patients and parents than any other members of the team and can judge how families deal with psychosocial problems of chronic illness, such as anxiety and depression. If they concur that the patient and family are ready for transition, the subject should be broached to the parents and child well ahead of time to prepare them.

PREPARATION AND SUPPORT

All parties—patients, providers, and facilities—must agree beforehand on a plan for transition, which is an orderly movement of the patient's medical care from one set of places and providers to another. This is a process that occurs gradually, in contrast to an abrupt transfer of locale. The idea of transition is mentioned a year or so before the process begins, to prepare families mentally; reading material can reinforce the concept between clinic visits. Patients and providers should make plans together to ensure they are clear to all. Providers can gauge success at each point, and patients may ask questions and voice concerns.

For parents, transition to adulthood entails loss of responsibility for, and control over, their child's medical care. They often have difficulty relinquishing the central role, and this can produce resistance to the transition effort. Reassurance that the pediatric and adult providers will remain in contact is important to alleviate the fear that the pediatricians are abandoning them. Patients, parents, and providers should view transition as a positive milestone. Together, they have achieved a significant step and should be congratulated. Adult providers then become positive additions to an already successful team.

One of the most effective ways to dispel fears of transition is to make contact with people who have gone through the process. Support groups with older adolescents and young adults are particularly helpful. Community events, such as picnics or holiday celebrations, often work better than meetings because they focus on activity rather than disability, and discussion is easier without health providers.

Institutional administrators are also important to support transition programs, which require personnel allocated by the administration. A single provider without nursing or social service support cannot deliver care or transition patients adequately. Some pediatric facilities have an upper age limit for inpatient care, and transition may be suboptimal if patients with delayed development are transferred to adult facilities just because of age.

TRANSFER PROCESS

The pediatric providers should introduce the adult team to the patient and parents in the pediatric setting first, if possible. In this familiar environment, the family will have a chance to clarify details of the transition before a last pediatric visit. Pediatric providers should not simply give patients the phone number and instruct them to call. At the last pediatric visit, providers should schedule the next appointment as they normally do, but it will be with the adult team. The first transferred clinic appointment is a crucial test of transition. A member of the adult team should escort the family to the new facility, and introduce them to the staff there. Patients with SCD may find it hard to locate a new clinic, especially if they are symptomatic. For example, a pain episode is not the best time to meet new providers in a strange place.

If the patient misses the next appointment, a pediatric team member (e.g., social worker) should call and work with the patient, parents, and adult providers to resolve any issues. A "no show" at the adult facility may be an indirect way to ask for more help with the transition process. Often, patients are reluctant because the adult clinic is unfamiliar, yet they will not return to the pediatric clinic, which they perceive to have discharged them. Continuity is lost, and patients may suffer a medical catastrophe.

Young adults with mild SCD tend to skip followup with specialists who can prevent complications of SCD. For example, asymptomatic retinal blood vessel proliferation may result in ocular hemorrhage unless treated by an ophthalmologist before visual loss occurs. Prevention is a key step in the management of SCD, but young people may be lost during the transition from pediatric to adult care and suffer unnecessarily. Intervention, coaching, and continued support can avert this potential disaster.

Other obstacles may exist, due to the infrastructure of the medical system. The best situation is where good programs for children and adults with SCD coexist, and efforts are coordinated easily. However, when health care delivery is unbalanced (e.g., a strong pediatric program but a weak adult one), transition is more difficult.

Most children with SCD are the offspring of heterozygous parents who have health insurance. They have fewer chronic complications than adults, and hospitalizations occur mainly for self-limited painful events. In contrast, adults with SCD have difficulty keeping steady jobs because their organ damage progresses. Thus they often require government assistance, but these programs lack full coverage, such as for transition programs. The combination of chronic illness and poor reimbursement deters some adult providers from the care of patients with SCD. Adult providers sometimes feel they are given only problem patients, while pediatricians keep those who are easiest to treat. Frequent transition team meetings where adult and pediatric providers discuss the

patients can dispel such misconceptions. In fact, institutional commitment to transition programs should be bolstered by data indicating that a well-organized adult care program for SCD is financially beneficial (10). Both professional and lay patient advocates should make this point known.

If no local adult care program exists, pediatricians may hold on to their patients and treat problems outside their area of expertise (e.g., ischemic heart disease). Nevertheless, they also should empower the patients to deal with an unfamiliar system. They should give parents a summary of the child's medical course for use in emergencies. This should include copies of basic records, such as immunizations, blood type, complications, and current medications, especially those that work during an acute pain episode.

SUMMARY

Transition programs prepare an adolescent to assume responsibility for his or her health care. The primary charge lies with the pediatric providers, whose first step is to assess the readiness of the patient and family. The transition process encourages the gradual maturation of relationships with adult providers via steps that are designed individually, due to differences among institutions, providers, and patients. Such development does not occur automatically, and a comprehensive transition program is not always possible. Nevertheless, adult providers and administrators should be enlisted to deliver continuous care, which can avert medical disasters.

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There have been significant improvements in the outlook for adults with sickle cell disease (SCD). The Cooperative Study of Sickle Cell Disease (CSSCD) and other observational studies have helped to define the prognosis and common complications that occur as the patients age. Improved management of infections and central nervous system (CNS) complications in childhood, active health maintenance for adults, new interventions, and improved psychosocial support have all contributed to a reduction in morbidity and mortality.

The prognosis in SCD has dramatically improved over the past 30 years. Estimates based on the mortality in the CSSCD indicate a median survival of 42 years for males and 48 years for females with SCD-SS disease and 60 years and 68 years, respectively, for SCD-SC disease (1). Patients are now living into the seventh and eighth decades. More than 90 percent of patients of all phenotypes will survive past age 20, and significant numbers are older than age 50 (1). Risk of early death in adults with SCD is associated with acute complications such as pain episodes, anemic events, acute chest syndrome, chronic renal failure, and pulmonary disease (2).

CHALLENGES

Improved survival provides opportunities to improve the quality of life for patients with SCD; however, it also provides unique challenges in health maintenance. The frequency of pain

episodes increases in early adulthood (3). Hydroxyurea provides the first pharmacologic intervention that reduces the frequency of pain episodes in adults (4). Proliferative retinopathy is a life-long risk that increases in prevalence with age (5). Vision may be compromised by these vascular changes that predispose to retinal hemorrhages, retinal detachments, and increased intraocular pressure (5). Renal glomerular disease is prevalent in adults and may cause increasing anemia, renal failure, and premature death (6-8). Prevalence of chronic pulmonary disease and pulmonary hypertension also increases as patients age, and may contribute to morbidity and mortality (9). Complications such as leg ulcers and osteonecrosis of the hips and shoulders cause chronic pain and disability, which require social and vocational adjustments (10,11). Essentially unstudied are the pain episodes that many women experience in association with menstruation and the increased frequency and severity of pain episodes near menopause. Geriatric challenges in patients with SCD are not well studied.

Health maintenance activities must also address interactions between SCD and other common health problems of the adult population. Individuals with relative hypertension and SCD have an increased risk of strokes and increased mortality, and therefore treatment for hypertension is an important aspect of health care (12) (see chapter 15, Cardiovascular Manifestations). Patients with SCD are not protected from developing cancer

as they age (13). Diabetes, asthma, arthritis, atherosclerotic vascular disease, and other chronic illnesses may occur concurrently and provide unique challenges in managing patients with SCD.

Many adults are well adjusted socially and psychologically. Others, however, experience problems including anxiety and depression, and have difficulty forming and maintaining relationships, finding and keeping employment, and participating in usual daily activities (14-16). There is an increased need for social and psychological support services to maximize adjustment and productivity in adults with SCD (14-16).

RECOMMENDATIONS

Ongoing care of the adult patient includes preventive health maintenance, early recognition and treatment of complications, continuous assessment of social status, psychological assessment and support, and continuing patient education. Such services can be effectively accomplished only during regularly scheduled well-patient visits where effective doctor-patient relationships are established and medical, social, and psychological issues are addressed.

INITIAL HEALTH MAINTENANCE VISIT

The initial visit provides an opportunity to establish rapport with the patient and his or her family and to determine the patient's medical and social needs, as well as psychological strengths and challenges. A complete database should be developed that includes the information outlined in table 1.

ONGOING HEALTH CARE VISITS

Initially, a number of visits every 1 to 2 weeks will facilitate developing rapport, discussing laboratory and other test results, completing the initial database, developing a problem list and care plan, and exploring active social or psychological issues. Routine medical evaluations are scheduled approximately every 2 to 6 months, depending on the patient's phenotype and active problems. The database is updated at every visit. Blood counts, reticulocyte counts, and urinalysis are repeated at each visit to establish a baseline and detect problems. Pulse oximetry at each visit is also helpful. Routine chemistry tests should be repeated at least annually. Complications such as chronic organ failure, other medical problems, or complex psychosocial problems often require more frequent visits and more extensive evaluations.

Patients with hypertension, proteinuria, increased creatinine, renal tubular acidosis, or hyperuricemia should have more extensive and regular evaluation of renal function (see chapter 19, Renal Abnormalities in Sickle Cell Disease). Individuals, especially those with sleep apnea or chronic hypoxia requiring oxygen therapy with pulmonary disease or symptoms, should have regular pulmonary function studies and evaluation of pulmonary hypertension. Patients should have an annual ophthalmology examination for retinopathy, increased ocular pressure, and refraction errors. Followup examinations of patients with significant proliferative retinopathy is scheduled by the ophthamalogist at more frequent intervals (see chapter 14, Sickle Cell Eye Disease).

In many populations, tuberculosis screening should be done annually. Tetanus immunizations are kept up to date, hepatitis vaccine is given, and influenza vaccines are administered annually based on recommendations of the

Table 1. Patient Database

Demographic Information
- Name, address, phone number, family contacts, social security number, birth date
- Insurance status

Historical Information
- Names, addresses, and phone numbers of past physicians
- History of SCD related complications and other medical problems since birth
- Characteristics of pain episodes:
  - frequency
  - duration
  - usual home treatment
  - usual emergency department treatment
  - average number and duration of hospitalizations
- Past medical treatment:
  - surgery
  - transfusions—number, reactions, alloantibodies
  - major complications, e.g., cerebrovascular event (CVA), liver, renal, or eye diseases
- Immunization history
- Medications and allergies
- Family history, including sickle cell, hypertension, diabetes, cancer, others
- Complete review of symptoms by system

Objective Data
- Complete physical examination
- Complete blood counts, reticulocyte count, hemoglobin phenotype, liver profile, electrolytes, BUN, creatinine
- If transfused, consider ferritin, hepatitis serologies, and red cell phenotype
- Urinalysis including testing for microalbuminuria
- Chest x ray and other x rays depending on historical and physical findings
- Electrocardiogram in older patients or those with cardiac symptoms or findings
- Ophthalmology evaluation for retinopathy

Social and Psychological Profile
- Level of education and school success
- Occupational history, hobbies, and leisure activities
- Financial resources
- Compliance with treatment and appointments
- Coping strategies, mental health, depressive symptoms, and stressors
- Family support, family participation in health care, past compliance
- Habits, including smoking history, alcohol use, and use of recreational drugs
- Sexual history, including birth control and safe-sex techniques

Centers for Disease Control and Prevention (CDC). Pneumococcal vaccine is repeated every 5 years. Annual testing for HIV and hepatitis C may be indicated for patients who are sexually promiscuous. Women should be taught to practice breast self-examination, have an annual breast examination by a physician, and have mammograms with a frequency based on family history and age as recommended by the American Cancer Society (ACS). Males should be screened for prostatic specific antigen after age 50. Screening for colon cancer is based on family history and age as recommended by the ACS.

PATIENT EDUCATION

Initial evaluation should include assessment of the patient's and family's understanding of SCD. Educational activities should focus on correcting deficits in knowledge about more common complications such as infection, gallstones, aseptic necrosis, acute chest syndrome, leg ulcers, and priapism. Patients should be taught to seek medical care for persistent fevers greater than 38°C (100°F); chest pain, cough, and shortness of breath; symptoms of acute anemia including weakness, dyspnea, or dizziness; abdominal pain with nausea and vomiting; respiratory infection with a productive

cough; symptoms of urinary infection; or unusually severe headaches. Preventive care includes learning physical limits and regularly participating in health maintenance, which includes following medication and immunization recommendations, protecting lower legs, and practicing safe sex. It is extremely important to discuss the specific risks to individuals with SCD associated with use of alcohol, cocaine, marijuana, and cigarettes.

All patients require education about appropriate management of pain. They must be taught to recognize the sources and intensity of their pain and to use appropriate therapeutic interventions. Headaches, menstrual cramps, strain, and muscle pains are best managed with aspirin, nonsteriodal anti-inflammatory drugs (NSAIDs), and acetaminophen. Treatment of SCD-associated pain is initiated with these agents. Physical therapy interventions—such as use of rest and heat, drinking fluids, and using relaxation or distraction—are taught. If the pain is not controlled by these measures, the patient is taught to seek medical care.

Patients and families should be reassured that appropriate use of narcotics to adequately control pain does not lead to addiction. They should be encouraged to use only the required dosages of medication, follow medical directions, and not use the medication for stress, anxiety, or other purposes.

The occurrence of chronic pain from avascular necrosis, leg ulcers, and other complications requires intense education so that patients understand that the goals of therapy for chronic pain are different from those for pain control during acute episodes. These goals are to minimize pain, increase pain coping skills, and maintain maximum social and physical functioning. In addition to pain medications, treatment may require nonpharmacologic

interventions such as occupational and physical therapy, behavior modification, and other neurocognitive interventions.

Nutritional counseling is also important, with the goal of maintaining ideal body weight. Underweight individuals may require nutritional support. A number of patients need weight reduction, especially if they are overweight and develop complications such as avascular necrosis and diabetes. Folic acid supplementation is recommended for patients with sickle cell anemia, although the optimum dose to normalize homocysteine levels has not been determined. Many patients take other vitamins and nutritional supplements, but there is no strong scientific evidence for their use.

Young adults with SCD must be taught to approach activities in a way that minimizes excessive stress, exhaustion, dehydration, and extremes in temperature. Moderation and self-monitoring of exertion level is the rule. Thus individual, rather than team, sports generally are preferred. Exercise is encouraged, but activities should be regular and slowly progressive. Hydration with water is important before, during, and after physical activities. Cold exposure is minimized by adequate dressing and avoidance of swimming in cold water. Patients with avascular necrosis should maintain ideal body weight, avoid vocations that require prolonged standing or heavy lifting, and refrain from power weight lifting and exercise that involves running or jumping.

With proper hydration, most patients can tolerate air travel in planes pressurized to 2,200 meters (17). Patients going above this altitude in the mountains or in unpressurized aircraft may experience pain episodes and other complications (17). With advance arrangements, most airlines will provide supplemental oxygen for patients who have experienced problems in the past or who have other medical problems

that may contribute to risk of complications. There is anecdotal evidence that persons with splenic function may be at higher risk during air travel.

Childbearing and birth control should be discussed with patients and their partners (see chapter 23, Contraception and Pregnancy). Discussions should include the risks during pregnancy, the potential for spontaneous abortion, and the physical and emotional challenges of raising an infant. Resources for patient support during and after the pregnancy should be explored. Preconception education should include genetic counseling and testing of the partner. Pre- or postconception genetic counseling should include discussion of prenatal diagnosis.

VOCATIONAL GOALS

Individuals with SCD should be encouraged to complete their education and pursue vocations. Jobs requiring strenuous physical exertion, long work hours, exposure to hypoxia, or extremes in temperature may not be tolerated and should be discouraged, especially if the patient has increased symptoms when engaged in the vocation.

Higher education and advanced vocational training can provide vocations and professions that are ideal for individuals with SCD. Many young adults seem to have more frequent and severe pain episodes during the first years of college. This may be related to the rigors of academic pursuits, excesses because of increased independence, or perhaps, directly related to the natural history of the disease (3). Carefully teaching the individual to establish excellent study habits and to practice moderation in social activities usually will reduce the frequency of complications. These changes, along with discussions with faculty and advisors, almost always allow motivated students

with SCD to complete their studies; however, more time may be required than is usual for students without medical problems.

Patients must also be encouraged to discuss their disease with their employers. Maintaining employment may require intervention by the health care provider to explain limitations to the employer, provide excuses for absences from work, and complete forms for the employer. Health care providers also should be familiar with legal protection against discrimination in the workplace, as provided by the Americans with Disabilities Act. Individuals with severe disease, cerebral vascular accidents, and avascular necrosis may truly be disabled. In these situations, the health care provider should actively assist in obtaining benefits for the patient.

COUNSELING

Social services and psychologic support activities are a critical component of comprehensive health maintenance in sickle cell patients (18). These activities are best accomplished if social workers and mental health professionals are integrated into the sickle cell care team. Social workers are invaluable in solving a myriad of social and family problems. Mental health workers can assist in managing psychiatric problems such as depression, teaching coping skills, and giving instruction in cognitive and behavioral management of pain. Nurses are an essential part of the support team because they have ongoing interactions with the patients and their families that facilitate identification of special patient and family needs. Nurses coordinate health care efforts and education about preventive health care, and provide ongoing psychosocial counseling.

Vocational rehabilitation services are also important in adult health maintenance. Patients with inadequate education can receive training

in order to acquire satisfying employment that supports independent and productive life styles. This greatly improves their self-image and often has a positive impact on their health and utilization of health care resources. For example, occurrence of avascular necrosis or leg ulcers in patients with jobs that require prolonged standing often requires training to allow them to qualify for desk jobs.

DENTAL CARE

Routine dental care is important to prevent loss of teeth and infections that may lead to other SCD complications. Dental procedures that require local anesthesia can be performed in the dentist's office as with any other patient. Procedures requiring general anesthesia necessitate hospitalization and may require the usual perioperative care recommended for sickle cell patients (see chapter 24, Anesthesia and Surgery). Patients with a history of rheumatic heart disease, mitral valve proplapse, heart murmurs, or those with implanted venous access catheters and orthopedic prothesis should receive antibodics for subacute bacterial endocarditis (SBE) prophylaxis with tooth extractions, aggressive dental hygiene activities, gum surgery, or root canal therapy.

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ONLINE RESOURCES

http://www.emory.edu/PEDS/SICKLE

COORDINATION OF CARE:

ROLE OF MID-LEVEL PRACTITIONERS

Patients with sickle cell disease (SCD) require multidisciplinary care. They often need assistance to navigate the subspecialties of required providers. Nurses, nurse practitioners, and physician assistants, often referred to collectively as mid-level practitioners (MLPs), are well-qualified to coordinate patient care because they are familiar with holistic approaches.

Patients and their families also need help to manage the daily problems of living with a chronic disease. Issues for MLPs include preventive and primary care, pain management, transfusion and chelation therapy compliance, and education of patients and other health care providers.

MULTIDISCIPLINARY AND SUBSPECIALTY COORDINATION

The MLP is a liaison between the patient, primary care provider (often the patient's hematologist), and specialists. The MLP's important functions are to make appointments, encourage patients to keep them, and implement the recommendations. Patients may require a number of specialists—surgeons for indwelling intravenous access devices; obstetricians/gynocologists for birth control counseling, PAP smears, and later, menopause management; nephrologists for renal evaluations; cardiologists for cardiac function tests (especially as patients age); psychologists for counseling; and social workers for help with welfare, social security, housing, or disability benefits.

PREVENTIVE CARE

Each patient encounter is a chance to stress the importance of preventive health care. Physical exams, eye exams, and PAP smears should be done yearly. Immunizations, EKGs, and pulmonary function tests are also important but, unfortunately, may get overlooked in busy practices. Ways to help patients remember their annual preventive care needs include timing appointments with their birthdays and reminder letters. Providers can review and track their patients' needs with the use of computerized databases and calendar functions.

Young patients and their families should be trained to recognize the signs of infection and other life-threatening complications of SCD. They also should learn how to use a thermometer and palpate the spleen. The MLP must stress constantly the importance of prophylactic penicillin and check that parents give it properly. Parents should be taught when to call their child's health care provider or seek care at a medical facility.

Discussions about sexuality start when patients are teenagers, since they are more likely to ask for help if the subject already has been raised. Because pregnancy poses a risk for women with SCD, they often are advised to use birth control, especially those taking hydroxyurea or deferoxamine mesylate (Desferal) (1,2). If no history of thromboembolism exists, they can safely use any method, including oral contraceptives, Depo Provera,

or Norplant. The MLP should ensure that patients use birth control properly and obtain annual PAP smears and STD checks as required.

Over time, as patients learn about their medical history and the importance of regular health care visits, they are encouraged to be proactive. They should be empowered to choose their own primary care providers and make their own appointments.

MANAGEMENT OF PAIN EPISODES

(SEE CHAPTER 10, PAIN)

HOME MANAGEMENT

Painful events are the most common manifestation of SCD. Oral analgesics can be used to manage most mild-to-moderate pain episodes at home. Nonmedical therapies, such as hot baths and showers, massage, distraction, and relaxation techniques, also can relieve pain. Patients should contact their health care providers for any symptoms such as fevers, chest pain, difficulty breathing, or pain that occurs in atypical locations or is more severe than usual. Providers must educate patients and their families about basic pain management principles, use of nonopioid medications [such as nonsteriodal anti-inflammatory drugs (NSAIDs) and antidepressants], use of opioid drugs, and the signs of overuse or abuse.

Adults with SCD often experience chronic pain, managed by daily use of prescription opioids. The MLP must be vigilant in checking the patient's intake of opioids at home, and should intervene if there is any suggestion of misuse. A computerized pharmacy database can help track usage over time. As few providers as possible should write prescriptions for a patient. When patients know they can only receive pain medication from one or two providers, they are less likely to try "shopping around" for multiple prescriptions. A team approach, which includes the primary care providers, pain management experts, and a social worker, is ideal to help patients manage chronic pain.

DAY TREATMENT CENTER MANAGEMENT

When a painful event no longer can be treated with oral analgesics, patients are encouraged to go to a day treatment center or emergency room (3,4). Hospitals with many sickle cell patients have dedicated day treatment clinics, but in locations without such facilities, sickle cell patients can be treated in chemotherapy infusion suites that have been developed for oncology patients. Outpatient day treatment has advantages over the use of emergency rooms, including the usually more prompt administration of intravenous or intramuscular pain medications. The MLP, who is familiar with the patient, acts as a resource for the day treatment staff and provides key information and recommendations about each patient's needs. The MLP also assesses the patient for any complications that require referral to a physician or admission. Again, the patient's need for preventive services, prescription refills, or any other general health issues should be reviewed. Aggressive outpatient treatment of moderate-to-severe pain, coupled with consistent, supportive care from familiar staff, often can prevent hospitalization.

INPATIENT MANAGEMENT

When hospitalization is needed for a pain episode or any other SCD complication, patients should be admitted consistently to the same unit if possible. They should be treated with intravenous opioids, by patient-controlled analgesia pumps, or even by patient-controlled epidural analgesia pumps if available and required (see chapter 10, Pain).

The MLP follows the patient and offers background about the usual course of illness, including the patient's behavior and response to treatment. This information makes patient care a better experience for the in-house staff. The MLP's input can help the patient receive appropriate and effective treatment, rather than being undertreated or viewed as "difficult" or "drug seeking." Regular phone contact or rounds with house staff provide education on disease management. MLPs also should schedule in-service training for nurses to improve care for sickle cell patients.

EMERGENCY DEPARTMENT CARE

By adulthood, all SCD patients have had many emergency room visits. The most common complaint about emergency care is inappropriate treatment of their disease (5,6). MLPs can educate emergency department staff about the course and complications of SCD and proper pain management. Emergency physicians often undertreat or overtreat painful episodes, not because of lack of knowledge about SCD but because of their unfamiliarity with certain patients. Given the rapid pace in most emergency rooms, quick access to individual patient care plans is essential. Computerized records, patient "identification" cards, or a phone call to the patient's health care provider are all ways to transmit information rapidly to emergency department personnel.

A two-sided identification card (7), about the size of a business card, can contain enough information to ensure prompt initial treatment for most sickle cell patients. The card contains pertinent medical history, baseline labs, allergies, outpatient medications, the usual treatment plan for the patient's pain episodes, and the name and telephone number of the patient's primary health care provider. The latter also signs the card to give it the

authority of a medical record. The card is laminated to be carried at all times by the patient.

TRANSFUSIONS AND CHELATION THERAPY

(SEE CHAPTER 25, TRANSFUSION, IRON-OVERLOAD, AND CHELATION)

For patients being transfused regularly, MLPs coordinate the schedules and tests for iron overload. Persons on transfusion regimens usually have few painful events, so they can go to school or work full time. Ideally, transfusions should not interfere with these activities, and they are given on evenings or weekends at many sickle cell centers. If transfusions can be arranged only during regular business hours, some patients will need help to discuss this issue with school staff or their employer.

SCD patients should be transfused with leukocyte-poor, antigen-matched blood to reduce the frequency of transfusion reactions and the development of antibodies (8). Finding antigen-matched blood is often difficult in areas where blood donors are primarily Caucasian. Providers should encourage blood donations by African Americans as part of their community education efforts.

When iron overload is documented, patients are started on iron chelation therapy. MLPs should teach children and their families about the serious complications of iron overload, and to understand that iron chelation is an integral part of transfusion therapy, not something to be ignored because of its inconvenience. Desferal, the only iron chelator available at this time, is given by slow, daily, subcutaneous infusion. MLPs need to monitor compliance with chelation therapy. If children are begun on Desferal soon after chronic transfusions start, compliance during the difficult teen years may be greater.

PREGNANCY MANAGEMENT

(SEE CHAPTER 23, CONTRACEPTION AND PREGNANCY)

Women with SCD can successfully carry pregnancy to term or near term. If a patient on hydroxyurea is planning or trying to conceive, the drug should be stopped immediately. The MLP informs the patient and her family that the frequency and severity of pain episodes may increase during pregnancy, but treatment is the same as that for nonpregnant patients, with hydration, oxygen, and analgesics, although doses of the last may be higher. Reassurance should be given that narcotic use during pregnancy does not jeopardize the baby's health, but if large doses of opioids are needed late in pregnancy, the newborn may require opioid weaning.

The pregnancy should be comanaged by high-risk obstetrics and primary and mid-level SCD health care providers. Patients are seen every few weeks to reinforce healthy behaviors. The MLP educates obstetric staff about current standards of treatment for SCD during pregnancy and advocates for patients to ensure proper treatment of painful events.

Prophylactic transfusions during pregnancy are not warranted unless there are complications such as acute chest syndrome that ordinarily would be treated with transfusions. There is no overall decrease in pain frequency, premature labor, or deliveries for women who are transfused prophylactically during pregnancy (9).

EDUCATING FAMILIES AND THEIR COMMUNITIES

Family education is an integral part of care for patients with SCD. Family members gradually should reduce their involvement in their child's health care so that the patient can become more independent. This process is not easy, and supportive assistance and counseling are important.

SCD health care providers can inform their patients' communities about SCD by speaking at meetings. Communities can become involved through providing social support, job opportunities, and blood donations. As patients go through different life stages, more of their contacts will have to be educated.

SUMMARY

MLPs want patients to be independent, well-informed, and active participants in their own health care. Therefore, coordination must balance fostering independence and ensuring optimal health care. Patient advocacy is a rewarding aspect of the MLP's experience of working with SCD patients.

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Psychosocial Management

Sickle cell disease (SCD) is a complex condition that affects the patient, the family, and the patient's and family's relationship with health care providers and the community. It is imperative that teaching the skills necessary for coping with this illness begin at the time of diagnosis and continue throughout the life of the patient, and that providers recognize that including the extended family and the community in the education process will ensure the most positive outcome.

SUMMARY OF THE STATE OF THE ART

No interventions are proven to work with all patients in all situations (1-15). While a team knowledgeable about chronic illness and existing intervention models is ideal, available staff sensitive to the special needs of these patients can provide effective interventions even in primary care settings. Providers must recognize that the complexities of SCD necessitate a team approach to management. Clinical management, pain control, coping skills, genetic counseling, and community interactions, including school and work intervention, require different expertise. The establishment of Comprehensive Sickle Cell Centers introduced the concept of comprehensive care for SCD and refined the multidisciplinary team approach to health care. Psychosocial support was recognized as a necessary, integral function of the health care team. However, psychosocial interventions should be woven across the spectrum of medical care.

Historically, psychosocial interventions were reserved for emergency situations. Psychologists or social workers were called for acting-out behaviors, housing emergencies, noncompliance issues, and other crises. Crisis situations may be minimized by identifying specific points at which psychosocial interventions may be necessary and planning for them, thus eliminating the frustration and ineffectiveness often experienced by patients and caregivers.

Pain, the most well-known symptom of SCD, is the reason for most hospitalizations and precipitates many psychosocial crises. Skills for coping with pain and other complications of SCD must be taught early and reinforced often (8,9). Which patients will have mild diseases and which will have a more severe course is not predictable; however, stress is known to play an important role in the severity of chronic illness and pain. Absence of the physical appearance of trauma in severe SCD pain episodes can confound a patient's ability to cope. In addition, many health care providers are not knowledgeable about sickle cell pain, its causes, and the best management options. This can lead to poorly controlled pain, continued treatment failure, and frustration of patients and providers.

RECOMMENDATIONS

PRENATAL

The availability of prenatal diagnosis offers the family choices regarding the continuation of the pregnancy. When the decision is made to continue, the practitioner has time to assist the family in preparing for the arrival of a child with SCD. This time must be spent educating the parents and family about the disease and the need for family and community support. The better educated the family and the community, the better care the patient will receive. Many communities have SCD support groups that provide an avenue for sharing anxieties, as well as helpful information (5). Whenever possible, satisfactory housing, accessible optimal medical care, and reliable transportation must be planned before the baby arrives.

INFANCY

Health insurance, emergency transportation, housing, and anxiety about recognizing symptoms are some of the issues new parents may need help acknowledging and addressing. Frequent clinic visits and home visits will allow the opportunity for parents and providers to establish a comfortable relationship to address these issues and help establish an ongoing pattern of compliance.

Although advances in medical research have increased the chances for longevity, lack of understanding on the part of providers may result in inappropriate treatment plans that defy adherence. The establishment of clinical practice guidelines in SCD has decreased—but not eliminated—preventable deaths. In addition, non-compliance may undermine the best care plans.

In many cases, a concerted effort to understand the causes underlying noncompliant behaviors is necessary. Skepticism of the health care system, as well as barriers to access—such as location of clinics, laboratories, and pharmacies—can all contribute to noncompliance (11).

CHILDHOOD

The most important task of childhood is obtaining an education. Teachers must understand that children with SCD should be expected to perform as well as their peers, although special education is often needed. Although undetectable micro-infarcts may cause brain injury, many of the learning difficulties these cause can be overcome with appropriate assistance. Failure to perform in school could be a function of neurological complications of SCD, but the lack of school success could also be confounded by socioeconomic factors. Disabilities and limitations must be acknowledged but, more important, strengths must be identified and inspired. Pediatric health care professionals, in their desire to protect children with chronic illness, often inadvertently erect barriers to normal childhood behaviors and accomplishments. While addressing special needs and routine childhood health care, allowances must be made for regular school attendance (by flexible scheduling of appointments), for activity (by offering alternatives to inappropriate sports), and for learning (by providing support and education to school staff).

ADOLESCENT HEALTH CARE AND TRANSITION

For a discussion of the transition from pediatric to adult health care, see chapter 6, Adolescent Health Care and Transitions.

Adult

As longevity of SCD patients increased, the need for continued comprehensive care became evident; however, while pediatric centers thrive, adult providers are scarce. Long-term management needs to focus not only on health care needs but on the other goals of psychosocial well-being—education, independence, and (eventually) marriage and family.

In adulthood, reproductive issues are of major concern and often are not addressed in a positive manner. Most individuals, including those with disabilities, hope to achieve normalcy, (e.g., independence, a meaningful job, and a family) (13). One barrier to care may be providers' lack of understanding of the multiple layers of learning needed to live with SCD and the realities of trying to be "normal" and fitting in. The pain experienced by many patients with SCD can be demoralizing and overwhelming. In addition to the psychological effects of inadequately treated pain, patients have the added stress of continually searching for effective pain relief, resulting in frequent emergency room visits and episodic care. This cycle can lead to depression, which is highest among the chronically ill and in the 20-40 age group, and is often not recognized or addressed. Continued comprehensive care—including a strong psychosocial component—for adults with SCD is most important, since prevention of complications is the key to longevity.

CONCLUSIONS

Psychosocial issues confronting patients, families, providers, and the community, though multiple and multifactorial, can be addressed and result in positive patient outcomes.

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TREATMENT OF ACUTE AND CHRONIC COMPLICATIONS

PAIN

The hallmark clinical manifestation of SCD is the acute vaso-occlusive event, or painful episode. This unique type of pain can start as early as 6 months of age, recur unpredictably over a lifetime, and require treatment with opioids. Painful events are the top cause of emergency room visits and hospitalizations, and are a major focus of home management (2). Management of pain in childhood affects a person's ability to cope as an adolescent and adult. Past, present, and anticipated experiences affect pain management, so pain must be assessed and treated in a developmental and psychosocial context.

Major barriers to effective management of pain are clinicians' limited knowledge of SCD, inadequate assessment of pain, and biases against opioid use. Biases are based on ignorance about opioid tolerance and physical dependence, and confusion with addiction. Unwarranted fear of addiction is common among patients and families, as well as health care workers. Clinicians should ask about pain

and use patients' reports as the primary source for assessment, except in infants where behavioral observations are the main basis for evaluation. Most SCD pain can be managed well if the barriers to assessment and treatment are overcome; a comprehensive psychosocial clinical assessment should be performed yearly (more often for patients with frequent pain).

TYPES AND CHARACTERISTICS OF PAIN ASSOCIATED WITH SICKLE CELL DISEASE

The most common pain states associated with SCD are summarized in table 1. When classified according to temporal characteristics, sickle cell pain can be described as acute, chronic, or mixed.

ACUTE PAIN

The acute painful event is the most common type of pain, characterized by an unpredictably abrupt onset without any other explanation. Intensity varies from a mild ache to severe and debilitating pain. Uncomplicated acute pain is self-limited and generally lasts hours to a few days, but it can persist or recur and may migrate from one site to another. With comorbid conditions or inadequate treatment, some painful events can last for weeks.

CHRONIC PAIN

Chronic pain often is defined as pain that lasts 3 to 6 months or more and that no longer serves a warning function. The time

distinction is arbitrary, and the condition may be difficult to distinguish from frequently recurring acute pain, as in SCD. Chronic pain (e.g., from bone changes) can be debilitating, both physically and psychologically. The involvement of sensation, emotion, cognition, memory, and context can pose difficult management problems (4).

MIXED PAIN

Pain frequently is mixed as to type and mechanism due to confounding factors. Acute pain can be superimposed on chronic pain, and frequent episodes of acute pain can resemble chronic pain. Neuropathic pain is insufficiently diagnosed in SCD but can result from nerve infarction, compression from bony structures, nociceptive substances, and/or iron overload neuropathy.

RECOMMENDATIONS FOR ASSESSMENT AND TREATMENT OF PAIN

A dedicated facility, such as a day hospital, which includes experts to manage SCD pain, can reduce overnight admissions and provide timely relief (5). Should this resource be unavailable, the following approach is recommended

for patients with painful episodes due to SCD. Patients should undergo a thorough history and physical examination to determine whether an illness might have precipitated the pain, so that the cause and symptom can be treated simultaneously. Patients should be seen immediately by a physician if they experience severe abdominal pain, recurrent vomiting, respiratory symptoms, neurologic signs of paresis or paralysis, acute joint swelling, priapism, or abrupt fall in hemoglobin. Superimposition of acute pain on chronic pain may confound assessment and treatment.

Clinicians should understand the pain in detail to tailor therapy to the needs of the patient. Assessment depends on chronologic age, developmental stage, functional status, cognitive ability, and emotional state, so these factors should be considered in the choice of measurement tools. Pain management should be aggressive to relieve pain and achieve maximum function. Physicians should reassess pain frequently and adjust treatment to provide relief.

ASSESSMENT OF PAIN IN SCD

The goals for assessment of acute and chronic pain are to characterize a patient's pain and related experiences, provide a basis for therapeutic decisions, and document the efficacy

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Table 1. Major Pain Syndromes in Patients with Sickle Cell Disease (3)

Acute Pain Syndrome	Chronic Pain Syndrome
Acute chest syndrome	Arthritis
Cholecystitis	Arthropathy
Hand-foot syndrome	Aseptic (avascular) necrosis
Painful episodes	Leg ulcers
Priapism	Vertebral body collapse
Right upper quadrant syndrome	
Splenic sequestration	

---

of pain control. Because pain is subjective, assessment requires patients' self-reports, valid tools, and measurements repeated over time. Clinically, self-reports are supplemented by physical findings, laboratory data, and diagnostic procedures. Figure 1 is a flowchart to guide clinicians in pain assessment.

There are two major kinds of assessment:

- Rapid assessment of an acute painful episode. This type of assessment deals with an isolated pain event and focuses on pain intensity, prompt treatment, and relief.

- Comprehensive assessment *for chronic pain or followup* of persons who have acute pain. This type of assessment usually occurs at the end of a painful episode, at office/clinic visits for chronic pain, or between episodes. The objective is treatment planning (4), which involves the patient, family (6), and health care team. Assessment is multidimensional and should include physiologic, sensory, affective, cognitive, behavioral, and sociocultural factors.

Figures 2 to 4 are examples of assessment instruments. Figure 2 is a unidimensional "Faces' Pain" intensity scale (7,8), and figures 3 and 4 show a visual analog scale (VAS) (9) and multidimensional scales for either chronic or acute pain assessment. Diaries are also useful for assessment of pain at home (10).

Rapid Assessment of Acute Pain Episodes

Severe pain should be considered a medical emergency that prompts timely and aggressive management (figure 5) until the pain is tolerable. The following recommendations are for treatment in the emergency room, day treatment center, or hospital if the patient is admitted directly.

- Begin hydration. Total fluids should not exceed 1.5 times maintenance (including volume for drug infusions). Initial fluid should be 5 percent dextrose + half-normal saline + 20 mEq KCl/L, adjusted for serum chemistry results.

- Assess the patient for the cause of pain and complications.

- Rapidly assess pain intensity using a simple measurement tool.

EMERGENCY TREATMENT OF ACUTE PAIN EPISODES

Initial Treatment

The patient in acute pain at an emergency room or clinician's office usually has exhausted all homecare options. Failure of home or outpatient therapy signals the need for parenteral medications, which include strong opioids like morphine. If a patient is on long-term opioids at home, tolerance may have developed, so the new episode can be treated with a different opioid or with a higher dose of the same drug if it is the only one the patient tolerates.

In general, medications and loading doses should be selected after assessment of the patient's current condition and consideration of the patient's history, including

- usual drugs, dosages, and side effects during acute pain.

- effective treatments at home.

- medications taken since the onset of present pain.

For patients with recurrent pain, the best initial dose of opioids for severe sickle cell pain is that which provided adequate analgesia at a previous time. Some patients and clinicians may prefer a loading dose of parenteral morphine, usually equivalent to 5-10 mg (0.1-0.15 mg/kg for children), depending on pain
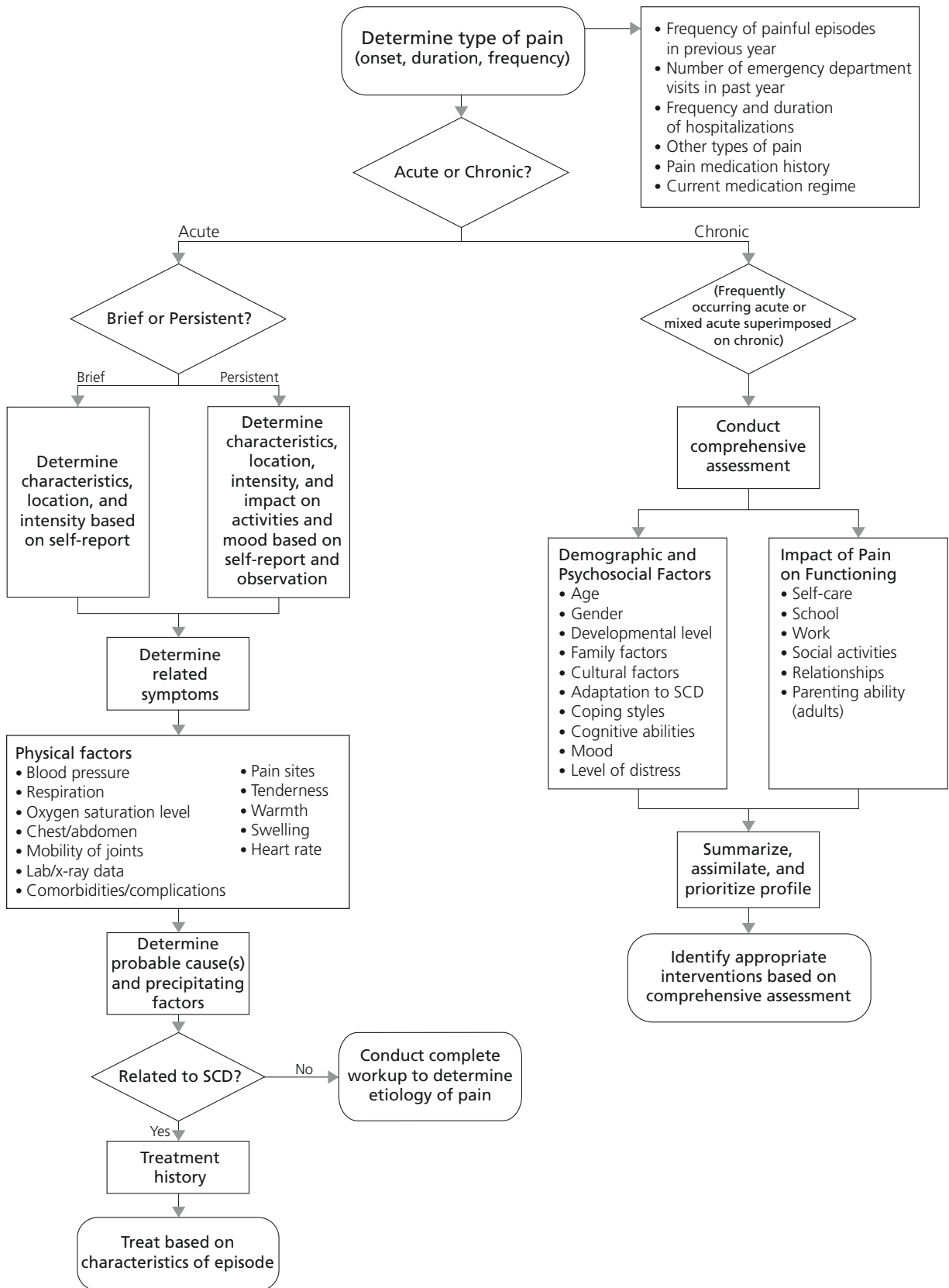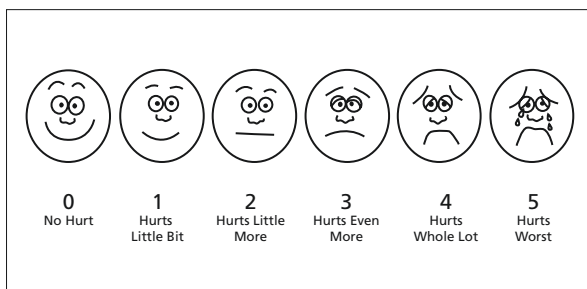
Figure 1. Assessment Overview

Figure 2. Wong-Baker Faces Pain Rating Scale (7,8)

intensity, patients' size, and prior opioid experience. Smaller doses of 2.5-5 mg (0.05-0.1 mg/kg for children) can be added later.

- Intramuscular administration of medication should be avoided, if possible, because absorption is unpredictable and children may find this method frightening and painful.

- For severe pain, intravenous (IV) administration is the route of choice. For patients with poor venous access, many opioids can be administered via the subcutaneous route by bolus dosing, continuous infusion, or patient-controlled analgesia pumps (PCA).

Patients who receive opioid agonists should not be given mixed opioid agonist-antagonists (e.g., pentazocine, nalbuphine, butorphanol), because they can precipitate withdrawal syndromes.

Frequent Reassessment
Assess the pain before pharmacological intervention, at the peak effect of the medication, and at frequent intervals, until the adequacy and duration of the medication's effects have been determined. Define the measure to be used in determining response to therapy. For example, on a scale of 0 to 4 (0 = none, 1 = little, 2 = moderate, 3 = good, and 4 = complete), relief could be defined as a score of 2 or greater and a pain intensity reduction of at

least 50 or 60 percent from the upper end of the pain scale. Evaluate the response to therapy 15 to 30 minutes after each dose by assessing pain intensity, relief, mood, and sedation level. Frequency of reassessment should take into account the route of administration. Record the pain assessment and reassessments, along with the patient's other vital signs, in the patient's chart and/or on a bedside flowsheet, so that the effectiveness of treatment can be evaluated in a timely manner.

Titration to Relief
The recurrent, lifelong nature of the pain must be considered for consistent management of acute pain episodes, so the pain is made tolerable and side effects are minimized. Figure 6 presents three titration methods used in different situations. Scheme 1 is an aggressive approach when close observation is possible. After the loading dose, one reassesses the patient at 30-minute intervals and, based on the results, treats with one-quarter to one-half of the loading dose until the patient experiences relief. Scheme 2 is for more gradual titration. The patient is started immediately on "by the clock" (BTC) doses based on prior history (e.g., morphine, 8 mg every 2 hours). "Rescue" doses are used for titration between BTC doses until relief is achieved. Scheme 3 is for titration using PCA.

Medications may be combined to enhance the efficacy/safety ratio. Anti-inflammatory agents, acetaminophen, antihistamines, and other adjuvant medications can be used with opioids. Side effects, such as respiratory depression, should be monitored and treated.

If a patient has pain between doses, the intervals could be decreased or the dose increased. For patients on large doses of opioids, an alternative approach is to change to one-half the equianalgesic dose of another opioid and repeat titration to relief.

Figure 3. Memorial Pain Assessment Card (9)

For adolescents and adults, the card is folded along the broken line so that each measure is presented separately in the numbered order.

4
Mood Scale

Worst mood |————————————————| Best mood

3
Relief Scale

No relief of pain |————————————————| Complete relief of pain

1
Pain Scale

Least possible pain |————————————————| Worst possible pain

2

Moderate   Just noticeable

Strong   No pain

Mild

Excruciating   Severe

Weak

Figure 4. Multidimensional Assessment of Acute Pain

DATE ____/____/_____   TIME ____:_____

1. Circle the number that describes your pain right now.

0   1   2   3   4   5   6   7   8   9   10
No pain   Worst possible pain

2. Circle the number that describes your pain relief.

0   1   2   3   4   5   6   7   8   9   10
No relief   Complete relief

3. Circle the number that best describes your mood.

0   1   2   3   4   5   6   7   8   9   10
Worst mood   Best mood

4. Circle the number that describes how drowsy you feel.

0   1   2   3   4   5   6   7   8   9   10
Not drowsy   Asleep

5. Shade the figure where you feel pain.

6. Mark an X where you hurt most.

FRONT

RIGHT   LEFT

BACK

LEFT   RIGHT

Change the medication delivery route or regimen if the pain is poorly controlled with boluses, or if doses are required too frequently for relief. Intraspinal analgesics, which require anesthesiology consultation, should not be considered before an adequate trial of maximal doses of systemic opioids and adjuvant medications; however, case studies suggest that epidural anesthetics alone or with fentanyl can be effective in acute refractory pain of SCD (11).

Disposition

After treatment in an emergency room, patients may be sent home or admitted as inpatients. Prescriptions for equianalgesic doses of oral opioids should be written for home use if needed to maintain pain relief. If pain does not diminish significantly after rigorous therapy, the patient should be admitted as an inpatient.

PHARMACOLOGICAL MANAGEMENT OF SICKLE PAIN

Analgesics are the foundation for the management of sickle cell pain, and their use should be tailored to the individual patient. Sedatives and anxiolytics alone should not be used to manage pain, because they can mask the behavioral response to pain without providing analgesia.

Management of pain associated with SCD consists of the use of nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and adjuvant medications (12,13). Management of mild-to-moderate pain should include NSAIDs or acetaminophen, unless there is a contraindication; these are nonsedating, so patient activities can continue. If mild-to-moderate pain persists, an opioid can be added.

Treatment of persistent or moderate-to-severe pain relies on repeated assessments and appropriate increases in opioid strength or dose. The type of oral preparation used depends on the characteristics and expected duration of the pain. If the patient's pain typically is of short duration (less than 24 hours), opioids or formulations with a short duration of action are appropriate, with the advantage of quicker onset of action. For patients whose pain requires several days to resolve, a sustained-release opioid preparation is more convenient to take and provides a more consistent analgesia.

The combination of nonopioid analgesics with opioids can permit lower doses of the latter. If an opioid like codeine is used, pain relief is accompanied by mild sedation that can facilitate rest.
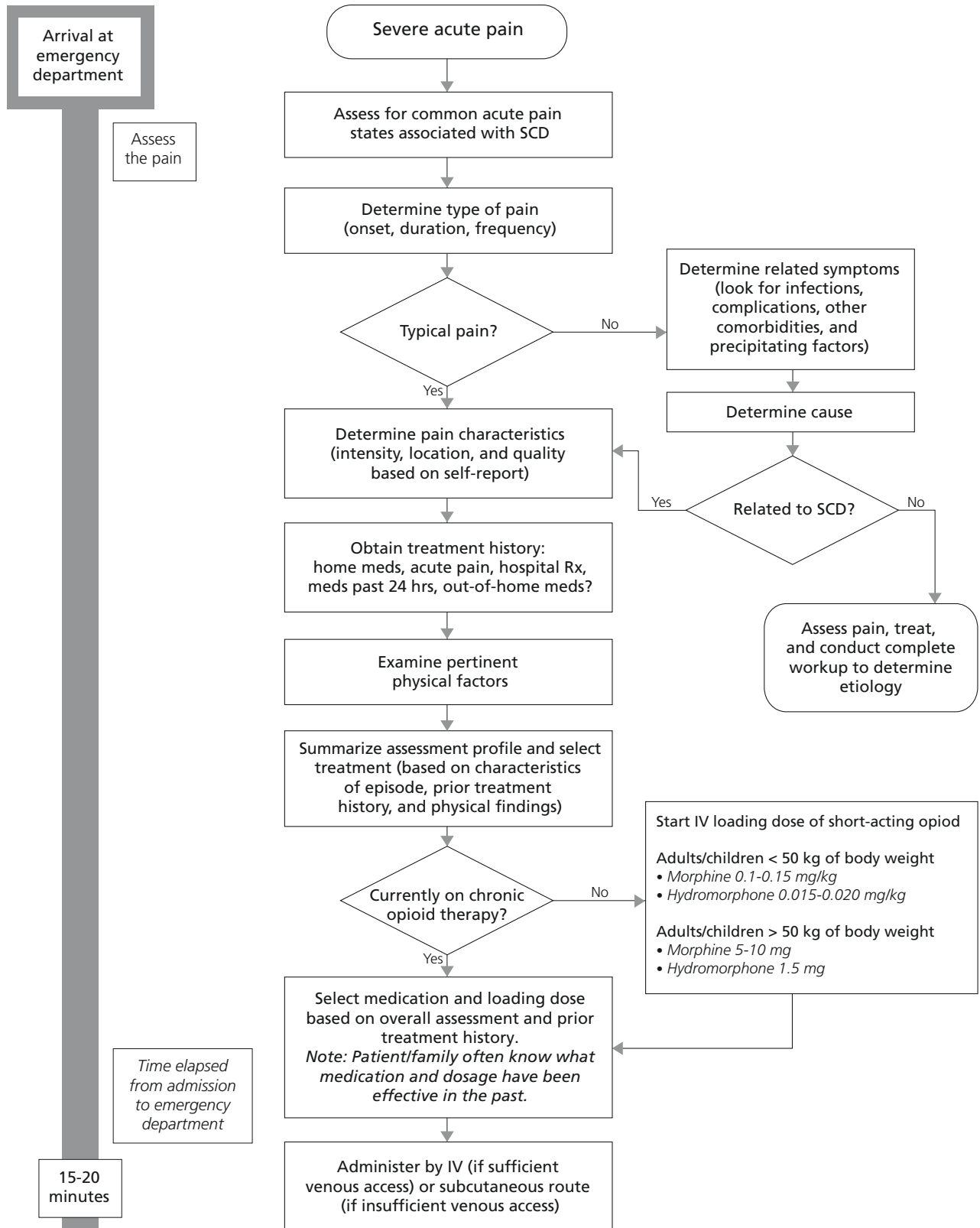
NSAIDs and Acetaminophen

Mild-to-moderate pain in children with a fever or viral syndrome generally is managed with NSAIDs or acetaminophen; aspirin is avoided due to a risk of Reye's syndrome. Acetaminophen is an analgesic but not an anti-inflammatory drug, and both NSAIDs and acetaminophen have ceiling doses above which escalation does not result in increased relief. Most NSAIDs are given only orally, except for ketorolac, which can be used orally or parenterally.

NSAIDs and acetaminophen are not benign. Many patients with SCD have varying degrees of hepatic impairment, and acetaminophen may be toxic when liver disease is present. NSAIDs also are contraindicated in patients with gastritis, peptic ulcers, coagulopathies, and renal failure. All NSAIDs are associated with renal failure when used on a long-term basis, and patients must be told not to exceed safe doses of these medications.
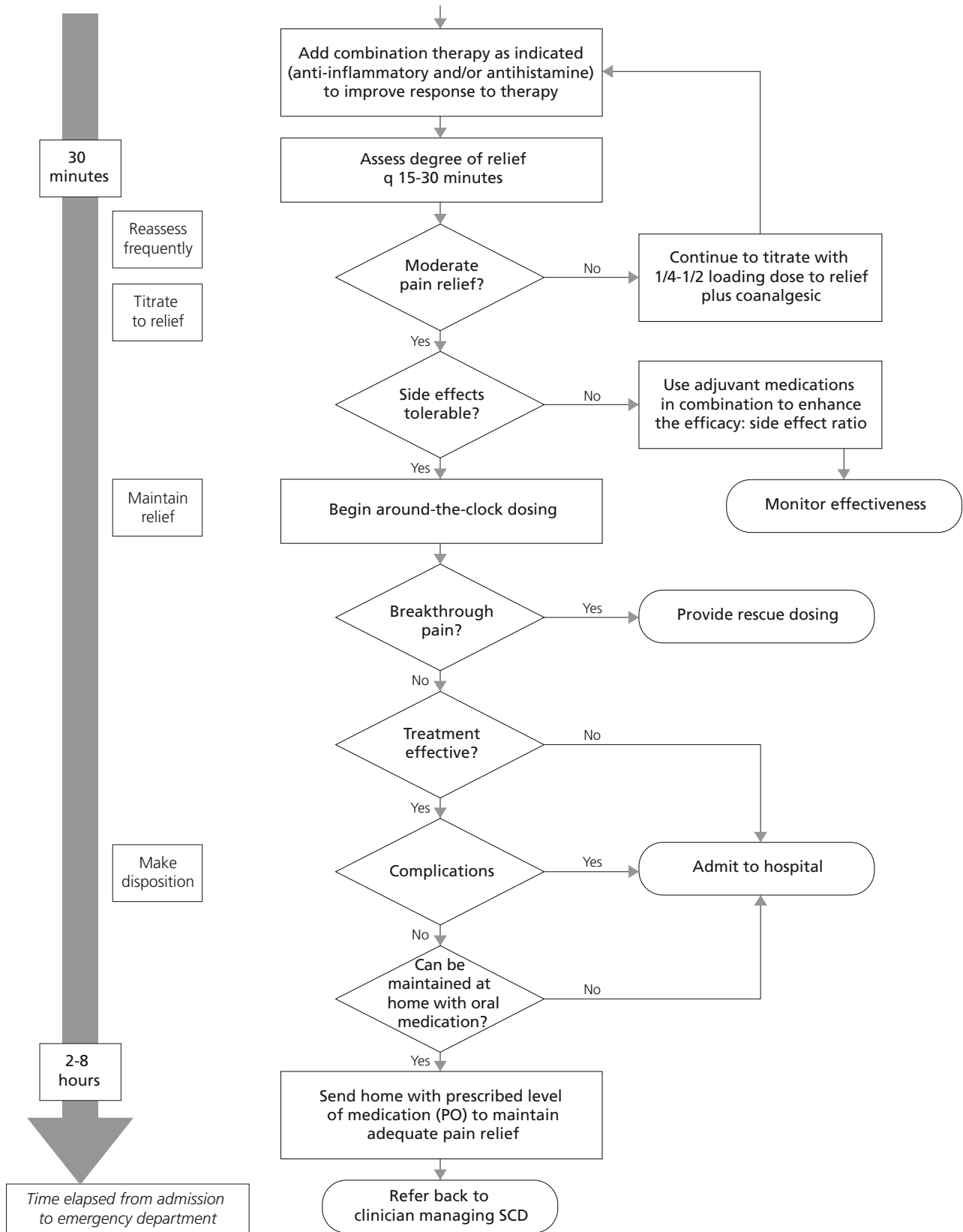
Clinicians should monitor doses and frequency of treatment, and order urinalyses and renal function tests every 3 to 6 months in chronic users. Current trials have been inconclusive regarding use of the parenteral NSAID

Figure 5a.

Figure 5b.

30 minutes	↓

Add combination therapy as indicated (anti-inflammatory and/or antihistamine) to improve response to therapy

Assess degree of relief q 15-30 minutes

Reassess frequently

Titrate to relief

Moderate pain relief? — No → Continue to titrate with 1/4-1/2 loading dose to relief plus coanalgesic

Yes

Side effects tolerable? — No → Use adjuvant medications in combination to enhance the efficacy: side effect ratio

Yes

Maintain relief

Begin around-the-clock dosing

Monitor effectiveness

Breakthrough pain? — Yes → Provide rescue dosing

No

Treatment effective? — No

Yes

Make disposition

Complications — Yes → Admit to hospital

No

Can be maintained at home with oral medication? — No

Yes

2-8 hours

Send home with prescribed level of medication (PO) to maintain adequate pain relief

Refer back to clinician managing SCD

Time elapsed from admission to emergency department

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ketorolac as a single agent. It may be added to opioids in situations in which opioids provide inadequate analgesia after optimal titration, or when the side effects of opioids are problematic. Due to the need for more safety data, the current recommendation is that ketorolac should not be used by any route or combination of routes for longer than 5 days in a given month because of the increased risk of toxicity (14).

Opioids

Moderate-to-severe pain is treated with opioids (figure 6, tables 2-3), with or without NSAIDs and adjuvant medications. Codeine-equivalent opioids, such as oxycodone and hydrocodone, are used for moderate pain. When opioids are given for the first time for severe pain, morphine sulfate or hydromorphone should be used. Other morphine-equivalent opioids include oxymorphone, levorphanol, meperidine, fentanyl, and methadone.

Considerations in opioid selection include type of pain, analgesic history, pain intensity, route of administration, cost, local availability, provider comfort with analgesic modalities, and patient preference. Patient preference should not be ignored, because it is likely that individual variations in drug metabolism contribute to differences in adverse effects or dose-response to analgesia. The recurrent nature of SCD pain often allows the patient to experience multiple treatment options and learn which regimen provides predictable relief.

Meperidine is the most commonly used opioid in hospitals for SCD patients with acute painful episodes. Many patients prefer meperidine because of long-standing prescribing practices of physicians, and they are apprehensive about changing to a different medication. There is general agreement, however, that *oral* meperidine should not be used for acute or chronic pain, and the indication for *parenteral*

meperidine use for acute sickle pain is controversial. Ideally, *parenteral* meperidine should no longer be used as *first-line* treatment of *acute* pain in SCD *because of CNS toxicity related to its metabolite, normeperidine.* It has a long half-life and is a cerebral irritant, so accumulation can cause effects ranging from dysphoria and irritable mood to clonus and seizures. Thus, meperidine should be reserved for brief treatments in patients who have benefited, who have allergies, or who are intolerant to other opioids such as morphine and hydromorphone.

Meperidine should not be used for more than 48 hours or at doses greater than 600 mg/24 hours (13). Because normeperidine is excreted by the kidneys, *meperidine is contraindicated for patients with impaired renal function as well as for patients who are taking monoamine oxidase inhibitor antidepressants.*

Fentanyl is in the same chemical family as meperidine and can be used parenterally. In addition, a transdermal fentanyl preparation can be an adjunct for managing *chronic* sickle pain because it has a 48-72 hour duration and provides continuous analgesic effect by a noninvasive, nonoral route of administration. Hypoventilation and respiratory depression can occur with the use of fentanyl (14).

Chronic Opioid Therapy. For patients with several days of pain, or who require chronic opioid therapy, sustained-release or long-half-life opioid preparations are more convenient and provide more consistent analgesia. Short-acting opioids may be used for rescue dosing early in the treatment regimen for breakthrough pain, or until the sustained-release preparation reaches steady-state levels. In these situations, the administration of adjuvant medications may be needed to control predictable opioid side effects such as pruritus, nausea, sedation, and constipation.
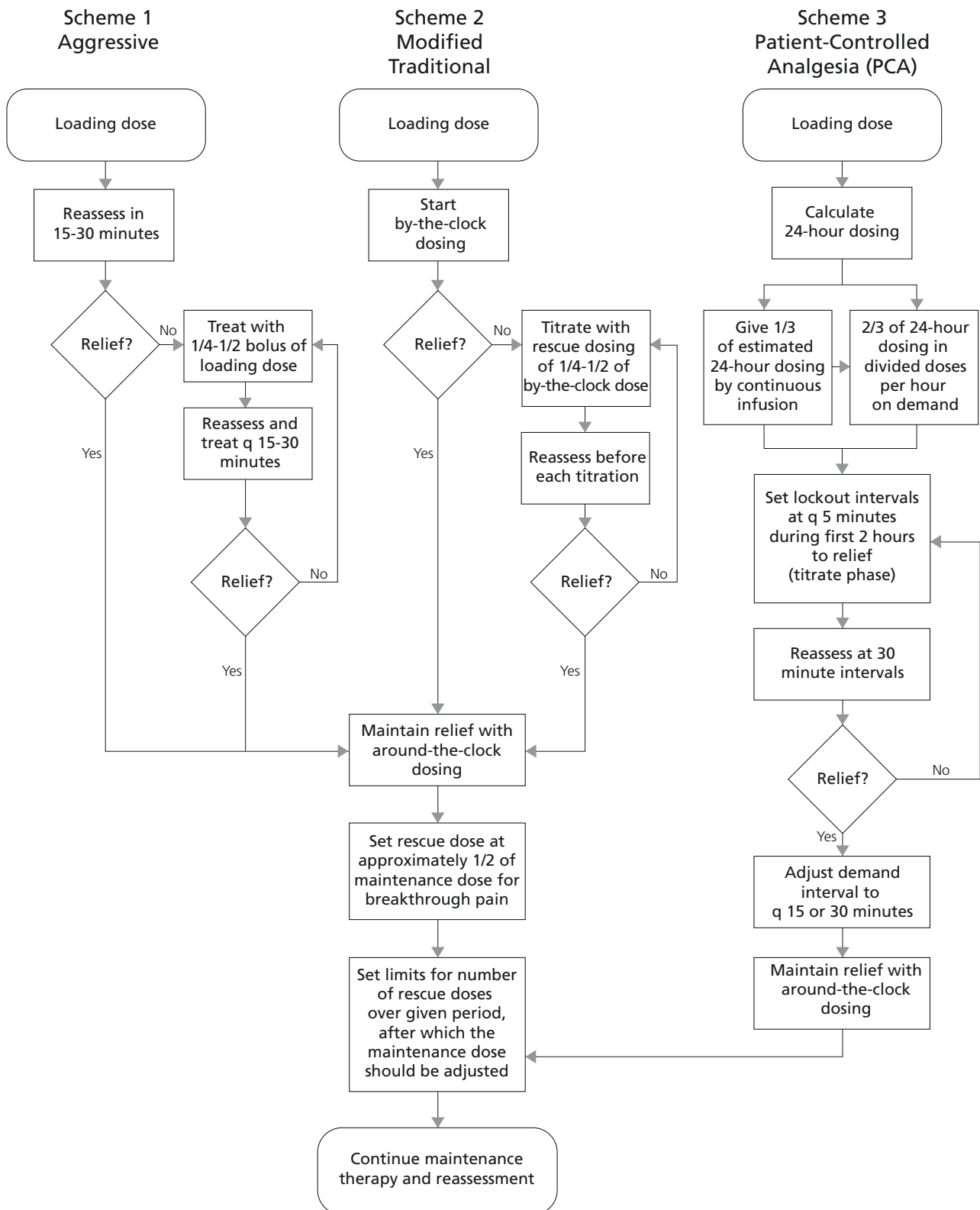
Figure 6. Titration Schemes

Scheme 1
Aggressive

Loading dose → Reassess in 15-30 minutes → Relief? — No → Treat with 1/4-1/2 bolus of loading dose → Reassess and treat q 15-30 minutes → Relief? — No (loops back) / Yes → Maintain relief with around-the-clock dosing. Relief? — Yes → Maintain relief with around-the-clock dosing

Scheme 2
Modified Traditional

Loading dose → Start by-the-clock dosing → Relief? — No → Titrate with rescue dosing of 1/4-1/2 of by-the-clock dose → Reassess before each titration → Relief? — No (loops back) / Yes → Maintain relief with around-the-clock dosing. Relief? — Yes → Maintain relief with around-the-clock dosing → Set rescue dose at approximately 1/2 of maintenance dose for breakthrough pain → Set limits for number of rescue doses over given period, after which the maintenance dose should be adjusted → Continue maintenance therapy and reassessment

Scheme 3
Patient-Controlled Analgesia (PCA)

Loading dose → Calculate 24-hour dosing → Give 1/3 of estimated 24-hour dosing by continuous infusion / 2/3 of 24-hour dosing in divided doses per hour on demand → Set lockout intervals at q 5 minutes during first 2 hours to relief (titrate phase) → Reassess at 30 minute intervals → Relief? — No (loops back) / Yes → Adjust demand interval to q 15 or 30 minutes → Maintain relief with around-the-clock dosing

Table 2. Usual Starting Doses of Opioid Analgesics in Opioid-Naive Adults and Children ≤ 50 kg Body Weight[1]

Medication	Usual Starting Dose for Moderate-to-Severe Pain	
	Oral	Parenteral
Short-acting opioid agonists[2]		
Morphine[3] (MSIR)	0.3 mg/kg every 3-4 h	0.1-0.15 mg/kg every 2-4 h
Hydromorphone[3] (Dilaudid)	0.06-0.08 mg/kg every 3-4 h	0.015-0.020 mg/kg every 3-4 h
Meperidine[4] (Demerol)	not recommended (1.1-1.75 mg/kg every 3-4 h only if deemed to be necessary after evaluation).	not recommended (0.75-1.0 mg/kg, 1.1-1.75 mg/kg every 3-4 h only if deemed to be necessary after evaluation).
Combination opioid/NSAID preparations[5]		
Codeine[6] (with aspirin or acetaminophen)	0.5-1mg/kg every 3-4 h	not recommended
Hydrocodone (in Lorcet, Lortab, Vicodin, others)	0.15-0.20 mg/kg every 3-4 h	not available
Oxycodone (Roxicodone, also in Percocet, Percodan, Tylox, others)	0.15-0.20 mg/kg every 3-4 h	not available
Long-Acting Opioid Agonists (e.g., morphine controlled-release, Levorphanol, methadone, and oxycodone controlled-release)	Because is not possible to determine the appropriate starting dose of controlled-release opioids without knowing the patients's opioid requirements as determined by immediate-release preparation, usual starting doses are not listed for these medications.	

[1]Caution: Doses listed for patients with body weight less than 50 kg cannot be used as initial starting doses for babies younger than 6 months of age.

[2]Caution: Recommended doses do not apply to patient with renal or hepatic insufficiency, or other conditions affecting drug metabolism and kinetics.

[3]Caution: For morphine, hydromorphone and oxymorphone, rectal administration is an alternate route for patients unable to take oral medications. Equianalgesic doses may differ from oral and parenteral doses because of pharmacokinetic differences.

[4]Chronic administration of meperidine may result in central nervous system stimulation, including agitation, irritability, nervousness, tremors, twitches myoclonus, or seizures, due to accumulation of the toxic metabolite normeperidine. The risk is much greater for patients with renal or hepatic impairment.

[5]These products contain aspirin or acetaminophen. Total daily doses of acetaminophen that exceed 6 grams may be associated with severe hepatic toxicity. Aspirin is contraindicated in children in the presence of fever or other viral disease because of its association with Reye's syndrome.

[6]Caution: Codeine doses higher than 65 mg often are not appropriate because of diminishing incremental analgesia with increasing doses but continually increasing nausea, constipation, and other side effects.

DO NOT REPRODUCE TABLES 2 AND 3 WITHOUT INCLUDING THIS WARNING.
NOTE: Published tables vary in the suggested doses that are equianalgesic to morphine. Clinical response is the criterion that must be applied for each patient; titration to clinical responses is necessary. Because there is not complete cross-tolerance among these drugs, it is usually necessary to use a lower than equianalgesic dose when changing drugs and to retitrate to response.

Table 3. Usual Starting Doses of Opioid Analgesics in Opioid-Naive Adults and Children ≥ 50 kg Body Weight[1]

Medication	Usual Starting Dose for Moderate-to-Severe Pain	
	Oral	Parenteral
Short-acting opioid agonists[2]		
Morphine[3] (MSIR)	10-30 mg every 3-4 h	5-10 mg every 2-4 h
Hydromorphone[3] (Dilaudid)	7.5 mg every 3-4 h	1.5 mg every 3-4 h
Codeine[4]	15-60 mg every 3-6 h	
Meperidine (Demerol)[5]	not recommended (50 -150 mg every 3-4 h only if deemed to be necessary after evaluation).	not recommended (50-150 mg every 3 h only if deemed to be necessary after evaluation).
Oxymorphone[3] (Numorphone)	not available	1-1.5 mg every 6 h or 0.5 mg IV and cautiously titrate upward
Oxycodone (Roxicodone, OXYIR)	10 mg every 4-6 h	not available
Long-Acting Opioid Agonists (e.g., morphine controlled-release, Levorphanol, methadone, and oxycodone controlled-release)	Because is not possible to determine the appropriate starting dose of controlled-release opioids without knowing the patients's opioid requirements as determined by immediate-release preparation, usual starting doses are not listed for these medications.	

[1]Caution: Recommended doses do not apply to adult patients with body weight less than 50 kg. For recommended starting doses for children and adults less than 50 kg body weight, see table 2.

[2]Caution: Recommended doses do not apply to patient with renal or hepatic insufficiency, or other conditions affecting drug metabolism and kinetics.

[3]Caution: For morphine, hydromorphone, and oxymorphone, rectal administration is an alternate route for patients unable to take oral medications. Equianalgesic doses may differ from oral and parenteral doses because of pharmacokinetic differences.

[4]Caution: Codeine doses higher than 65 mg often are not appropriate because of diminishing incremental analgesia with increasing doses but continually increasing nausea, constipation, and other side effects.

[5]Chronic administration of meperidine may result in central nervous system stimulation, including agitation, irritability, nervousness, tremors, twitches, myoclonus, or seizures, due to accumulation of the toxic metabolite normeperidine. The risk is much greater for patients with renal or hepatic impairment.

Equianalgesic doses of oral opioids are prescribed for home use if needed for the pain relief achieved in the emergency room or day hospital, or for recurrence of severe pain. Opioid tolerance and physical dependence are expected with long-term opioid use and should not be confused with psychological dependence (addiction). Opioids should be tapered carefully in patients at risk for withdrawal syndromes.

Side Effects of Opioids. Sedation usually precedes one of the most feared side effects of opioids, respiratory depression. Fortunately, tolerance to this side effect develops faster than to the analgesic action; nevertheless, nurses should monitor sedation levels when patients are at risk. *If sedation persists after prompt intervention, then pulse oximetry, apnea monitors, and blood gas levels may be needed.*

Nausea and vomiting can be treated with antiemetics such as compazine, metochlorpropamide, or hydroxyzine. Pruritus can be treated with hydroxyzine or with diphenhydramine; smaller doses given more frequently may be more effective, causing less sedation than larger doses administered less often. Patients should not be considered allergic to an opioid only on the basis of itching. If opioids are prescribed for home use, patients also should take stool softeners daily to prevent constipation.

Adjuvant Therapies

Adjuvant medications are used to increase the analgesic effect of opioids, reduce the side effects of primary medications, or manage associated symptoms such as anxiety. No controlled studies of adjuvant medications in SCD have been done, and guidelines for their use are derived from use in other pain states.

Sedatives and anxiolytics can be given to reduce anxiety associated with SCD if pain also is being treated. When used alone, however, these drugs can mask the behavioral response to pain without analgesic relief. If they are combined with potent opioids, care must be taken to avoid excessive sedation. Although much distress and anxiety in patients is related to unpredictable interruption of normal activities and the uncertain duration of pain, some symptoms may be reduced by a consistent treatment plan.

Antidepressants, anticonvulsants, and clonidine can be used for neuropathic pain, and antihistamines may counteract histamine release by mast cells due to opioids.

TRANSFUSIONS
(SEE CHAPTER 25, TRANSFUSION, IRON OVERLOAD, AND CHELATION)

A small percentage of patients have unusually frequent and severe pain episodes. They have a poor quality of life and cannot perform daily activities. There is empirical evidence that chronic transfusions may reduce debilitating pain (15), but patients must be assessed periodically as part of a multidisciplinary pain program.

TOLERANCE, PHYSICAL DEPENDENCE, ADDICTION, AND PSEUDOADDICTION

A major barrier to effective management of sickle cell pain is a lack of understanding of opioid tolerance, physical dependence, and addiction. Tolerance and physical dependence are expected pharmacologic consequences of long-term opioid use and should not be confused with addiction.

- **Tolerance** is a physiologic response to the exogenous administration of opioids, and the first sign is decreased duration of medication action. When tolerance develops, larger doses or shorter intervals between doses may be needed to achieve the same analgesic effect.

- **Physical dependence** also is a physiologic response to the exogenous administration of opioids. It requires no treatment unless withdrawal symptoms—such as dysphoria, nasal congestion, diarrhea, nausea, vomiting, sweating, and seizures—occur or are anticipated. The risk varies among individuals, but when opioids are given for more than 5 to 7 days, doses definitely should be tapered to avoid physiologic symptoms of withdrawal.

- **Addiction** is a not physical dependence but, rather, a psychologic dependence. Addiction is a complex phenomenon with genetic, psychologic, and social roots. The use of opioids for acute pain relief is not addiction, regardless of the dose or duration of time opioids are taken. Patients with SCD do not appear to be more likely than others to develop addiction. The denial of opioids to patients with SCD due to fear of addiction is unwarranted and can lead to inadequate treatment.

- **Pseudoaddiction** (16) applies to patients who receive inadequate doses of opioids or whose doses are not tapered, and therefore they develop characteristics that resemble opioid addiction.

Understandably, some patients whose pain is managed poorly will try to persuade medical staff to give them more analgesic, engage in clock-watching, and request specific medications or dosages. Staff often regard this as manipulative or demanding behavior. Patients with SCD often are quite knowledgeable about the medications they take for their condition and the doses that have worked in the past. Requests for these specific medications and doses should not be interpreted as indications of drug-seeking behavior. In addition, patients who have had frequent painful episodes often behave in ways learned from prior experiences. A patient, for example, who believes that a medication will not be given unless he or she appears to be in severe pain may lie quietly when alone but begin to writhe and moan when a nurse or physician enters the room. Pseudoaddiction or clock-watching behavior usually can be resolved by effective communication with the patient to ensure accurate assessment and by adequate opioid doses.

As in the general population, some persons with SCD will use illicit drugs, such as cocaine. Patients who have problems with substance abuse require individual treatment to provide competent and humane management of their pain. *The treatment of patients who have problems with substance abuse is complex and is beyond the scope of this chapter; consultation with appropriate specialists should be considered.*

PATIENT EDUCATION

Education about pain management is the basis for collaboration among patients, families, and health care providers for optimal treatment. SCD is incurable, except possibly by bone marrow transplantation. Health care professionals should tell patients about hydroxyurea, the drug that is used prophylactically to reduce the frequency of acute painful events in severe cases. While no drug is approved for treatment of SCD itself during an acute episode, patients must be assured that when they do experience pain, it will be taken seriously and managed optimally with a plan.

Because patient needs change over time, the care plan must be assessed and modified accordingly. Nurses and physicians who care for inpatients with sickle cell pain should be trained to assess and manage pain so they do not unwittingly dismiss a patient's pain or cause an exacerbation of pain-related behaviors. Education of clinicians who work in emergency rooms or day treatment centers is also important because inconsistent or adversarial care given in these settings can cause mistrust or other problems that affect patients' relationships with other health care professionals.

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Infection is a major complication of sickle cell disease (SCD). Special preventive measures against infection exist in addition to routine immunizations; treatment regimens are based on local formularies and antibiotic sensitivity tests.

PREVENTION

STREPTOCOCCUS PNEUMONIAE SEPSIS

The single most common cause of death in children with SCD is *Streptococcus pneumoniae* sepsis (1,2). The unusual susceptibility results from two problems: splenic malfunction, and failure to make specific IgG antibodies to polysaccharide antigens. Two prevention strategies are recommended: vaccination and prophylactic penicillin.

Vaccination
Standard practice is to give a 23-valent *Streptococcus pneumoniae* polysaccharide vaccine (PPV23) to all children with SCD at 24 months of age (see chapter 5, Child Health Care Maintenance). Children with SCD typically do not respond to the vaccine as well as normal children, but it causes a rise in IgG antibody against the most immunogenic polysaccharides, and a lower response to less immunogenic polysaccharides. For example, previously immunized children with SCD at age 5 have specific IgG antibody concentrations comparable to healthy nonimmunized

children, without evidence of a "booster" effect (3). Unfortunately, the less-immunogenic antigens are probably responsible for vaccine failures, but the vaccine still should be administered to all children at age 2. Although it has not been shown formally to reduce *Streptococcus pneumoniae* sepsis,* the vaccine has potential benefits that compare favorably to the risks. The adverse effects are limited to local reactions in previously immunized individuals. Fortunately, a new conjugated *Streptococcus pneumoniae* vaccine has been developed, and it holds promise for being more immunogenic than the previous one, even in infants.

Prophylactic Penicillin
The single most important clinical study in SCD in the past 20 years was a randomized, placebo-controlled trial that demonstrated that the administration of penicillin twice a day prevents 80 percent of life-threatening episodes of childhood *Streptococcus pneumoniae* sepsis (4). This important milestone was the impetus for the aggressive newborn screening program enacted by most states. The goal is to identify all newborns with SCD and start them on prophylactic penicillin as early as possible. The recommended regimen is:

■ Newborn to 3 years:
 Penicillin VK, 125 mg orally twice daily
 (PO BID)

■ 3 to 5 years:
 Penicillin VK, 250 mg PO BID

To test the effectiveness of prophylaxis beyond 5 years of age, a followup study randomized 400 children (age 5 years) who had been on prophylactic penicillin to receive placebo or continue penicillin. After about 3 years of followup, there was no significant difference between the groups in the incidence of *Streptococcus pneumoniae* meningitis or sepsis (table 1).

The study demonstrated that it was safe to discontinue prophylactic penicillin at age 5 (5). Despite these results, some clinicians still continue prophylaxis beyond age 5, but this approach is less popular now that penicillin-resistant organisms have emerged (6). Prophylaxis does not eliminate nasopharyngeal colonization with *Streptococcus pneumoniae,* and it is associated with increased resistance to penicillin and other antibiotics in some series (7) but not others (8). An alternate (but unproved) approach for children older than age 5 is to prescribe penicillin for the onset of fever. This theoretically provides some treatment while the patient is on the way to the doctor. This "just in time" approach some-times is recommended as an alternative to prophylaxis for children with SCD-SC or SCD-S β^+-thalassemia, where the incidence of *Streptococcus pneumoniae* sepsis is lower than in sickle cell anemia (SCD-SS).

HEMOPHILUS INFLUENZAE AND *NEISSERIA MENINGITIDIS*

Historically, *Hemophilus influenzae* was a significant pathogen in children with SCD as well as normal children. Routine immunization with conjugated *Hemophilus influenzae* vaccine has reduced markedly the risk of infection. Another encapsulated organism, *Neisseria meningitidis*, classically infects individuals with poor or absent splenic function but is not a common pathogen in SCD. Routine immunization against this organism is not recommended unless there is an exposure or outbreak.

INFLUENZA

Viral influenza infections can cause severe morbidity in individuals with SCD. Yearly vaccination recommendations should be followed.

HEPATITIS

Intrahepatic sickling, dietary and transfusional iron overload, and transfusion-related hepatitis contribute to liver dysfunction in SCD. To minimize additional risk, some clinicians advise hepatitis B immunization. This is now routine for children and should be considered serious-ly for seronegative adults. Very little evidence supports routine vaccination against hepatitis A, although the rationale would be the same.

Table 1: Sepsis and Meningitis in Children after 5 Years of Penicillin Prophylaxis Who Were Randomized To Stop Prophylaxis at Age 5

Group	Number with Infection, N=200	95% Confidence Interval
Placebo	4 (2%)	0.5-5.0
Penicillin	2 (1%)	0.1-3.6

PREVENTION IN ADULTS

Virtually all adults with sickle cell anemia are functionally asplenic, but their immune systems have matured to allow type-specific polysaccharide antibody production. Because they are not as susceptible as children to overwhelming sepsis and the incidence of sepsis is relatively low, there is only anecdotal evidence about preventive strategies. *Streptococcus pneumoniae* vaccination is recommended for adults with SCD. Some patients keep penicillin on hand for fever, but most are not prescribed penicillin prophylaxis routinely.

EMPIRIC THERAPY

Most antibiotic treatments are started empirically, before culture results are available. Table 2 summarizes the pathogens that should be covered in different clinical situations (9-12). Additional information on some specific situations follows.

FEVER WITHOUT A SOURCE

Febrile patients with SCD should be evaluated and treated in the context of functional asplenia. In essence, this means more rapid and intensive evaluation (exam, blood counts, cultures, x rays) and lower threshold for empiric therapy than in a general population. Because minor febrile illnesses are common in children, and the risk of death from overwhelming *Streptococcus pneumoniae* sepsis is so high, aggressive management is critical. The following represent key principles in the management of febrile children (13-15):

■ Parents and clinicians should be taught that a temperature over 38.5°C is an emergency.

■ Basic laboratory evaluation includes CBC, U/A, chest x ray and/or oxygen saturation, and cultures of blood, urine, and throat.

■ "Toxic-looking" children and those with temperatures above 40°C should be treated promptly with parenteral antibiotics— before obtaining x rays or laboratory results. They should be admitted to the hospital for treatment.

Table 2: Pathogens To Be Covered by Empiric Therapy

Empiric therapy for:	Should include coverage for:	Consider broadening to include:
Fever without source (rule out sepsis)	*Streptococcus pneumoniae* *Hemophilus influenzae*	*Salmonella* Gram-negative enterics
Meningitis	*Streptococcus pneumoniae* *Hemophilus influenzae*	*Neisseria meningitidis*
Chest syndrome	*Streptococcus pneumoniae* *Mycoplasma pneumoniae* *Chlamydia pneumoniae*	*Legionella* Respiratory syncytial virus
Osteomyelitis/septic arthritis	*Salmonella* *Staphylococcus aureus* *Streptococcus pneumoniae*	
Urinary tract infection	*Escherichia coli* Other gram-negative enterics	

- Lumbar puncture should be performed on "toxic" children and those with signs of meningitis.

- Nontoxic children with temperatures below 40°C but with any of the following should receive prompt parenteral antibiotics and be admitted:

  –Infiltrate on chest x ray or abnormal oxygen saturation (see chapter 16, Acute Chest Syndrome and Other Pulmonary Complications)

  –White blood cell count greater than 30,000/μL or less than 5,000/μL

  –Platelet count less than 100,000/μL

  –Hemoglobin less than 5g/dL

  –History of sepsis

- Candidates for outpatient treatment may include nontoxic children with temperatures less than 40°C who have never been septic and have normal chest x ray or oxygen saturation, baseline white cell count, platelet count, and hemoglobin. They can be observed at home after parenteral administration of a long-acting antibiotic that covers *Streptococcus pneumoniae* and *Hemophilus influenzae* (e.g., ceftriaxone, 75 mg/kg) if:

  –They have remained clinically stable for 3 hours after the antibiotic dose.

  –Endemic *Streptococcus pneumoniae* in the community are likely to be antibiotic-sensitive.

  –The parents have been appropriately trained, have a history of compliance with prophylactic penicillin, keep appointments reliably, and have emergency access to the hospital.

  –A followup program is in place to assure assessment and retreatment within 24 hours.

- Documented bacteremia should be treated parenterally for 7 days, and children with meningitis should have at least 14 days of treatment.

ACUTE CHEST SYNDROME

The acute chest syndrome is covered in chapter 16. Please refer to table 2 above to guide antibiotic choice.

BONE PAIN WITH FEVER

Acute bone pain is caused by marrow ischemia. When necrosis and inflammation are associated with ischemia, the painful event resembles osteomyelitis or septic arthritis—including fever, leukocytosis, local swelling and tenderness, effusions, and abnormal imaging studies. Aspiration of some purely ischemic bone and joint lesions may yield purulent material. The overlap in physical, radiographic, and laboratory findings requires an unambiguous bacterial diagnosis to be established. Blood, joint fluid, or subperiosteal fluid must be cultured before antibiotics are started to treat osteomyelitis or septic arthritis. Once these cultures are obtained, empiric treatment should cover the pathogens in table 2.

MISCELLANEOUS INFECTIONS

See chapter 12, Transient Red Cell Aplasia, for discussion of Parvovirus B19, and chapter 25, Transfusion, Iron Overload, and Chelation, for discussion of transfusion-transmitted infections.

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Transient Red Cell Aplasia

Because the life span of red blood cells is greatly shortened in sickle cell disease (SCD), temporary suppression of erythropoiesis can result in severe anemia. Transient red cell aplasia (TRCA) typically is preceded by or associated with a febrile illness. The infectious nature of TRCA is apparent from the fact that several members of families with congenital hemolytic anemia may be affected within a period of several days.

ROLE OF PARVOVIRUS B19

Between 70 and 100 percent of episodes of TRCA are due to infection by human par-vovirus B19, also the cause of *erythema infec-tiosum* ("fifth disease") (1). Aplasia is the result of direct cytotoxicity of the parvovirus to ery-throid precursors, although other progenitors may be affected in some conditions. Patients may present with increased headache, fatigue, dyspnea, more severe anemia than usual, and a severe decrease in reticulocytes (usually <1 percent or 10,000/μL). Patients may have fever, signs of upper respiratory infection, and/or gastrointestinal symptoms. Skin rashes are characteristically absent. Reticulocytopenia begins about 5 days postexposure and contin-ues for 7 to 10 days. Exacerbation of anemia develops shortly after reticulocytopenia. Hemoglobin levels reached a mean nadir of 3.9 g/dL in one series (2). Patients who pre-sent in the convalescent phase may be thought mistakenly to have a hyperhemolytic process because of severe anemia and high reticulocyte

levels. However, the diagnosis of TRCA is supported by increased B19 parvovirus IgM levels. In at least 20 percent of patients with serologic evidence of past B19 parvovirus infection, there was no acute severe anemia. Following B19 infection, parvovirus-specific IgG concentrations are increased in most patients and protective immunity appears to be life-long; no cases of recurrent disease have been reported in children with SCD (1,3). Recovery is often heralded by a massive outpouring of nucleated red blood cells (>100/100 white blood cells).

Although the majority of adults have acquired immunity to B19 parvovirus, hospital workers who are susceptible and are exposed to patients with TRCA are at high risk of con-tracting nosocomial *erythema infectiosum* (4). Because infection during the mid-trimester of pregnancy may result in hydrops fetalis and stillbirth, isolation precautions for pregnant staff are a necessity if a parvovirus problem is suspected (5).

MANAGEMENT

No experimental trials have been reported regarding the management of TRCA. Although many patients recover spontaneously, red cell transfusions should be considered for those who become symptomatic (see chapter 25, Transfusion, Iron Overload, and Chelation). If patients are beginning to show evidence for red cell production, as determined by the reti-culocyte count, they may not need transfusions.

Transfusion was required in 87 percent of children with SCD-SS and TRCA in a large Jamaican series (2), but it is much less commonly needed for SCD-SC. Because parvovirus is so contagious, siblings and close contacts with SCD should be monitored for the development of aplastic events.

A single case report describes an alternative to transfusion in a child with Hb SD whose mother was a Jehovah's Witness and refused transfusion (6). This patient was treated with a single dose of intravenous immune globulin (1 g/kg) and daily infusions of erythropoietin (100 units/kg) and exhibited a reticulocytosis beginning on day 4 after onset of this treatment. Intravenous immune globulin is now the treatment of choice for parvovirus and aplasia since it will clear the parvovirus infection (7).

In the past decade, it has become apparent that a number of complications of B19 parvovirus infection besides TRCA can occur in patients with SCD. Complications reported at single centers or in small series include bone marrow necrosis with pancytopenia (8), glomerulonephritis (9), stroke (10), acute chest syndrome (11), and splenic or hepatic sequestration (12,13). Treatment must then be based on these manifestations.

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STROKE AND CENTRAL NERVOUS SYSTEM DISEASE

Stroke is one of the major complications of sickle cell disease (SCD). The Cooperative Study of Sickle Cell Disease (CSSCD) showed that the prevalence and incidence of stroke in patients with SCD-SS was four times that of those with SCD-SC (1). Because of this difference in risk, and because most of the available data are from patients with SCD-SS, screening of neurologically asymptomatic patients and primary stroke prevention recommendations pertain to those with SCD-SS, not SCD-SC. Recommendations for treatment of symptomatic patients and secondary prevention pertain to all SCD patients.

Children with SCD may have a variety of anatomic and physiologic abnormalities involving the central nervous system (CNS) even if they appear to be neurologically "normal" (2). The abnormalities may be associated with deterioration in cognitive function with effects on learning and behavior and may increase the risk for clinical and subclinical damage to the CNS in the future.

The approach to management depends on the specific brain manifestation of interest and the age of the patient. Therefore, this chapter is divided into sections based on the major CNS concerns of children and adults.

STROKE AND CENTRAL NERVOUS SYSTEM DISEASE IN CHILDREN

TRANSIENT ISCHEMIC ATTACK (TIA) AND BRAIN INFARCTION

Brain dysfunction occurs when oxygen supply to the brain falls below a critical level based on need. Symptoms of brain ischemia include hemiparesis; visual and language disturbances; seizures (especially focal seizures); and altered sensation, mentation, and alertness. There is evidence that oxygen demands are higher in children than in adults, making the child with SCD who also has significant anemia at particular risk.

As soon as brain ischemia is suspected, a prompt and thorough evaluation and consideration for therapy is recommended (figure 1). After initial stabilization and evaluation, patients should receive urgent noncontrast computed tomography (CT) scan of the brain to rule out hemorrhage or other nonischemic etiologies. Consideration should be given to the possibility that the symptoms are due to CNS infection, trauma (e.g., subdural hematoma), or intoxication—particularly if focal signs are not prominent.

In the acute stage of ischemic stroke for the general non-SCD adult population, the only approved therapy is recombinant tissue plasminogen activator (t-PA) if given within 3 hours (3), but there are no data establishing

Figure 1. Child with SCD and Symptoms
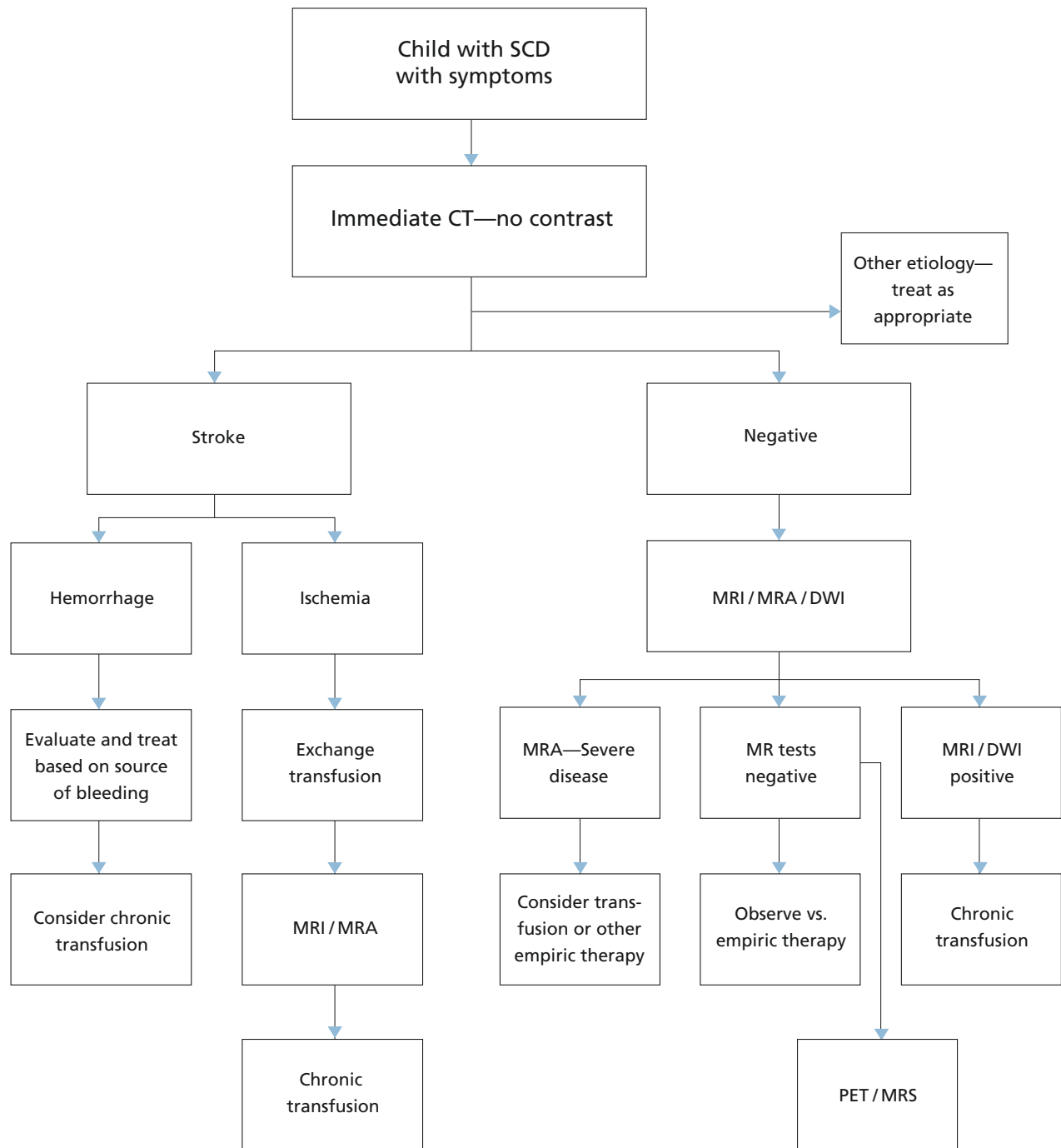
its use in children with SCD where the patho-physiology may differ completely. Therefore, it is not recommended.

The usual treatment for pediatric patients in the acute stage of ischemic stroke is hydration with transfusion, although there are no controlled treatment studies. Exchange transfusion is preferred, as it avoids the theoretical risk of increasing blood viscosity that may accompany rapid elevations in hematocrit, but care must be taken to avoid hypotension that may worsen cerebral ischemia (4). Because fever increases cerebral metabolism, any degree of hyperthermia should be treated. Hypothermia to treat stroke is promising but not supported by data adequate to form a recommendation. Acute treatment in an intensive care unit (ICU) or stroke unit will facilitate close observation and treatment. Seizures should be treated, but prophylactic therapy or corticosteroids are not recommended. Hypoxemia and hypotension should be treated and normoglycemia maintained. There are no proven neuroprotective therapies as yet to lessen damage or promote recovery.

In early ischemia (less than 3 hours), the cranial CT may be negative or show only subtle signs. Magnetic resonance imaging (MRI) provides better detail of the areas of ischemia, and diffusion weighted imaging (DWI) shows hyperintense areas of brain ischemia within minutes after onset of severe ischemia. Unless the diagnosis is in doubt, MRI should be deferred until treatment has been initiated. Evaluation within the first hours to days with MRI is recommended, because MRI-based studies provide significant additional information, such as the ability to detect very early and sometimes clinically silent acute lesions with DWI and prior infarction that may not be seen on CT. Imaging of the arteries by magnetic resonance angiography (MRA), may show large vessel occlusive dis-

ease (5) or aneurysms. EEG is recommended only if there is a clinical suspicion of seizure.

In the subacute phase, evaluations should be undertaken to make a final determination of the cause. In many cases, evaluation of the intracranial vessels will show occlusive vasculopathy characteristic of SCD. Even though intracranial arterial vasculopathy is the most likely cause of stroke in this setting, consideration should be given to other etiologies that cause stroke in young persons (6). If there is a history of head or neck trauma and arterial dissection is suspected, the radiologist should be notified so that appropriate changes in the magnetic resonance (MR) acquisition protocol can be made prior to study.

Other causes of stroke in children—such as infection, cardiac embolism, and clotting disorders including anticardiolipin antibodies—should be considered (7). While hemiparesis typically improves, cognitive deficits are often significant and long lasting; formal testing should be carried out to identify rehabilitation and educational needs.

TIAs have been defined as ischemic events in which the symptoms resolve in less than 24 hours. Because TIAs are a strong predictor of stroke in other settings and in SCD as well, there is a general recommendation that all patients with TIA receive appropriate therapy for stroke prevention. In this particular setting there are few data. The diagnosis of TIA is difficult in children, especially those who are very young, and painful episodes can mimic hemiparesis or paraparesis. In cases where the history is weak for the event actually being a TIA, caution is advised, especially if long-term transfusion is being considered.

In the case of a child in which a TIA is observed or strongly suspected, a prior recommendation is reiterated as a reasonable approach (2): if

the patient has significant large vessel disease on imaging, transfusion should be undertaken. If the patient has not been screened for stroke risk by transcranial Doppler (TCD) ultrasound (8), this should be done and treatment initiated according to the discussion under "Prevention of Brain Infarction," below, and figure 2. Alternatively, other tests, if available, such as positron emission tomography (PET) (9) or MR spectroscopy, could be employed. If these indicate significant "brain at risk," prophylactic treatment with transfusion can be undertaken on the basis that the child's brain blood supply has already failed once, even if transiently, and is at significant risk for subsequent deterioration.

Antiplatelet agents are usually recommended for TIAs in cases without SCD, but there are very few data on efficacy in SCD. Agents such as aspirin, clopidogrel, and combination dyprimadole/aspirin are used in adults and in cases where transfusion is not undertaken.

INTRACRANIAL HEMORRHAGE

The clinical presentation of intracranial hemorrhage is dramatic and may include severe headache, vomiting, stupor, or coma. However, hemiparesis may be present, especially with intraparenchymal bleeding. A child with such a presentation requires rapid but careful evaluation to rule out meningitis, sepsis, hypoxemia, drug intoxication, or other metabolic derangements. A noncontrast cranial CT should be performed as soon as possible. Intracranial hemorrhage should be approached based on the location of the blood on the CT scan, as described below.

Subarachnoid hemorrhage (SAH)

The usual cause of subarachnoid hemorrhage (SAH) is rupture of a berry aneurysm. The aneurysm may not be seen on CT, but can sometimes be inferred by the location of blood. Minor subarachnoid hemorrhages may have no identifiable cause even when angiography is performed, but an angiogram is recommended to identify aneurysms or arteriovenous malformations (AVM) if surgery is being considered. This is clinically relevant because aneurysms may rebleed, and SCD patients may have multiple aneurysms that require management. Surgical clipping, as well as AVM removal, has been successfully performed in many patients with SCD. Although aneurysms can be identified using MR, MRA is not a definitive test for aneurysms unless special techniques are used (20). However, MRI/MRA can reliably detect AVM.

The initial treatment of subarachnoid hemorrhage is stabilization in a neurological intensive care unit or pediatric ICU, depending on local expertise and the age of the child. Initial care includes intravenous normotonic fluids to avoid dehydration. The effect of transfusion on the course and outcome of hemorrhage is not known; however, reduction of sickle hemoglobin (Hb S) to less than 30 percent of total hemoglobin is recommended. Nimodopine, a calcium antagonist that improves outcome after SAH by counteracting delayed arterial vasospasm, is indicated in adults with SAH (10). Use in this setting with young children is not approved but is reasonable on an empiric basis. The adult dosage of 60 mg orally every 4 hours for 21 days should be adjusted by weight.

Intraparenchymal Hemorrhage

If the CT shows blood primarily confined to the parenchyma, the cause may still be an AVM, but an aneurysm is not likely unless there is also subarachnoid bleeding. Intraparenchymal bleeding may be associated with large vessel vasculopathy, especially if a moyamoya formation is present. In some

Figure 2. Child with Hb SS and No Symptoms
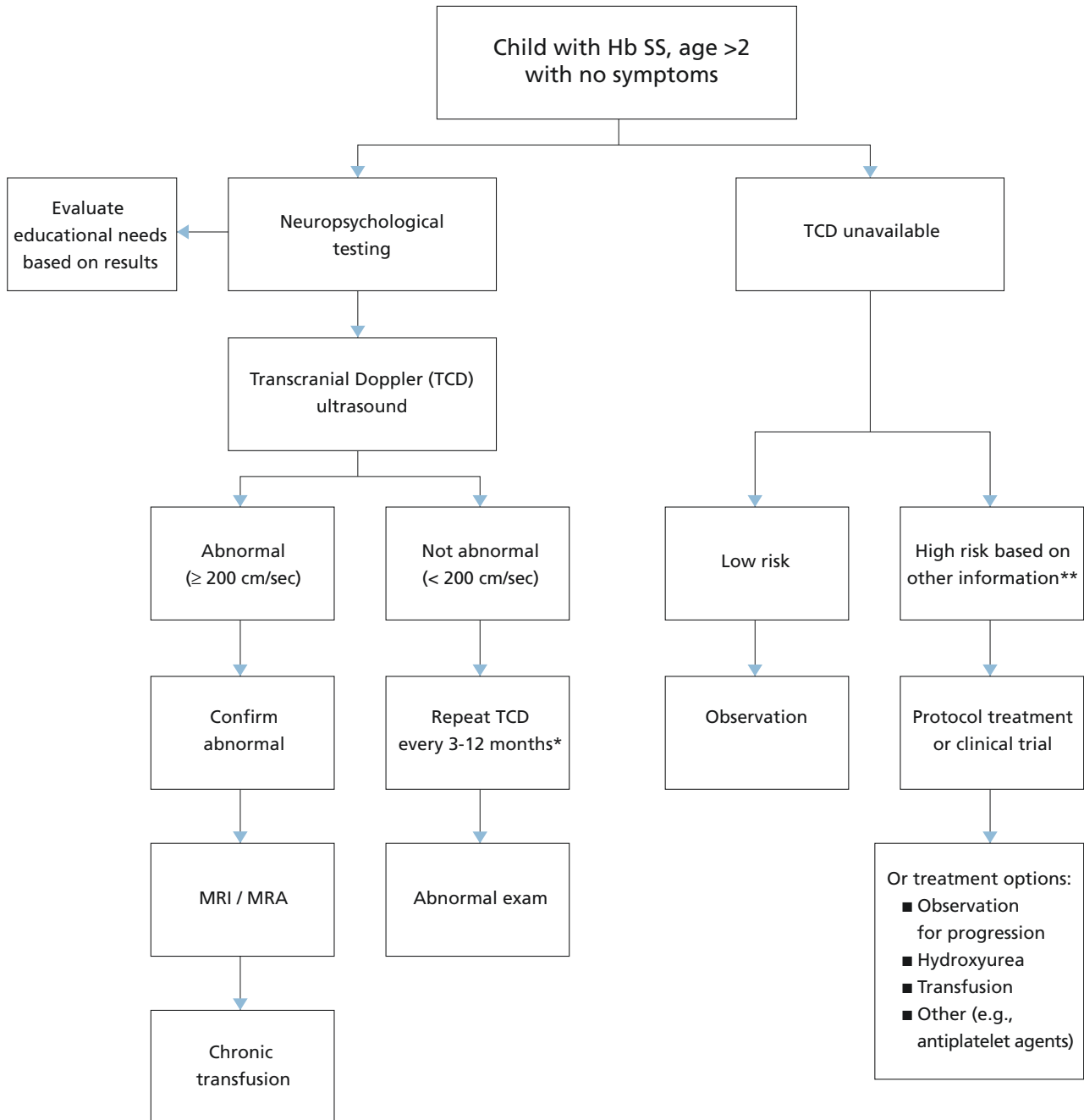
* Optimal frequency of rescreening not established. Younger children with velocity
closer to 200 cm/sec should be rescreened more frequently.
** Prior TIA, low steady state Hb, rate and recency of acute chest syndrome, elevated systolic blood pressure.

patients, no vessel pathology can be seen on angiography. Evaluation of these patients with MRA may be sufficient if there is no subarachnoid blood, because an aneurysm is not likely as the source of bleeding. Better definition of the vasculature can be obtained with conventional angiography.

Initial management depends on the size and location of the bleeding. A rapid search for coagulopathy should be made with a determination of the activated partial thromboplastin time (aPTT) and prothrombin time (PT) and correction of any coagulopathy. Management of the hematoma includes medical control of intracranial pressure and consideration for surgical removal in selected cases, particularly if there is a large (>3 cm) cerebellar hematoma. Rebleeding in this setting in the short term is rare. Normotonic fluids and avoidance of hypotension are important (11).

Intraventricular Hemorrhage

Intraventricular hemorrhage is unusual but may be seen in the case where fragile moyamoya vessels near the ventricular wall rupture into the ventricular space. In such cases the pediatric patient is at risk for acute hydrocephalus and death if ventricular flow is obstructed. The child should receive prompt neurosurgical evaluation for intraventricular catheter placement for drainage. After acute stabilization, evaluation of the cerebral vessels (best done by conventional angiography) should be undertaken to try to identify the underlying cause.

PREVENTION OF BRAIN INFARCTION

Secondary Prevention

Several uncontrolled studies have documented a reduction in recurrent cerebral infarction using chronic blood transfusion with the target of reducing Hb S to less than 30 percent of total hemoglobin (12,13). The reduction in recurrent stroke risk is significant, but patients may still have a stroke despite adequate transfusion and low Hb S levels. If a patient on transfusion has a "breakthrough" cerebral infarction or TIA, the Hb S level should be checked to ensure that it is being maintained at 30 percent or below, and the etiology of ischemia should be evaluated. Consideration should be given to risk factors beyond SCD-related vasculopathy, including elevated homocysteine or a hypercoagulable state. Elevated homocysteine can be reduced with folate, as is recommended for patients without SCD (14). Data suggest that some SCD patients have elevated antiphospholipid antibodies (15) and protein C and S deficiencies (16). If the abnormalities are severe enough, anticoagulation with warfarin should be considered. Treatment of these conditions has not been tested in randomized clinical trials but is reasonable based on pathophysiology.

After several years of transfusion therapy, it may be reasonable to allow Hb S levels to rise up to 50 percent by reducing the intensity of transfusions; this has not been formally tested, however. Moreover, the duration of time after which transfusion can be safely stopped has not been defined. Some studies have reported high rates of recurrent stroke (17), although others have suggested that transfusion may be safely withdrawn in older patients who have been extensively treated (18). Current recommendations are that transfusion should be continued for at least 5 years or at least until the child reaches the age of 18. Chronic transfusion induces iron overload, which must be managed along with the transfusions (see chapter 25, Transfusion, Iron Overload, and Chelation).

Patients with stroke have received bone marrow transplantation (19). The current indications, efficacy, and outcome of this therapy are discussed in chapter 27, Hematopoietic Cell Transplantation. Hydroxyurea is used for reduction of painful episodes in adults with SCD, but the trial establishing its use provides no guidance on whether hydroxyurea is a suitable alternative to transfusion for prevention of stroke. Clinical studies in children have reported short-term safety, but these studies have not established hydroxyurea as an alternative to transfusion for stroke prevention in this setting (20). Anticoagulants and antiplatelet agents have not been studied in this indication.

PRIMARY STROKE PREVENTION

The CSSCD established that patients with SDC-SS have rates of stroke in childhood in the range of 0.5-1 percent per year (1). In the Stroke Prevention Trial in Sickle Cell Anemia (STOP) study, children between 2 and 16 years of age who were at risk for first-time stroke, as determined by having TCD velocity greater than 200 cm/sec, were randomized to receive either periodic transfusions to maintain the Hb S level below 30 percent or standard supportive care (21). An interim analysis demonstrated that periodic transfusions were efficacious in preventing first-time stroke, in the children randomized to the transfusion arm. At the end of the trial, all participants were offered periodic transfusion therapy. The main side effects of the transfusion therapy were iron accumulation and alloimmunization, through the rate of occurrence was low. A new trial, known as STOP II, is now in place to determine whether transfusions need to be continued indefinitely of if they can be stopped after some period of time when risk of stroke has diminished.

TCD can be performed with either the dedicated 2-MHz pulsed Doppler device used in STOP or with TCD attachments to ultrasound imaging machines (transcranial Doppler imaging, or TCDI) that have also been used in this setting (22).

IDENTIFICATION OF PATIENTS AT RISK

In addition to TCD, a number of other approaches have been used to identify children at risk for stroke (figure 2). The CSSCD identified five significant risk factors in a long-term prospective study: prior TIA, low steady-state hemoglobin, rate and recency of acute chest syndrome (ACS), and elevated systolic blood pressure. The newborn cohort of the CSSCD identified three early life (first 2 years) predictors of severe outcomes such as stroke (23). These were dactylitis, severe anemia, and leukocytosis.

Other clinical and laboratory indicators of stroke risk that have been reported include stroke in a sibling, subtle neurological abnormalities, severe anemia, high leukocyte count, certain β^s-gene haplotypes, and no α-gene deletion (2).

SUBCLINICAL BRAIN DISEASE

The CSSCD confirmed that about 13 percent of children with SCD have "silent" brain lesions on MRI, in predominantly frontal and parietal cortical, subcortical, and border-zone locations (24,25). These lesions are associated with poor performance on neuropsychological testing. Recent evidence from the CSSCD confirms an earlier smaller study indicating that the risk of clinical stroke is increased if MRI is abnormal. The presence of these lesions should prompt evaluation of the child for learning and cognitive problems, and evaluation of cerebral vessels for primary stroke prevention (see above). Silent lesions are evidence of brain injury and should also lead to reevaluation of the patient's history, which

may reveal symptoms that were not previously recognized, as well as reexamination of the patient's clinical and laboratory risks for stroke. The rate of stroke in children with positive MRI and with TCD that do not reach current treatment guidelines is not clear, and the risks and benefits of prophylactic transfusion based on silent MRI lesions have not been determined. Intervention in patients with silent lesions and additional indicators of cerebral dysfunction or abnormality have been suggested, but no recommendation for treatment can be made at this time.

STROKE AND BRAIN DISEASE IN ADULTS WITH SCD

INFARCTION

The CSSCD confirmed the relatively high rates of stroke in adults with SCD and the predominance of hemorrhage compared with infarction in adults with SCD. There is less information on treatment and prevention in adults with SCD. The clinician must decide whether to approach a patient with TIA or stroke who has SCD in a manner similar to that used in children with SCD, or along guidelines established for adults without SCD (26,27). The interaction of SCD-specific risk factors with risks factors for stroke seen in adults without SCD has not been determined, although high blood pressure was identified as a stroke risk in the CSSCD. Specifically, the role of chronic transfusion is unclear. The recommendations that follow are based primarily on current recommendations for treatment and prevention in patients without SCD (figure 3).

Treatment of hyperacute ischemic stroke in adults is accomplished using recombinant tissue plasminogen activator (t-PA). It is not clear whether t-PA, which has a significant risk of bleeding, is appropriate for patients with SCD; no experience with its use has been

reported. However, there is no clear justification to exclude SCD patients from t-PA therapy, and it remains the only therapy approved by the U.S. Food and Drug Administration for treatment of ischemic stroke.

According to established guidelines, use of t-PA is indicated when:

- the patient is at least 18 years old.

- the patient's National Institutes of Health Stroke Scale score is greater than 4 (ischemic stroke in any vessel with a clinically significant deficit).

- t-PA therapy can begin within 3 hours of symptom onset.

- cranial CT shows no evidence of hemorrhage.

Thrombolytic therapy cannot be recommended if:

- stroke duration is longer than 3 hours.

- INR is greater than 1.7 or PT of 15 seconds.

- patient received heparin in last 48 hours and has a prolonged aPTT.

- platelet count is less than 100,000/μL.

- patient has had a stroke or serious head injury in the past 3 months.

- patient underwent major surgery within the preceding 14 days.

- pretreatment blood pressure is greater than 185 mmHg systolic or 110 mmHg diastolic.

- patient has rapidly improving neurological signs or isolated ataxia, sensory loss, dysarthria or minimal weakness.

- patient has a history of intracranial hemorrhage.

- blood glucose is less than 50 mg/dL or greater than 400 mg/dL.

Figure 3. Adult with SCD and Symptoms
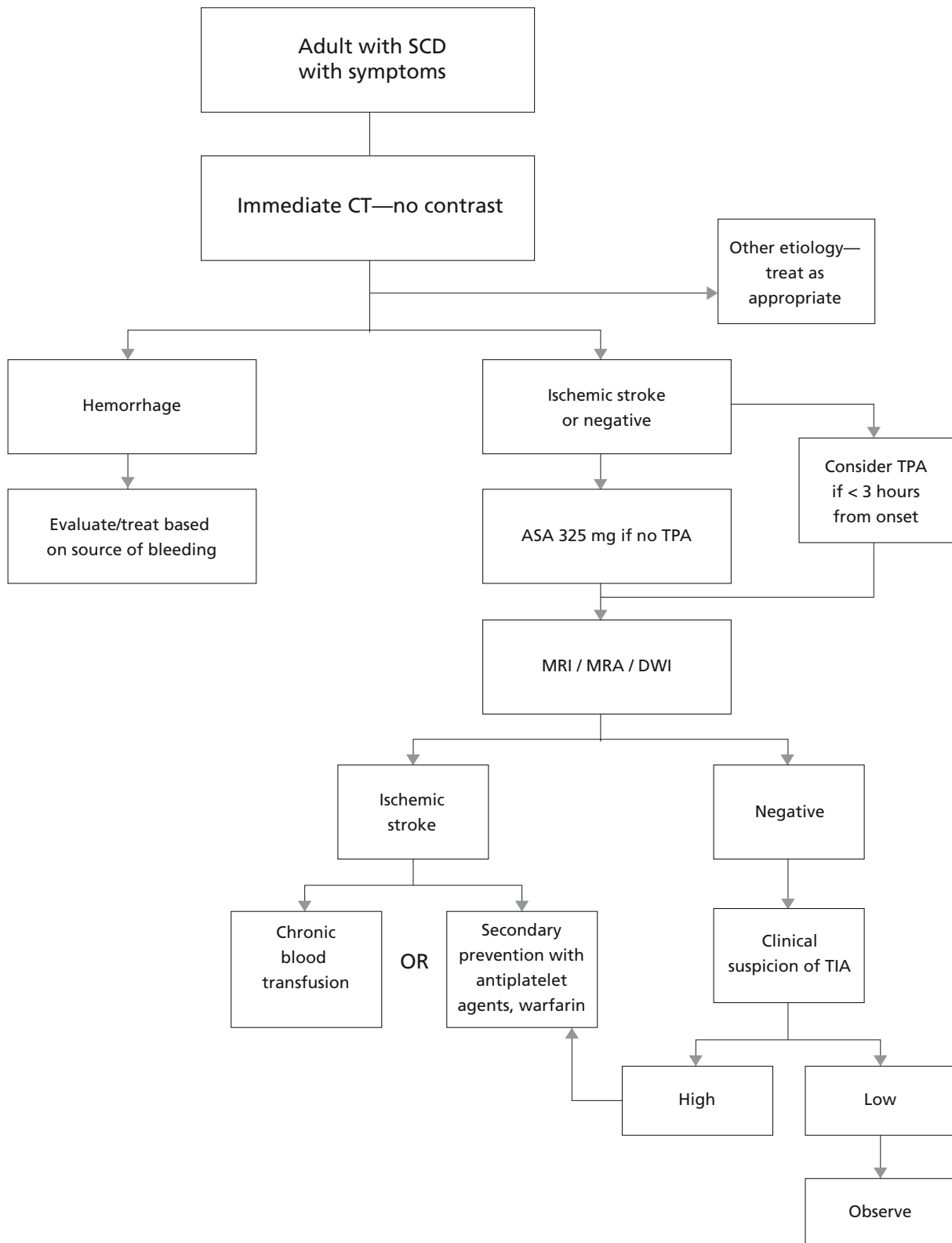
- patient had seizure at onset of symptoms.

- patient has experienced GI or GU bleeding within the preceding 21 days.

In addition, t-PA should not be given unless emergent care and appropriate facilities are available. Caution is advised before giving t-PA to patients with severe stroke, and careful explanation of the risk of bleeding to patient and family is advised. There is a 6.4 percent risk of symptomatic brain hemorrhage, and about half of these are fatal. If a hemorrhage occurs, the guidelines suggest red cell transfusions as needed (for extracranial bleeds) and urgent administration of 4 to 6 units of cryoprecipitate or fresh frozen plasma and 1 unit of single donor platelets. Surgical drainage of intracranial hemorrhage should be considered. Although t-PA can be given to patients on antiplatelet agents, these drugs, as well as any dose of heparin, should not be given for the first 24 hours after using t-PA. There is evidence that aspirin (325 mg one-time dose) within the first 48 hours after stroke onset has a small beneficial effect and is recommended if t-PA is not used.

The acute evaluation of the patient requires a noncontrast CT scan to rule out hemorrhage. After the decision is made regarding t-PA, an MR study of the brain is recommended to better delineate the area of ischemia/infarction.

Prevention of stroke in patients with TIA or stroke is accomplished with either antiplatelet agents or warfarin, based on the likely cause of the symptoms.

The following workup is recommended for adults presenting with TIA or ischemic stroke: CBC with differential and platelet count; EKG; transthoracic echocardiogram with consideration given to transesophageal echocardiogram, especially in younger patients; aPTT; PT; and a brain study to include MRI, DWI, and MRA, and/or TCD and carotid duplex ultrasound or CT angiography to determine the status of the intracranial and extracranial vessels. Blood tests for protein C and S deficiency, homocysteine elevation, and anticardiolipin antibodies may be appropriate. Health care providers also should consider etiologies seen in young patients with stroke without SCD, including CNS infection, illicit drug use, and arterial dissection.

Table 1. Use of Antithrombotic Agents in Patients With TIAs

Event	Recommended Therapy	Therapeutic Options
TIA (atherothrombotic)	acetylsalic acid (aspirin, ASA) 50–325 mg/d	extended-release dipyridamole (ER-DP) 200 mg + ASA 25 mg Clopidogrel 75 mg/d ASA 50–1300 mg/d
TIA (atherothrombotic) and aspirin-intolerant[1], or if TIA occurs during ASA therapy[2]	ER-DP 200 mg + ASA 25 mg BID Clopidogrel 75 mg/d	Warfarin (INR 2–3) ASA 50–1300 mg/d
TIA (cardioembolic)	Warfarin, target INR 2.5 (range 2–3)	ASA 50–325 mg/d (if warfarin is contraindicated)

[1] Neither ER-DP + ASA or ASA alone is recommended for patients who are allergic to aspirin or unable to take low-dose aspirin.
[2] The recommended antithrombotic agents have not been specifically tested in patients who have experienced a TIA during ASA therapy.

There are currently three options for antiplatelet therapy for secondary stroke prevention. Table 1 summarizes the American Stroke Association's recommendations regarding these agents.

These guidelines are similar to those for prevention of stroke after completed brain infarction (26,28).

Alternative therapy is chronic blood transfusion as used in children with SCD. Recently, surgical bypass has been reported in a patient with SCD. Surgical procedures that have been developed to treat moyamoya syndrome may be considered, due to the similarity in anatomic location of the arterial disease in moyamoya and SCD (29). These procedures may be last-resort options for patients who cannot be otherwise treated or who continue to have brain infarction despite medical therapy. However, risk and benefit in this setting have not been established and no recommendation can be made.

INTRACRANIAL HEMORRHAGE

Adults with intracerebral hemorrhage should be approached in the manner outlined above for children, with the exception that nimodopine is recommended without qualification for patients with subarachnoid hemorrhage (11).

SUMMARY OF RECOMMENDATIONS

CHILDREN

- Primary prevention (figure 2). Children with SCD 2 to 16 years of age should be screened for stroke risk using TCD. (Chronic transfusion should be strongly considered in those with confirmed abnormal TCD.) If TCD is unavailable or technically inadequate, or if TCD

results do not meet criteria for treatment in the presence of other strong indications of high risk, consideration should be given to intervention on an individualized basis unless enrollment in appropriate treatment trials is an option.

- Children with ischemic stroke should undergo acute evaluation with CT scanning followed by intravenous hydration and exchange transfusion to reduce Hb S to <30 percent total hemoglobin. In most cases this should be followed by chronic transfusion (figure 1).

- Children with intracranial hemorrhage should be evaluated for a surgically correctable lesion. Following this, chronic transfusion is recommended in cases of severe vasculopathy or unrepaired aneurysm (figure 1). Acute hydration and short-term exchange transfusion may be beneficial as well.

ADULTS

- Adults presenting with acute ischemic stroke should be evaluated for t-PA treatment (figure 3). If t-PA is not used, aspirin (325 mg) is appropriate. Adults with TIA or ischemic stroke should be evaluated for the cause of the ischemia and therapy should be guided by these findings. Alternatives include antiplatelet agents and warfarin. Chronic transfusion is an option, as used in pediatric stroke prevention.

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Sickle Cell Eye Disease

Sickle cell vaso-occlusive events can affect every vascular bed in the eye, often with devastating visual consequences. Because early stages of sickle cell eye disease do not usually result in visual symptoms, the disease can go undetected unless a formal eye exam is performed by an ophthalmologist. The examination should include an accurate measurement of visual acuity, assessment of pupillary reactivity, careful evaluation of the anterior structures of the eye using a slit-lamp biomicroscope, and a thorough examination of the posterior and peripheral retina through a dilated pupil. This last examination should include fluorescein angiography. Patients with sickle hemoglobinopathies should have yearly eye examinations beginning in childhood and continuing through adulthood.

CLINICAL FINDINGS

The clinical manifestations of sickle hemoglobinopathies are grouped according to the presence or absence of neovascularization in the eye. The distinction is clinically relevant because proliferation of new blood vessels on the retina is the key biological event that sets the stage for progression to vitreous hemorrhage and retinal detachment.

NONPROLIFERATIVE DISEASE

Non-neovascular ocular manifestations of sickle hemoglobinopathies include conjunctival vascular occlusions that transform smooth vessels into comma-shaped fragments, iris atrophy, retinal hemorrhages, retinal pigmentary changes, and other abnormalities of the retinal vasculature, macula, choroid, and optic disc. These clinical findings are readily apparent on dilated ophthalmoscopy, and all occur due to local vaso-occlusive events but rarely have visual consequences.

PROLIFERATIVE DISEASE

Progression to neovascularization or to the proliferative stage involves the growth of abnormal vascular fronds that place patients at risk of vitreous hemorrhage and retinal detachment. The initiating event in the pathogenesis of proliferative disease is thought to be peripheral retinal arteriolar occlusions. Local ischemia from repeated episodes of arteriolar closure is presumed to trigger angiogenesis through the production of endogenous vascular growth factors, such as vascular endothelial growth factor and basic fibroblast growth factor (1,2). Goldberg has defined five stages of proliferative retinopathy (3). In stage I, peripheral arteriolar occlusion is present. In stage II, vascular remodeling occurs at the boundary between perfused and nonperfused peripheral retina with the formation of arteriovenous anastomoses. In stage III, actual preretinal neovascularization occurs. The neovascular fronds typically assume a shape that resembles the marine invertebrate *Gorgonia flabellum*, known commonly as the "sea fan." Stage IV is defined by the presence of vitreous hemorrhage, and stage V is defined by the presence of retinal detachment. This last complication

results from mechanical traction created by chronic, enlarging fibrovascular retinal membranes, with or without hole formation in the retina.

Although peripheral vaso-occlusion may be observed as early as 20 months of age (4), clinically detectable retinal disease is found most commonly between 15 and 30 years of age (5). Sickle retinopathy is found more often and earlier in SCD-SC, but is also common in SCD-SS and sickle thalassemia. Observational cohort studies have also shown that stages IV and V retinopathy occur more often in SCD-SC subjects than in those with SCD-SS (6). It is a paradox that despite the less dramatic systemic consequences of their disease, subjects with SCD-SC and sickle thalassemia are more likely than SCD-SS patients to have serious ocular manifestations. Research has not been able to explain the reason for this profound discrepancy in the severity of the retinal and systemic manifestations among the various sickle hemoglobinopathies (see the introductory material and chapter 2, Neonatal Screening, for an overview of disease subtypes).

Diagnosis of proliferative retinopathy requires examination through a dilated pupil utilizing a wide-field indirect ophthalmoscope. Evaluation of retinal blood flow is performed with fluorescein angiography. Any patient identified with retinopathy should be followed by an ophthalmologist who specializes in diseases of the retina.

TREATMENT

Treatment is reserved for eyes that have progressed to proliferative retinopathy, since patients are at risk for severe visual loss from bleeding and retinal detachment. Given the high rate of spontaneous regression and lack of progression of neovascularization in some eyes, the indications for treatment of retinal neovascularization are not always clear. Therapeutic intervention usually is recommended in cases of bilateral proliferative disease, spontaneous hemorrhage, large elevated neovascular fronds, rapid growth of neovascularization, and cases in which one eye has already been lost to proliferative retinopathy. The goal is early treatment to induce regression of neovascular tissue before bleeding and retinal detachment occur. Techniques such as diathermy, cryotherapy and laser photocoagulation have been used to cause involution of neovascular lesions. Of all of these methods, laser photocoagulation has the fewest side effects.

If retinal detachment or nonclearing vitreous hemorrhage is present, surgical intervention is usually required. Surgical techniques include vitrectomy with or without the placement of a scleral buckle. Although modern vitreoretinal microsurgery can improve vision for many patients with advanced sickle retinopathy, it should be emphasized that surgery carries a significant risk of intraoperative and postoperative complications including severe ocular ischemia, recurrent hemorrhage, and elevated eye pressure (7). To minimize the risk of such complications, partial exchange transfusion has been recommended prior to surgery, usually with a target of about 50 to 60 percent normal red cells, although there has never been a controlled study demonstrating the efficacy of this maneuver (8).

INDICATIONS FOR URGENT OPHTHALMOLOGIC CONSULTATION

Immediate consultation with an ophthalmologist familiar with the management of individuals with hemoglobinopathies is required for any individual with a sickle hemoglobinopathy, including sickle trait, who sustains eye trauma. Anterior segment trauma may result in hemorrhage into the anterior chamber of the eye, allowing sickled erythrocytes to clog the trabecular outflow channels and raise the intraocular pressure, producing glaucoma. In patients with sickle hemoglobinopathies, even a moderate increase in eye pressure may cause a significant reduction in perfusion of the optic nerve and retina, putting the eye at risk for ischemic optic atrophy and retinal artery occlusion. In such instances patients may require an emergent surgical washout of the anterior chamber.

Trauma considerations aside, any patient with a sickle hemoglobinopathy who has an acute change in vision always should be referred immediately to an ophthalmologist for a full evaluation.

RECOMMENDATIONS

Beginning in childhood, all patients with sickle hemoglobinopathies should have yearly dilated examinations by an ophthalmologist with expertise in retinal diseases. Any patient with a sickle hemoglobinopathy who experiences a change in vision should be referred for ophthalmologic consultation immediately. Central retinal artery occlusion, an event which usually results in permanent, devastating loss of vision, is one of the few bona fide ophthalmic emergencies which demands intervention within minutes to hours after the onset of symptoms. Treatment consists of hyperoxygenation combined with rapid reduction of eye pressure utilizing surgical and medical techniques. Vision loss from hemorrhage or retinal detachment also calls for urgent care, but, unlike acute vascular occlusion, can be addressed appropriately within 24 to 48 hours. Any individual with a sickle hemoglobinopathy who sustains ocular or periocular trauma should be examined immediately by an ophthalmologist because of the increased risk of visual loss from elevated eye pressure associated with hemorrhage into the anterior chamber (hyphema).

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ONLINE RESOURCE

http://www.dr4eyes.com/sickle-cell.htm

CARDIOVASCULAR MANIFESTATIONS

CRITICAL REVIEW

Cardiac exam findings are rarely normal in sickle cell disease (SCD); the heart is usually enlarged and the precordium hyperactive, systolic murmurs are found in most patients, and premature contractions are often present in adults (1). Physical work capacity is reduced to about half in adults with sickle cell anemia and 60 to 70 percent in children; this is related to the severity of the anemia. Cardiomegaly and heart murmurs often raise the question of whether or not congestive heart failure is present. Contractility is normal and overt congestive heart failure is uncommon, especially in children (2). When heart failure is present, it often can be related to secondary causes such as fluid overload. Cardiac output is increased at rest and rises further with exercise (1). Electrocardiograms often have non-specific abnormalities and can show signs of ventricular enlargement. At rest, cardiac index is 1.5 times normal value, and increases further during exercise; it is not completely explained by hemoglobin level or oxygen content, suggesting increased tissue extraction of oxygen.

One study evaluated cardiac function by echocardiogram in 200 persons with SCD who were 13 years of age or older (3). Compared to normal controls, patients had increased left and right ventricular and left atrial chamber dimensions, increased interventricular septal thickness, and normal contractility. These dimensions, except for those of the right ventricle, were inversely related to

the hemoglobin level and indicated cardiac dilatation. Cardiac dilatation was also dependent on age. When homozygous α-thalassemia-2 was present, left ventricular dimensions were more normal, but wall thickness was increased (4). This difference was postulated to be a result of the higher hemoglobin levels caused by α-thalassemia. Nevertheless, the response to exercise was not improved, perhaps because of the properties of abnormal sickle erythrocytes. Pericardial effusions were present in 10 percent of patients and were also inversely related to hemoglobin level (3).

As a group, patients with anemia have lower-than-expected systolic and diastolic blood pressures and individuals with SCD are no exception (5,6). This may be due to renal sodium wasting; however, its cause is not known for certain. The blood pressure of patients with SCD is higher than expected given the severity of their anemia, suggesting the possibility that they have "relative" hypertension (7). In a study of 89 patients, there was an association between higher blood pressures and stroke. Survival decreased and the risk of stroke increased as blood pressure rose, even though the blood pressure at which these risks increased was below the level defining early hypertension in the normal population. This suggested that "relative" hypertension was pathogenetically important. Increased longevity, a higher prevalence of sickle cell nephropathy, and the consumption of high-calorie, high-salt diets probably all contribute to the rising prevalence of absolute hypertension in

patients with SCD. When this is added to the apparent risks of even relative hypertension and the fact that reducing blood pressure in people without SCD can prevent the consequence of hypertension, it seems reasonable to consider antihypertensive therapy in patients with SCD with borderline hypertension.

RECOMMENDATIONS

Chest pain, a common entity in SCD, often leads to patients being told they have had a heart attack. Obvious myocardial infarction is unusual, but it has been reported. Paradoxically, coronary artery occlusion is not common, suggesting that small vessel disease is responsible for the cardiac damage (2). Ischemic heart disease can be present in patients with SCD and should be considered in all individuals with chest pain (8).

Sudden unexpected and unexplained death is common in adults with sickle cell anemia (9,10). Patients with SCD can have autonomic nervous system dysfunction that may contribute to sudden death. A recent study in 24 patients found 14 patients (58.3 percent) to have cardiovascular autonomic dysfunction based on abnormal values for at least two cardiovascular autonomic function tests, whereas 10 (41.7 percent) had preserved cardiovascular autonomic function. In contrast, all control subjects had normal cardiac autonomic function (9).

Documented congestive heart failure in sickle cell anemia should be treated with the usual methods. Severely anemic patients with symptoms of congestive heart failure or angina pectoris may be helped by cautiously increasing their hemoglobin concentration by transfusion or, if possible, with hydroxyurea (see chapter 25, Transfusion, Iron Overload, and Chelation and chapter 26, Hydroxyurea, for general information about treating anemia).

Currently, no trials in patients with sickle cell anemia can guide decisions regarding when to begin antihypertensive treatment, what agents are most effective, what the blood pressure goals of treatment should be, and whether blood pressure reduction can reduce the incidence of stroke or prolong life. A reasonable approach, based on experience in the general hypertensive population where the risk of stroke begins well below the normal blood pressure of 140/90 mmHg, is to carefully evaluate the patient and consider beginning antihypertensive treatment when systolic blood pressure rises by 20 mmHg or the diastolic blood pressure increases by 10 mmHg. When there is evidence of target organ damage from heart disease, nephropathy and peripheral vascular disease, treatment might be started at pressures above 130/85 mmHg. Treatment at pressures of 120/75 mmHg may be indicated when proteinuria is higher than 1 gram per day. ACE inhibitors and calcium antagonists may be especially useful treatments; the former appears to reduce proteinuria and preserve renal function, and the latter may induce a higher rate of response in black patients. Theoretically, diuretics, by causing hemoconcentration, might predispose to vaso-occlusion. In practice, it is not clear whether this occurs, and their use is not contraindicated. Diuretic dosing should take into consideration the additive effects of obligate hyposthenuria in patients with SCD. β-adrenergic receptor blocking agents can also be used. Renin-dependent hypertension can result from focal areas of renal ischemia. Severe blood pressure increases in individuals with SCD should be evaluated thoroughly to exclude this and other forms of secondary hypertension.

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ACUTE CHEST SYNDROME AND OTHER PULMONARY COMPLICATIONS

The lung is a major target organ for acute and chronic complications of sickle cell disease (SCD). Acute chest syndrome (ACS) is a frequent cause of death in both children and adults (1-3) with SCD. Pulmonary problems not directly related to sickle cell vaso-occlusion, such as pneumonia or asthma, can worsen SCD because local or systemic hypoxia increases sickle hemoglobin (Hb S) polymerization. Multiorgan failure often is preceded or accompanied by pulmonary involvement, as observed with fat embolization in pain episodes. There is more frequent recognition of chronic pulmonary hypertension in adult patients, as this complication gives a poor prognosis even though pulmonary artery pressures are not very high compared to those in patients with primary pulmonary hypertension.

Few of the management recommendations below are based on randomized clinical trials, since such trials are largely unavailable. The proposed guidelines are based on reviews of small case series in the literature, and on consensus among clinicians with experience in SCD treatment.

ACUTE CHEST SYNDROME

SUMMARY OF THE STATE OF KNOWLEDGE

ACS is an acute illness characterized by fever and respiratory symptoms, accompanied by a new pulmonary infiltrate on a chest x ray. Because the appearance of radiographic changes may be delayed (3), the diagnosis may not be recognized immediately. A major risk factor for the development of ACS is the hemoglobin genotype: the highest incidence is seen in β^s/β^s genotype (12.8 events/100 person-years) and the lowest in β^s/β^+ thalassemia genotype (3.9 events/100 person-years) (4). ACS is the second most common cause of hospitalization in sickle cell patients and the most common complication of surgery and anesthesia (5). Children have higher incidences of ACS (21 events/100 person-years, β^s/β^s genotype) but lower mortality (<2 percent) than adults (8.7 events /100 person-years and 4-9 percent mortality) (3,6). In SCD-SS persons, the incidence of ACS is related to low fetal hemoglobin (Hb F) levels and high steady-state hematocrits and white cell counts, but not to coexistent α-thalassemia (4). Children have seasonal variation in ACS incidence: lower in the summer, but higher in winter when respiratory infections are frequent (6). The seasonal pattern is less marked in adults. Even though the ACS usually is self-limited, it can present with or progress to respiratory failure, characterized by noncardiogenic pulmonary edema and severe hypoxemia. These critically ill patients need both respiratory support and emergency transfusions (see below).

The Multicenter Acute Chest Syndrome Study (MACSS) group enrolled 538 patients with 671 ACS episodes in a comprehensive, standardized diagnostic and management protocol (3). The protocol included bacteriology, virology, and serologic studies, as well as

examination of bronchoscopy-obtained secretions or deep sputum samples. In 108 of 364 episodes (30 percent) with complete diagnostic data, all results were negative, which led, by exclusion, to the diagnosis of pulmonary infarction. Fifty-nine of the 364 episodes (16.2 percent) had pulmonary fat embolization (PFE) defined by the finding of lipid-laden macrophages in broncho-alveolar lavage specimens. About one-third of the PFE cases showed evidence of infection. Previous studies on mostly older patients had reported higher prevalences of PFE (44 to 77 percent) in ACS (7,8). Patients with PFE tend to be older and have lower oxygen saturations (3). An infectious agent was identified in 197 episodes (54 percent) but a wide variety of microorganisms was found, the most common of which were chlamydia (48 episodes, 13 percent), mycoplasma (44 episodes, 12 percent) and viruses (43 episodes, 12 percent). In 30 ACS episodes (8.2 percent), bacteria were isolated, which included *Staphylococcus aureus, Streptococcus pneumoniae*, and *Hemophilus influenzae.*

The MACSS reported findings from the first ACS episode in 128 adults and 409 children (82 percent with Hb SS genotype) (3). This study used strict criteria to define ACS: a pulmonary infiltrate consistent with consolidation, plus at least one of the following: chest pain, fever over 38.5°C, tachypnea, wheezing, or cough. An earlier series, the Cooperative Study of Sickle Cell Disease (CSSCD) enrolled 252 adults and 687 children (76 percent with SS genotype) who had a total of 1722 episodes of ACS (6) defined by the appearance of a new pulmonary infiltrate on the chest x ray. Table 1 summarizes findings from both of these prospective series.

Clearly, the MACSS enrolled more severely ill patients than did the CSSCD, as shown by more frequent use of red cell transfusions, longer hospital stays, and higher death rate, particularly in adult patients. In the MACSS, multilobe involvement, history of cardiac disease, and lower platelet counts independently predicted respiratory failure. Low platelet counts also were associated with neurologic complications.

TREATMENT RECOMMENDATIONS

Oxygen

Assessment of blood oxygenation requires determination of baseline arterial blood gases (ABG), and estimation of the alveolar-arterial (A-a) oxygen gradient and the PaO_2/FiO_2 ratio. Oxygen should be administered to moderately hypoxemic patients (PaO_2 = 70-80 mmHg, O_2 saturation = 92-95 percent) nasally at a rate of 2 liters per min. Chronically hypoxemic patients in whom the admission PaO_2 is no lower than in their steady state may still benefit from oxygen because they may not tolerate additional hypoxemia due to ACS. Control of chest pain and incentive spirometry can prevent hypoventilation in most patients (9). The efficacy of these interventions should be checked with repeated ABGs as needed to monitor the A-a gradient, which appears to be the best predictor of clinical severity (10). Patients with worsening A-a gradients should be managed in an intensive care unit for adequate cardiorespiratory support.

Transfusions

Simple transfusions (or exchange transfusions) decrease the proportion of sickle red cells and are indicated for the treatment of ACS (3,11) (see chapter 25, Transfusion, Iron Overload, and Chelation). Transfusions will increase the

Table 1. Clinical Presentation and Course of Acute Chest Syndrome: Cooperative Study
of Sickle Cell Disease (CSSCD) and Multicenter Acute Chest Syndrome Study (MACSS)

Presenting symptoms and signs (percent)	CSSCD	MACSS
Fever	80	80
Cough	74	62
Chest pain	57	44
Shortness of breath	28	41
Tachypnea	2	45*
Wheezing	11	26
Rales	46	76
Dullness	31	nr**
Normal auscultation	35	nr
X-ray and laboratory findings		
Multiple lobe involvement, adults (percent)	36	59
Multiple lobe involvement, children (percent)	24	74
Pleural effusion, adults (percent)	21	27
Pleural effusion, children (percent)	3	38
Mean hemoglobin level (g/dL)	7.9***	7.7
Mean change from steady-state Hb (g/dL)	- 0.7	- 0.8
Mean WBC/µL	21.1×10^3	23.0×10^3
Mean PaO_2 at diagnosis (mmHg)	71****	70
Mean O_2 saturation at diagnosis (percent)	nr	92
Bacteremia (percent)	3.5	nr
Hospital course, treatment, mortality		
Respiratory insufficiency, adults (percent on ventilator)	nr	22
Respiratory insufficiency, children (percent on ventilator)	nr	10
Neurologic event, (percent patients)	nr	11
Antibiotics given (percent patients)	nr	100
Bronchodilators used (percent patients)	nr	61
Transfusions used (percent patients)	26	72
Mean number of units given	nr	3.2
Mean hospital stay, adults (days)	10	12.8
Mean hospital stay, children (days)	5.4	9
Death rate, adults (percent)	4.3	9
Death rate, children (percent)	1.1	<2

* Tachypnea was an inclusion criterion in the MACSS but not in the CSSCD series.
** Not reported.
*** SCD-SS patients.
**** Only 56 percent had arterial blood gas determinations.

Table 2. Mean Room Air PaO_2 in ACS before and after Transfusions

Authors	Before Transfusion	After Transfusion	p
Emre et al. (18)	65 mmHg	86 mmHg	0.0001 (N=16)
Vichinsky et al. (3)	63 mmHg	71 mmHg	0.001 (N=387)

oxygen affinity of blood in sickle cell patients (12). The main indication for transfusion therapy is poor respiratory function. The goal is to prevent progression of ACS to acute respiratory failure. Two studies, though non-randomized, demonstrate the effect of blood transfusion on oxygenation in ACS patients (table 2).

From the data above, it would appear that transfusions or exchange transfusions should be initiated at the first sign of hypoxemia (PaO_2 below 70 mmHg on room air). For patients with chronic hypoxemia, a drop in PaO_2 of greater than 10 percent from baseline seems to be a reasonable transfusion trigger. Transfusions may not be needed if the A-a oxygen gradient is due to splinting from pain, that is, if the gradient corrects with analgesia and incentive spirometry. Transfusion therapy should not be delayed, particularly in deteriorating patients. Altered mentation in such patients is often erroneously attributed to opioid excess, delaying the therapy of progressive acute chest syndrome.

Antibiotics

Intravenous broad-spectrum antibiotics should be given to febrile or severely ill ACS patients since it is difficult to exclude bacterial pneumonia or superinfection of a lung infarct. The MACSS used erythromycin and cephalosporin. A macrolide or quinolone antibiotic always should be included because atypical microorganisms are common (3).

Other measures

Optimal pain control and incentive spirometry are important to prevent chest splinting and atelectasis. A randomized controlled study showed that incentive spirometry reduced the risk of development of ACS by 88 percent in patients hospitalized with thoracic bone ischemia/infarction (9). Airway hyperreactivity occurs in up to one-fourth of ACS patients and is treated with bronchodilators. Fluid overload should be avoided by the use of 5 percent dextrose in water or 1/2- or 1/4-normal saline, and by limiting the infusion rate to 1.5 times maintenance requirements (3). More studies are needed to establish the safety and efficacy of the use of dexamethasone (13) and other approaches, such as nitric oxide inhalation (14), in the treatment of ACS.

PREVENTION AND PROGNOSIS

The short-term prognosis of ACS with limited lung involvement and only mild hypoxemia is good. Some reports suggest an association between chronic pulmonary disease and frequent ACS episodes (15,16), but others did not find long-term lung damage in patients with recurrent ACS (17). In any case, frequent ACS episodes or painful events are associated with shorter lifespans (4). The frequency of ACS can be reduced by about 50 percent with hydroxyurea treatment (18). Nonrandomized observations suggest that transfusion regimens can prevent ACS. A preliminary report from the Stroke Prevention Trial in Sickle Cell

Anemia (STOP) showed that patients randomized to receive transfusions had significantly fewer ACS events (2.2/100 person-years), compared to patients in the nontransfused arm (15.7/100 person-years, p<0.001).

SYSTEMIC FAT EMBOLIZATION SYNDROME

SUMMARY OF THE STATE OF THE ART

Bone marrow infarction and necrosis is a known complication of SCD (19). When an infarct is massive, necrotic marrow and fat embolize to the pulmonary vasculature. Fat droplets can enter the systemic circulation, which results in systemic fat embolization (SFE) syndrome. Thus, in addition to respiratory insufficiency, patients can develop multiorgan failure from emboli in organs such as the brain and kidneys. SFE can affect patients with even the mildest forms of SCD. Few case reports are available (20,21), but risk factors for SFE appear to be a β^s/β^c genotype, pregnancy, and prior corticosteroid treatment. Clinical signs of SFE vary and depend on the organs involved and the degree of involvement. Initially there may be a painful event, but patients can present with or develop a fever, hypoxemia, azotemia, liver damage, altered mental state, or coma. Hematologic signs include progressive anemia, normoblastemia, thrombocytopenia, and disseminated intravascular coagulation. A high index of suspicion for SFE should be maintained, even though this diagnosis is hard to prove. Fortunately, SFE is often preceded or accompanied by pulmonary involvement (severe chest syndrome, pulmonary fat embolism), so that transfusions given to hypoxemic ACS patients may prevent or inhibit its development.

RECOMMENDATIONS

Because SFE is life-threatening but difficult to recognize, a proposal for management includes the following:

- A high index of suspicion for SFE should be maintained, and all cases of ACS are considered to be at risk. Treatment of SFE should not await proof of diagnosis, since only two premortem findings prove SFE in sickle cell or trauma patients: detection of fat droplets within retinal vessels and a biopsy of petechiae (22) that shows microvascular fat. Urine fat stains are unreliable. Indirect evidence of SFE in sickle cell patients includes positive fat stain in bronchial macrophages, lung microvascular cells, or venous blood buffy coat (23) and multiple areas of necrosis on bone marrow scans. The descriptions of these signs are anecdotal in SCD-related SFE (and in non-SCD patients with fat emboli due to trauma).

- As in cases of severe ACS, support in a critical care setting is essential to manage respiratory insufficiency and multiorgan failure. Case reports suggest that prompt transfusion or exchange transfusion may prevent some deaths from SFE (20). Since fat embolism causes severe hypoxemia which promotes Hb S polymerization, it seems likely that transfused normal blood will dilute the patient's sickle cells and improve pulmonary and systemic microvascular circulation. Survival in sickle cell patients with SFE has been reported only in those treated with transfusions.

REACTIVE AIRWAY DISEASE

Airway hyperreactivity (asthma) is not a classical feature of SCD, but transgenic mouse models of SCD have airway obstruction that is responsive to albuterol. Cold air challenge

induced hyperresponsiveness in 83 percent of asymptomatic children with SCD who had a history of reactive airways (24). Also, two large prospective studies of ACS described above reported wheezing in 11 percent (6) and 26 percent (3) of patients on admission. In the latter group, the mean predicted forced expiratory volume was 53 percent, and 61 percent of patients were treated with bronchodilators. Twenty percent of ACS patients improved with bronchodilators and had a 15 percent increase in predicted forced expiratory volume (3). Like nonhemoglobinopathy subjects, asthmatic sickle cell patients are treated with inhaled bronchodilators, with or without inhaled steroids. Steroids can be added systemically to manage acute asthma, but sickle cell patients should be monitored for the development of vaso-occlusive events.

PULMONARY HYPERTENSION

SUMMARY OF THE STATE OF THE ART

Pulmonary hypertension (PHT), defined as a mean pulmonary artery pressure above 25 mmHg, can be secondary to SCD (20), but its prevalence is not known. In sickle cell patients the frequency of chronic lung disease with cor pulmonale is reported at 4.3 percent. PHT is probably more frequent in adult patients (20), although it was not listed as an underlying condition in 209 adult CSSCD patients who died during that study (25).

The mechanisms for PHT in SCD are not known. One or more of the following factors could be responsible: sickle cell-related vasculopathy, chronic oxygen desaturation or sleep hypoventilation (26), pulmonary damage from recurrent chest syndrome (15), repeated episodes of thromboembolism (27), or high pulmonary blood flow due to anemia. The last reason, combined with decreased lung

vasculature, also was given as a cause of PHT in thalassemia intermedia (28). Regardless of the exact mechanism, the development of PHT raises the risk for cor pulmonale, recurrent pulmonary thrombosis, and worsened hypoxemia, all of which increase the frequency and severity of vaso-occlusive episodes (pain events, ACS) in SCD (15).

The diagnosis of PHT should be considered in sickle cell patients with (a) increased intensity of the second heart sound, (b) right ventricular enlargement on chest x ray, EKG, or echocardiogram, or (c) unexplained oxygen desaturation. As PHT worsens, patients complain of chest pain and dyspnea, and have hypoxemia at rest. Additional problems are right-sided heart failure, syncope, and a risk of sudden death from pulmonary thromboembolism, systemic hypotension, or cardiac arrhythmia. Unless an echocardiogram shows tricuspid regurgitation with increased pulmonary artery pressure, the diagnosis of PHT requires right-sided cardiac catheterization. In a few patients whose catheterization results were published, the pulmonary pressures were lower and cardiac outputs (measured by thermodilution) were higher than in primary PHT (20).

RECOMMENDATIONS

There is no proven treatment for sickle cell-related PHT. Therefore, recommendations are tentative and based mostly on what is known about the treatment of primary PHT. During cardiac catheterization, vasodilators or oxygen may be given to see if they reduce pulmonary pressure acutely in order to predict the benefit of long-term administration. Continuous infusion of prostacyclin, a vasodilator and inhibitor of platelet aggregation, improves pulmonary artery pressure and survival in primary PHT (29), and also may be effective in secondary PHT (30). This drug also causes some patients

with SCD-related PHT to respond during cardiac catheterization (31), but there are no published data on long-term use. Other agents used to treat primary PHT are the calcium-channel blockers nifedipine and diltiazem (32), and these or similar medications could be tried in responsive sickle cell patients. Long-term anticoagulation with warfarin [to an international normalized ratio (INR) of 2-3] is used in primary PHT because of the risk of thromboembolism (29) and also may be useful for SCD-related PHT (27). Continuous or nocturnal oxygen therapy decreases pulmonary artery pressure in patients who are hypoxemic from various lung disorders. It should be used in SCD-related PHT if it lowers pulmonary pressure at cardiac catheterization, and in chronically hypoxemic patients (PaO_2 <60 mmHg, O_2 saturation <90 percent). A red cell transfusion program would help to reduce the incidence of vaso-occlusive events, ACS, lung scarring, and PHT in some patients. Hydroxyurea would be expected to have the same effect, but it does not seem to prevent the development of PHT in SCD.

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GALL BLADDER AND LIVER

Dysfunction of the liver and biliary tract is a common complication of sickle cell disease (SCD) and its variants. Despite nearly 200 reports in the past 15 years on the hepato-biliary aspects of the sickling disorders, the frequency and pathophysiology responsible for hepatic lesions remain unclear.

Hepato-biliary complications of the sickling disorders can be separated into broad categories of disorders related to hemolysis, the problems of anemia and transfusion management, the consequences of sickling and vaso-occlusion, and diseases unrelated to sickle hemoglobin (Hb S). These complications of the sickling disorders are most common in sickle cell anemia (SCD-SS), but also occur to a lesser extent in the compound heterozygous sickle diseases, SCD-SC and the β-thalassemia syndromes (SCD-S β° thal and SCD-S β⁺ thal).

CHOLELITHIASIS AND BILIARY SLUDGE

Chronic hemolysis, with its accelerated bilirubin turnover, leads to a high incidence of pigment gallstones. Ordinarily, bilirubin levels in SCD patients do not exceed 4 mg/dL from hemolysis alone, and the conjugated fraction is less than 10 percent (1,2). Marked increases in the unconjugated fraction have been reported in association with the UDP-glucuronyltransferase genetic defect of Gilbert's syndrome (3).

Ultrasound surveys of patient populations indicate the onset of cholelithiasis occurs as early as 2 to 4 years of age and progressively increases in prevalence with age (4); nearly 30 percent of patients develop cholelithiasis by age 18. African populations appear to have a substantially lower prevalence than that of Jamaican or North American patients (5); this variation is attributed to differences in dietary cholesterol or fiber, although other factors (genetic or environmental) also may have an influence. Xenobiotics such as the third generation cephalosporins may crystallize in the gallbladder, and differences in the use of such antibiotics could account for some of the geographic variation in cholelithiasis frequency. The coinheritance of α-thalassemia appears to reduce the frequency of stones as the result of a lesser degree of hemolysis (6). Common duct obstruction is frequently incomplete because pigment stones are small but they still can cause the characteristic biochemical changes of cholestasis. Gallstones have been known to pass with or without pancreatitis.

Biliary sludge is a viscous material detectable by nonacoustic shadowing on ultrasonography (7) and may be a precursor of gallstone development. Certain antibiotics such as ceftriaxone seem to promote sludge formation. Studies in patients with SCD indicate that sludge is often found with stones, but sludge alone may or may not progress to stone formation. However, the period of followup of such studies is short (8,9).

ACUTE AND CHRONIC CHOLECYSTITIS

Fever, nausea, vomiting, and abdominal pain are common events with a wide differential diagnosis, including hepatic, intestinal, pancreatic, vertebral, neurologic, and pulmonary disorders (table 1).

A careful clinical evaluation is necessary to establish a clear diagnosis. Biliary scintigraphy might be helpful, but its use is controversial because of a high false positive rate and low positive predictive value. However, it has a high negative predictive value since a normal study indicates that the cystic duct is patent. False positives can result from prolonged fasting, severe hepatocellular disease, extrahepatic obstruction, chronic cholecystitis, or narcotic-induced spasm of the sphincter of Oddi (10).

Table 1. Unusual Causes of Right Upper Quadrant (RUQ) Pain and Abnormal Liver Tests Reported in Sickling Disorders

Biloma

Focal nodular hyperplasia of the liver in children

Fungal ball

Hepatic artery stenosis

Hepatic infarct/abscess

Hepatic vein thrombosis

Mesenteric/colonic ischemia

Pancreatitis

Periappendiceal abscess

Pericolonic abscess

Pulmonary infarct/abscess

Renal vein thrombosis

The Tc-99 RBC scan may prove more useful in detecting the hyperemia of acute cholecystitis, but its use with these patients has not been reported.

Treatment of acute cholecystitis does not differ from that for the general population and consists of antibiotics and general supportive care with consideration for elective cholecystectomy several weeks after the acute episode subsides.

CHOLECYSTECTOMY

Laparoscopic cholecystectomy on an elective basis in a well-prepared patient has become the standard approach to symptomatic patients. However, symptoms attributed to cholecystitis often persist after cholecystectomy. Because intraoperative cholangiography (IOC) has a false positive rate estimated at 25 percent, endoscopic retrograde cholangiopancreatography (ERCP) at the time of laparoscopic cholecystectomy is preferred. IOC is still useful, however, for delineating the anatomy of the cystic duct and its artery. The decision to proceed to cholecystectomy should be based on the natural history of the disorder in this patient population. The Jamaican data (4) provide the strongest argument for a conservative approach, but Jamaican patients seem to be substantially less symptomatic than are North American patients. An aggressive approach provides the benefit of reducing the risk of the morbid complications of cholelithiasis, as well as eliminating gallbladder disease as a confounding item in the differential diagnosis of right upper quadrant pain. For asymptomatic patients, the data support a conservative approach, but there is considerable controversy.

VIRAL HEPATITIS

Acute viral hepatitis has the same clinical course in patients with sickling disorders as in the general population, but with a higher peak bilirubin level because of hemolysis.

Surveys for serologic evidence of hepatitis B infection show a wide range of prevalence, related to the endemicity of the virus as well as to past transfusion practices (1). Fulminant hepatitis occurs with a high mortality in 0.5 percent of the general population, and chronicity is inversely related to age. Thus vaccination early in life seems to be indicated; patients with SCD respond as well as the general population.

Similar surveys for hepatitis C infection indicate that this infection is clearly related to transfusion practice and geographic location and that chronic hepatitis is as frequent in patients with SCD as in the general population (11). In the general population, fulminant hepatitis is unusual, but as many as 65 percent will develop chronic hepatitis and cirrhosis. Chronic hepatitis is subtle, with only 25 percent of patients having AST/ALT as high as twice normal values. In SCD, cirrhosis occurs, and liver transplants are now being done (12). Chronic hepatitis C is associated with extrahepatic manifestations that can confound the management of SCD. These include a cutaneous leucocytoclastic vasculitis and essential mixed cryoglobulinemia with purpura, arthralgias, glomerulonephritis, and peripheral neuropathy.

In studies of patients with persistent elevations of AST/ALT, biopsy invariably shows evidence of chronic hepatitis (13,14). Treatment of chronic viral hepatitis is based upon observations that sustained suppression of viral replication renders patients noninfectious, reduces the inflammatory process, and slows the subsequent development of cirrhosis and hepatocellular carcinoma.

Indications for treatment of hepatitis B include HBsAg positivity for more than 6 months, HBV DNA positivity, and persistent elevation of ALT or biopsy evidence for chronic hepatitis.

For hepatitis C, persistent elevation of AST/ALT, positive PCR for viral RNA, or biopsy evidence of chronic hepatitis are indications for treatment.

AUTOIMMUNE HEPATITIS

Autoimmune hepatitis has been reported in 5 patients (15). It is characterized histologically by dense T-cell infiltrates in periportal areas with bridging fibrosis and piecemeal necrosis and by a marked polyclonal gammopathy. It is associated with extrahepatic manifestations of arthropathy, rash, and leg ulcers. Treatment of sickle cell patients with plasma exchange has been successful. Data from the hepatology literature indicate that prednisone and azathioprine given for 24 months initially induce a clinical remission that is followed by biochemical, then histological, remission.

HEMOSIDEROSIS/ HEMOCHROMATOSIS

Iron overload develops as a result of frequent transfusions, although genetic hemochromatosis does occur. Hepatic iron stores can be measured biochemically or by a superconducting quantum interference device susceptometer, but this instrument is not widely available. Magnetic resonance imaging (MRI) comparing the signal intensity of liver, pancreas, and spleen to that of muscle is useful for detecting iron overload, but MRI is not very sensitive

to gradations of iron load. Decrease in signal intensity from the pancreas is a very useful index for hemochromatosis. Serum ferritin levels may be disproportionately elevated relative to the degree of iron stores because of factors such as ascorbate deficiency, inflammation, or liver disease (16). The isotope Ga-67 is carried by transferrin, and Ga-67 citrate may prove to be useful in the demonstration of iron overload but requires further study.

The importance of iron load is illustrated by results from a study of children receiving transfusion for the prevention of stroke; their serum ferritin levels rose 10-fold at an average followup of 42 months and this increase was associated with an 8-fold rise in AST/ALT (17). In a study of women receiving supportive transfusion during pregnancy, incidental liver biopsy performed during abdominal surgery showed that two-thirds had significant hepatocyte iron accumulation after an average transfusion burden of 13.6 units (18).

The standard subcutaneous regimens for deferoxamine therapy successfully chelate excess iron. Complications of therapy include ophthalmic- or oto-toxicity, allergic reactions, growth failure, and unusual infections (*Yersinia*, fungi).

Poor patient compliance is an unresolved problem. Because poor compliance can be an issue, periodic intensive intravenous deferoxamine therapy is often given. Aggressive chelation with intravenous doses of 6 to 12 grams daily has produced rapid declines in serum ferritin and ALT, and improvement in cardiac function and other indices. Adverse effects have not been noted in short-term therapy, although zinc excretion is increased (19).

Vascular Occlusion

The hepatic complications attributed to vascular occlusion encompass a variety of clinical syndromes for which our understanding of the relationships among clinical presentation, biochemical findings, and histologic features remains unclear. In many patients, the liver is generally enlarged throughout life, especially when its measurement is adjusted for body size (20).

Hepatic crisis, or right upper quadrant syndrome (RUQ), consists of RUQ pain, fever, jaundice, elevated AST/ALT, and hepatic enlargement. It occurs in as many as 10 percent of patients with acute vaso-occlusive crisis (VOC). The rapid decrease in AST/ALT differentiates this condition from the slower decline characteristic of acute viral hepatitis. In one study of 30 patients, liver tests taken at the time of uncomplicated VOC and 4 weeks later in the steady state showed that the alkaline phosphatase level was 30 percent higher during VOC; ALT was three-fold higher, and bilirubin was elevated two-fold, primarily due to elevation of the conjugated fraction (21). Treatment with supportive care was the only modality needed.

RUQ pain and jaundice present a problem in differential diagnosis because prominent abdominal pain is associated with a wide variety of conditions that affect SCD patients (table 1). Additional imaging techniques are useful in establishing these diagnoses. Hepatic infarction is seen as a characteristic wedge-shaped, peripherally located hypointense lesion on CT scan. Single or multiple abscesses have been described with an irregular shape on CT scan. Focal nodular hyperplasia of the liver has been seen with a characteristic avascular mass on angiography.

HEPATIC SEQUESTRATION

Acute hepatic sequestration, a rarely recognized complication of VOC, is characterized by a rapidly enlarging liver accompanied by a decrease in hemoglobin/hematocrit and a rise in reticulocyte count. The liver is smooth and variably tender. The bilirubin may be as high as 24 mg/dL (or even higher) with a predominance of the conjugated fraction. The alkaline phosphatase can be as high as 650 IU/L or may be normal; the transaminases may be elevated only minimally but are often normal. Ultrasonography and CT scanning show only diffuse hepatomegaly. Liver biopsy shows massively dilated sinusoids with sickled erythrocytes and Kupffer cell erythrophagocytosis. Intrahepatic cholestasis with bile plugs in canaliculi may be seen. Hepatocyte necrosis is unusual. Recurrence is common.

Simple transfusion, exchange transfusion, or supportive care alone can resolve hepatic sequestration. In one patient, treated with simple transfusion, resolution of sequestration was accompanied by a rapid increase in the concentration of circulating hemoglobin, representing return of sequestered red cells to the circulation; this resulted in a fatal acute hyperviscosity syndrome (22). Because of this risk with simple transfusion, exchange transfusion is preferred; however, careful monitoring still is required.

Acute hepatic failure has been reported in several cases where massive hepatic necrosis was seen in the absence of markers for viral hepatitis. However, clinical and biological profiles improved rapidly after exchange transfusion therapy.

CHOLESTASIS

Acute and chronic cholestatic syndromes have been attributed to a wide variety of clinical entities in patients with SCD.

A benign cholestatic picture has been described in which there are striking elevations of bilirubin with only modest elevations of alkaline phosphatase and transaminases; there is no impairment of hepatic synthetic function, as reflected by the prothrombin time and activated partial thromboplastin time. The patients are asymptomatic except for jaundice or pruritus. Fever, abdominal pain, and gastrointestinal upset are conspicuously absent. Drug reactions can be implicated in some cases, and measurement of anti-kidney/liver microsomal antibodies can assist in diagnosis. In all instances, resolution of cholestasis occurs within months in the absence of specific therapy (1,23).

In contrast, progressive cholestasis in the absence of cirrhosis has been reported in a number of cases. These cases are characterized by RUQ pain, extreme elevation of bilirubin, striking elevation of alkaline phosphatase, and variable elevation of transaminases. Renal failure, thrombocytopenia, and severe prolongation of coagulation test results are present. Liver histology in both benign and progressive forms of cholestasis shows intrasinusoidal sickling and Kupffer cell hyperplasia with phagocytosis of sickled erythrocytes. Mortality due to uncontrollable bleeding or hepatic failure is common (1,24). All survivors have been treated with exchange red cell transfusion; plasmapheresis with fresh frozen plasma and platelet transfusion support have been used to control bleeding due to hemostatic failure.

RECOMMENDATIONS

Biliary sludge is best managed by serial ultrasound examinations at 12- to 24-month intervals unless cholestasis occurs; at that point, laparoscopic cholecystectomy is indicted. Elective laparoscopic cholecystectomy has become the procedure of choice for symptomatic cholelithiasis (25) because of the shortened hospital stay, lower cost, and fewer immediate surgical complications. One approach to asymptomatic or minimally symptomatic cholelithiasis is careful observation until symptoms dictate surgery. Bacteremia, ascending cholangitis, empyema, and other hyperacute biliary complications require surgery on a more urgent basis, consistent with good surgical practice.

The management of chronic hepatitis is beyond the scope of this treatise but requires close coordination with gastroenterologists and the judicious use of liver biopsy to guide diagnosis and therapeutic decisions.

Iron overload can be managed by the standard subcutaneous protocols, but the intensive intravenous approach is attractive because of the claim of improved compliance (19).

The syndromes attributable to intrahepatic vaso-occlusion appear to be treated best with exchange red cell transfusion because of the remote risk of acute hyperviscosity (22). Plasmapheresis and platelet transfusion support are useful in cases associated with coagulopathy.

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ONLINE RESOURCES

American Association for the Study of Liver Diseases
http://www.aasld.org

The American Gastroenterological Association
http://www.gastro.org

American Liver Foundation
http://www.liverfoundation.org

Centers for Disease Control and Prevention
http://www.cdc.gov

Hepatitis B Coalition
http://www.immunize.org

Hepatitis B Foundation
http://www.hepb.org

Hepatitis Foundation International
http://www.hepfi.org

National Institutes of Health Consensus Statement
http://www.consensus.nih.gov

SPLENIC SEQUESTRATION

Acute exacerbation of anemia in the patient with sickle cell disease (SCD) is a significant cause of morbidity and mortality. The most common process leading to this complication is acute splenic sequestration.

ACUTE SPLENIC SEQUESTRATION COMPLICATION

Acute splenic sequestration complication (ASSC) is caused by intrasplenic trapping of red cells which causes a precipitous fall in hemoglobin level and the potential for hypoxic shock. ASSC remains a leading cause of death in children with SCD. ASSC may be defined by a decrease of at least 2 g/dL from the steady-state hemoglobin concentration, evidence of increased erythropoiesis such as a markedly elevated reticulocyte count, and an acutely enlarging spleen. ASSC has been reported as early as 5 weeks of age (1) and in adults (2), but in most cases the first episodes in SCD-SS patients occur between 3 months and 5 years of age. The attacks are often associated with viral or bacterial infections. Acute chest syndrome occurred in 20 percent in one series (3). The usual clinical manifestations are sudden weakness, pallor, tachycardia, tachypnea, and abdominal fullness. ASSC has been reported in 30 percent of children with sickle cell anemia in Jamaica (3) and 7.5 percent of children seen at Duke University (4). In Jamaica, the mortality rate for first attacks was 12 percent (5). Recurrent splenic sequestration events are common, occurring in approximately 50 percent of those who survive the first

episode, and the mortality rate in these patients may be 20 percent (5). There are no clear prognostic factors for the occurrence of ASSC, although the fetal hemoglobin (Hb F) level at 6 months of age is somewhat lower in children who develop this complication (3). Although ASSC occurs most commonly among children with SCD-SS, it has been reported in 5 percent of children with SCD-SC disease at a mean age of approximately 9 years (6) and in adults with SCD-SC disease and SCD-S β^+-thalassemia (7).

TREATMENT OF ACUTE SPLENIC SEQUESTRATION

The immediate treatment of acute splenic sequestration is directed toward correction of hypovolemia with red blood cell transfusion. Because severe ASSC can be fatal within a few hours, emergent transfusion is required (see chapter 25, Transfusion, Iron Overload, and Chelation). Once transfusion is employed, red cells sequestered in the spleen are remobilized, splenomegaly regresses, and the hemoglobin level increases, often to a level greater than predicted on the basis of the volume of red cells administered.

The rate of recurrent splenic sequestration is high and greatly influences subsequent management, which may be divided into observation only, chronic transfusion, and splenectomy. Indications for these approaches are not clearly defined. Questions which bear on management decisions include: Does splenectomy

increase the risk of invasive infection above that of the patient with functional asplenia? Does a partial splenectomy allow maintenance of some splenic function? Does chronic transfusion effectively restore splenic function? Does chronic transfusion maintain the spleen's potential for sequestration by delaying autoinfarction?

Observation

Children who have ASSC are at risk for recurrent, potentially fatal episodes and should receive immediate medical attention. Observation for adults is common because episodes tend to be mild (8).

Chronic Transfusion

Rao and Gooden (9) treated 11 children with subacute splenic sequestration with short-term transfusion for 1 to 3 years. Seven patients had recurrent sequestration when transfusions were discontinued near 5 years of age and subsequently underwent splenectomy. There were no deaths. The authors concluded that the time gained from short-term transfusion therapy was beneficial in reducing the risk of acute sequestration and temporarily reversing splenic dysfunction. In contrast, Kinney et al. (4) compared short-term transfusion (n=12) with observation (n=7) and immediate splenectomy (n=4) in a group of 23 children with ASSC. Despite a reduction in the concentration of sickle hemoglobin (Hb S) to less than 30 percent in the chronically transfused patients, the risk of recurrent sequestration appeared unaffected by transfusion. Seven of 10 evaluable patients with chronic transfusion had recurrences either during the transfusion period or shortly after transfusion was discontinued; 4 of 7 patients who were observed had recurrences. Overall, splenectomy was performed in 61 percent of patients. The authors concluded that short-term transfusion to prevent recurrent splenic sequestration was of limited benefit. An intermediate recommendation came from

Grover and Wethers (10), who advised a year or more of long-term transfusion therapy for the child with ASSC under age 3 and prompt splenectomy after the first episode of ASSC in the child 5 years of age or older.

Topley et al. (5) reported that one third of patients with ASSC develop hypersplenism. They noted that chronic transfusion may simply delay episodes of ASSC to a later age and may not restore splenic function. In fact, Rogers et al. (11) reported that pitted red cell counts rose to asplenic levels after an episode of ASSC and rarely, if ever, returned to values compatible with normal splenic function.

Splenectomy

Powell et al. (8) described 12 patients with ASSC. One patient died; 3 patients with minor episodes had no recurrences, and 8 patients had prompt splenectomy. The researchers recommended splenectomy after the first major episode of ASSC and reasoned that removal of a poorly or nonfunctioning spleen does not increase susceptibility to infections. Although chronic blood transfusion can delay splenectomy and temporarily restore splenic function, these advantages were thought to be outweighed by the risks of chronic blood administration. In addition, Topley et al. (5) suggested that any child with a history of one classical episode of ASSC or a minor episode followed by the development of sustained hypersplenism should undergo splenectomy.

An analysis of 130 Jamaican patients with SCD-SS treated by splenectomy (46 for recurrent ASSC), and a control group matched for sex, age, and duration of followup in a retrospective review by Wright et al. (12) found that mortality and bacteremic episodes did not differ between the splenectomy and control groups. Painful events and acute chest syndrome were more common in the splenectomy

group. The authors concluded that splenectomy does not increase the risk of death or bacteremic illness in patients with SCD-SS and, if otherwise indicated, should not be deferred.

Partial splenectomy has been recommended for children with recurrent ASSC as a means of preventing further recurrence and retaining splenic function (13,14). However, one patient died of overwhelming sepsis when this approach was used (15).

EDUCATION

Emond et al. (3) describe a parental education program in Jamaica to facilitate early diagnosis of ASSC. The program, which involved more than 300 children with SCD-SS, led to an increase in the incidence of ASSC from 4.6 to 11.3/100 patient-years, probably reflecting increased awareness of the complication. However, the mortality rate fell from 29.4/100 events to 3.1/100 events, a dramatic decline resulting from improved medical management and earlier detection.

RECOMMENDATIONS

All reports regarding the management of ASSC (and chronic hypersplenism) were descriptive, retrospective, and uncontrolled. Clinical evidence derived from controlled clinical trials is relatively weak.

The following are current recommendations:

- Early education should be provided to parents of infants with SCD regarding palpation of the spleen, symptoms of progressive anemia, and appropriate action for obtaining rapid evaluation and treatment.

- Patients who have a life-threatening episode of ASSC that requires transfusion support should have a splenectomy shortly after the event or be placed on a chronic transfusion program.

- Alternatively, patients who have a severe episode of ASSC and are below 2 years of age should be placed in a chronic transfusion program to keep Hb S levels below 30 percent until a splenectomy can be considered after 2 years of age.

- Patients with chronic hypersplenism also should be considered for splenectomy.

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The kidney in patients with sickle cell disease (SCD) exhibits numerous structural and functional abnormalities, changes that are seen along the entire length of the nephron. The medullary region of the kidney is composed of renal tubules and medullary blood vessels that are collectively referred to as the *vasa recta* system. The environment of the renal medulla is characterized by hypoxia, acidosis, and hypertonicity. Because these conditions promote hemoglobin S (Hb S) polymerization and red cell sickling, this area of the kidney is particularly susceptible to malfunction. Microradioangiographic studies carried out on the kidneys of patients with SCD show significant loss of the *vasa recta*. Those few medullary blood vessels that remain are markedly dilated with a spiral configuration, and appear to end blindly (1). Changes are most marked in patients with homozygous sickle cell anemia (SCD-SS), but are also seen in those with compound heterozygous states (SCD-SC, thalassemia) and the sickle cell trait. Table 1 summarizes renal abnormalities associated with SCD.

HYPOSTHENURIA

Hyposthenuria, an inability to concentrate urine maximally, is perhaps the most common renal abnormality in SCD (2). In individuals with SCD-SS, hyposthenuria typically becomes apparent during early childhood as enuresis, whereas in the other syndromes,

it may occur later in life. This dysfunction in urinary concentrating ability is frequently associated with nocturia.

As a result of the inability to maximally concentrate the urine, patients with SCD are more susceptible than are normal individuals to dehydration, a factor that often precipitates vaso-occlusive events. Patients with SCD should therefore be encouraged to drink liberal amounts of liquids in order to compensate for the fluid loss that is brought on by hyposthenuria.

TUBULE DYSFUNCTION

Defective urinary acidification also is well described in SCD (3). Typically, however, patients have normal aldosterone and renin responses (4). The primary abnormality is an incomplete distal renal tubular acidosis (RTA), and the severity of the acidification defect is related, at least in part, to the severity of the hyposthenuria.

Defects in potassium excretion also are seen in SCD. Although not clinically apparent under normal circumstances, hyperkalemia does become manifest as overall renal function deteriorates. In addition, even SCD patients with normal renal function are at risk for hyperkalemia following administration of drugs such as ACE inhibitors, beta-blockers, and potassium-sparing diuretics (2).

Table 1. Summary of Renal Abnormalities in SCD

Renal Abnormality	Comments
Abnormalities in distal nephron function	
Hyposthenuria	Not due to anemia
Impaired urinary acidification	Incomplete distal tubular acidosis
Impaired potassium excretion	Occurs despite normal renin/aldosterone
Supranormal proximal tubule function	No pathological significance
Increased β-2-microglobulin reabsorption	
Increased phosphate reabsorption	
Increased uric acid secretion	
Increased creatinine secretion	
Hemodynamic changes	Mediated by prostaglandins
Increased renal plasma flow	
Increased glomerular filtration rate	
Decreased filtration fraction	
Hematuria	Occurs in left kidney in 80 percent of cases
Renal medullary carcinoma	Requires thorough workup of hematuria
Papillary necrosis	Infrequently produces renal failure
Acute renal failure	May be associated with rhabdomyolysis
Urinary tract infection	Especially in pregnant women
Glomerular abnormalities	With older age or CAR β^s-haplotype
Proteinuria	
Nephrotic syndrome	
Chronic renal failure	

Increased creatinine secretion causes a lower serum creatinine level and thus an overestimation of the glomerular filtration rate (GFR) in SCD-SS patients. Differences of up to 30 percent have been reported when creatinine clearance is compared to inulin clearance (5). The significance of this enhanced proximal tubular function in the pharmacokinetics of drugs in which tubular secretion is a major pathway of elimination is uncertain (2). Despite increased secretion of uric acid, patients with SCD often have hyperuricemia and are vulnerable to secondary gout.

HEMATURIA

Hematuria, a common renal abnormality in SCD, appears to result from the Hb S polymerization and red cell sickling in the renal medulla. It may be a manifestation of papillary necrosis. In most cases, bleeding originates from the left kidney; a small minority of patients have bilateral kidney involvement (6).

The treatment of hematuria in SCD involves bed rest, maintenance of a high urinary flow documented by monitoring of intake and output, and, if blood loss is significant, iron replacement and/or blood transfusion.

Vasopressin and epsilon-amino caproic acid (EACA) have both been used with variable success (7,8). However, caution must be exercised when using EACA as this antifibrinolytic agent may predispose to the formation of clots that can obstruct the urinary collecting system. If prolonged and life-threatening bleeding is coming from one kidney, local resection of the bleeding segment is preferred. Unilateral nephrectomy is a last resort since bleeding may recur from the other kidney.

Hematuria that occurs in SCD is not always a consequence of red cell sickling and papillary necrosis. Other, nonsickling causes also should be considered. For example, renal medullary carcinoma in young subjects with SCD and sickle cell trait (Hb AS) has been reported (9,10). Therefore, a thorough evaluation is recommended when hematuria is initially found in individuals with SCD and Hb AS.

ACUTE RENAL FAILURE

Acute renal failure occurs as a component of the acute multiorgan failure syndrome (AMOFS) in patients with SCD (11). This syndrome is characterized by the sudden onset of severe dysfunction of at least two major organ systems (e.g., kidney, lung, liver) during an acute painful vaso-occlusive episode in patients with SCD. The pathophysiology of AMOFS appears to be due to diffuse, small vessel occlusion, which in turn results in tissue ischemia and organ dysfunction. The renal failure in this syndrome also may be related to the accompanying rhabdomyolysis. Prompt initiation of transfusion therapy or exchange transfusion may reverse this syndrome.

GLOMERULAR ABNORMALITIES AND CHRONIC RENAL FAILURE

Proteinuria, which can progress to the nephrotic syndrome, is the most common manifestation of glomerular injury in SCD patients. Moreover, as many as 40 percent of SCD-SS patients with nephrotic syndrome may go on to develop end-stage renal disease (ESRD) (12). Therefore, patients with persistent proteinuria should have a urine collection obtained for the determination of 24-hour protein excretion, and a nephrology consultation should be requested for consideration of other, nonsickling causes of proteinuria and possible renal biopsy.

ACE inhibitors ameliorate pathological changes such as perihilar focal and segmental glomerulosclerosis. They also decrease urinary protein excretion in patients with early manifestations of sickle cell nephropathy (13).

Renal insufficiency occurs earlier in SCD-SS patients than it does in SCD-SC patients (12). Factors that appear to predict renal failure in SCD-SS patients include hypertension, proteinuria, increasingly severe anemia, and hematuria (13). Finally, the risk of renal failure is increased in those SCD-SS patients with the Central African Republic (CAR) β^s-gene cluster haplotype.

As there is no proven treatment for sickle cell nephropathy, every attempt should be made to slow its rate of progression. The amount of proteinuria can be decreased by the administration of ACE inhibitors, and it is conceivable that the progression of sickle cell nephropathy may be slowed by a prolonged course of these drugs. Patients should avoid nonsteroidal anti-inflammatory drugs (NSAIDs) because NSAIDs have been shown to produce significant declines in the rates of glomerular filtration and renal blood flow in patients with SCD (5,14).

Effective control of blood pressure has been reported to slow the progression of ESRD in patients with SCD; they should be treated with standard approaches (15). Optimum target blood pressure has not been defined. Because dehydration can precipitate vaso-occlusive events, caution should be exercised in the use of diuretic agents in an individual with obligate hyposthenuria.

Every effort must be made to avoid additional renal damage due to urinary tract infection. Infection must be recognized and treated vigorously. Followup should be maintained longer than for patients without SCD.

Although erythropoietin levels are generally high in steady-state SCD-SS patients, they are not increased to the level that would be expected for the degree of anemia (16). One explanation for the relatively decreased erythropoietin levels is the right-shifted hemoglobin-oxygen dissociation curve seen in SCD patients (17). Erythropoietin levels in SCD patients fall still further as renal function worsens, and these patients may require substantially higher doses of erythropoietin than are required for patients with other forms of ESRD (18). If erythropoietin is ineffective, transfusions can be given; they must be done carefully, however, to avoid volume overload (see chapter 25, Transfusion, Iron Overload, and Chelation).

As with all patients who develop ESRD, SCD patients can be treated with both hemodiaylsis and peritoneal dialysis, and they can undergo renal transplantation. Although early reports suggested poor allograft survival and other disease-specific problems in SCD patients, others have reported graft and patient survival rates comparable to those of other nondiabetic patients (19). A more recent study of renal transplantation in SCD reported short-term patient and allograft outcomes comparable to other age-matched African Americans. However, there was a shorter cadaveric graft survival and high risk of graft loss with longer followup in the SCD patient group (20). There was a trend toward improved survival in those SCD patients who received transplants compared to those on chronic dialysis.

Although many SCD patients have done well after renal transplantation, several unique complications have been described. Patients may experience a resumption of frequent vaso-occlusive events which presumably are related to an increase in whole blood viscosity accompanying a higher hemoglobin level. Renal infarction, a probable secondary consequence of Hb S polymerization, cell sickling, and vaso-occlusion, has been reported to occur as early as 6 days following transplantation (21). The reappearance of sickle cell nephropathy in the donor kidney has also been reported (22).

It is possible that the availability of new immunosuppressive drugs may further improve the outcome renal transplantation in SCD patients. Hydroxyurea is excreted by the kidney and thus its use in patients with renal failure requires careful monitoring. SCD patients receiving renal transplants may benefit from exchange transfusion or even from periodic phlebotomy, particularly when hemoglobin levels are high.

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ONLINE RESOURCES

The Sickle Cell Information Center: Problem Oriented Clinical Guidelines
http://www.emory.edu/PEDS/SICKLE/prod04.htm

Sickle Cell Disease
http://www.familyvillage.wisc.edu/lib_scd.htm

Priapism

Priapism, defined as a sustained, painful, and unwanted erection, is a well recognized complication of sickle cell disease (SCD) (1-3). According to one study, the mean age at which priapism occurs is 12 years, and by the age of 20, as many as 89 percent of males with SCD will have experienced one or more episodes of priapism (1). Priapism in males with SCD is due to vaso-occlusion, which causes obstruction of the venous drainage of the penis. Priapism can be classified as *prolonged* if it lasts for more than three hours or *stuttering* if it lasts for more than a few minutes but less than three hours and resolves spontaneously; however, such stuttering episodes may recur or develop into more prolonged events. Prolonged priapism is an emergency that requires urologic consultation. Recurrent episodes of priapism can result in fibrosis and impotence, even when adequate treatment is attempted. Currently, there is no single standard of care for the treatment of priapism; the information provided below represents current efforts with respect to the treatment of this complication of SCD.

PSYCHOSOCIAL AND COUNSELING ASPECTS OF PRIAPISM

Beginning in early boyhood, males need to know that priapism is one aspect of SCD and that this is not an event that should embarrass them. One study found that only 7 percent of boys and men with SCD who had not experienced priapism knew that it could be a complication of SCD (1). This information prompted the authors to prepare a brochure explaining priapism, which was distributed to all males and their families. Boys and young men, as well as their families, need to know that they should be prepared to seek medical attention as soon as an episode begins and that if untreated, priapism can result in impotence in the future. The males should know that a full bladder can trigger priapism, and they therefore need to urinate regularly. They also should avoid prolonged sexual activity, which can trigger an episode. If they have had more than one episode, medications can be prescribed that may prevent recurrences.

EVALUATION AND TREATMENT

When evaluating a patient with priapism, the physician or nurse should document the time of onset of the episode as well as the presence of any other inciting factors, such as trauma, infections, or the use of drugs (e.g., cocaine, alcohol, psychotropic agents, sildenafil, testosterone) (4-6). A careful physical examination should reveal a hard penis with a soft glans.

The goal of therapy is to ease pain, make the erection go away, and preserve future erectile function. If treatment is given within 4 to 6 hours, the erection can generally be reduced with medication and conservative therapy. Most of the articles in the literature concern anecdotal reports and few randomized trials are available.

ONSET OF PRIAPISM

Patients should be advised to drink extra fluids, use oral analgesics, and attempt to urinate as soon as priapism begins.

EPISODES LASTING MORE THAN TWO HOURS

Patients should go to the emergency room to receive intravenous hydration and parenteral analgesia. According to one protocol (7), if detumescence does not occur in 1 hour after the patient has arrived in the emergency room, penile aspiration is initiated (procedure should be performed within 4 to 6 hours from onset of priapism). The patient receives conscious sedation and local anesthesia; blood is then aspirated from the corpus cavernosum with a 23-gauge needle followed by irrigation of the corpora with a 1:1,000,000 solution of epinephrine in saline. In a prospective nonrandomized unblinded study, this procedure was successful in producing immediate detumescence in 15 males on 37 of 39 occasions (7). This study was performed in males who were teenagers or younger and has not been validated in an older population.

The concomitant use of automated red cell exchange transfusions to reduce the sickle hemoglobin (Hb S) level to less than 30 percent can also be considered, especially if early intervention with irrigation fails (8). It is unclear if simple transfusion is equivalent to exchange transfusion.

The clinical response to exchange transfusions is variable, and side-effects range from headaches or seizures to obtundation requiring ventilatory support. The association of SCD, priapism, exchange transfusion, and neurological events has been given the name ASPEN syndrome (9). Recurrent priapism is strongly associated with the development of impotence, therefore some physicians transfuse patients as though they were on a stroke protocol (maintenance of Hb S level below 30 percent). These programs should be limited in duration (6 to 12 months), and patients should be assessed often.

If there is recurrence despite aspiration and local instillation of vaso-active drugs, shunting may be considered. In this procedure, known as the Winter procedure, a shunt is created between the glans penis and the distal corpora cavernosa with a Tru-cut biopsy needle; this allows blood from the distended corpora cavernosa to drain into the uninvolved corpus spongiosa (10). A larger shunt can be created if this is not successful.

Additional medications used for reversal of priapism have included α-agonists and β-agonists such as terbutaline (11-13). Clinicians in France and West Africa have used an α-agonist (etilefrine) that can be injected by patients into the cavernous sinus (12-13); however, this agent is not available in the United States. None of these agents has been validated in a well-controlled trial and thus cannot be endorsed at this time.

Complications of priapism and treatment include bleeding from the holes placed in the penis as part of the aspiration or shunting procedures, infections, skin necrosis, damage or strictures of the urethra, fistulas, and impotence. If impotence persists for 12 months, the patient may wish to consider implantation of a semirigid penile prosthesis (14).

PREVENTING FUTURE EPISODES

There are no large clinical studies documenting ways to prevent priapism. Some physicians prescribe 30 mg of oral pseudoephedrine at night as an attempt to prevent further episodes in those who have had priapism and have required aspiration and irrigation (7). Injections of leuprolide, a gonadotropin-releasing hormone analogue that suppresses the hypothalamic-testicular axis and the production of testosterone, also has also been used with some degree of success as prophylaxis against further episodes (15). A small (11 patients) double-blind, placebo-controlled crossover study found that oral stilbestrol in doses of 5 mg daily for 3 to 4 days could abort episodes of priapism and that much smaller doses could prevent recurrence (16). Although hydroxyurea may potentially be of benefit (17), clinical studies to determine its efficacy in preventing priapism have not been performed.

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BONES AND JOINTS

Musculoskeletal manifestations of sickle cell disease (SCD) are common and may lead to severe morbidity. Bone and joint involvement result from three main causes: 1) bone marrow hyperplasia, which causes distortion and growth disturbance, particularly in the skull, vertebrae, and long bones; 2) vaso-occlusive events that lead to infarction of metaphyseal and diaphyseal bone and to osteonecrosis of juxta-articular bone; and 3) hematogenous bacterial infection that results in osteomyelitis and septic arthritis.

BONE MARROW HYPERPLASIA

The chronic hemolytic anemia of SCD results in erythroid hyperplasia. Cellular proliferation in the marrow spaces results in bone deformities, most notably in the skull where trabeculae may be oriented in a radial pattern ("hair on-end"), and an increase in the distance between the inner and outer tables of the frontal bone, which results in "bossing" of the forehead. Growth disturbance in the maxilla may result in protrusion of the incisors and an accentuated over-bite. In the long bones, osteopenia may predispose to pathologic fractures (1,2). Similar changes occur in the vertebral bodies, and resulting compression fractures may lead to flattening and to kyphotic deformity of the spine (3). Acetabular protrusion has been noted in one or both hips of some patients with SCD and is attributed to osteopenia associated with marrow hyperplasia (4,5).

VASO-OCCLUSIVE EVENTS

METAPHYSEAL AND DIAPHYSEAL INFARCTS

Bones and joints are major sites of pain in vaso-occlusive events. It is hypothesized that relative hypoxia in the sinusoids of the marrow spaces predisposes to sickling and to thrombosis. Sudden infarction causes acute symptoms and signs that must be differentiated from those of bacterial infection. Infarction may occur in any bone, but common sites include the spine, pelvis, and long bones. Vertebral infarction may cause collapse of the end plates, resulting in the so-called "codfish" vertebra. The most common sites of involvement in the long bones are the humerus, tibia, and femur (in that order) (6). The distal segment is most often involved.

Local tenderness, warmth and swelling are common, as is impaired motion in the adjacent joints. In contrast to cases of osteomyelitis, fever is usually absent or low-grade, and the white blood cell differential rarely demonstrates a left shift. Aspiration of the affected site yields negative cultures. Radiographs are unremarkable in the acute stage. Once healing and remodeling occur, radiographs demonstrate patchy sclerosis and local thickening of the cortices (1). In metaphyseal and diaphyseal infarcts of the long bones, long term sequelae are minimal. Because it may be difficult to differentiate between acute infarction and acute

osteomyelitis (7), close followup examinations, blood cultures, aspiration of the affected site, and repeated white blood cell counts are appropriate until a diagnosis is firmly established.

DACTYLITIS, OR THE "HAND-FOOT" SYNDROME

Dactylitis, or the "hand-foot" syndrome, is a limited phenomenon that occurs in the hands and feet of infants and young children. One to four extremities may be involved at the same time. The syndrome presents with pain in the metacarpals, metatarsals, and phalanges of the hands and feet. Swelling typically occurs over the dorsum of the hands and feet, extending into the fingers and toes. Radiographs eventually reveal periosteal elevation and a moth-eaten appearance of involved bone (3). Symptoms usually resolve in 1 to 4 weeks, and the condition results in no long-term sequelae (8). The patient should receive analgesia and hydration, and the parents should be given reassurance. Transfusions, antibiotics and other measures are usually not necessary. Although it is rare, infection should be considered if conservative management yields no benefit. At least one study has indicated that an episode of dactylitis within the first two years of life, particularly in association with leukocytosis and severe anemia, may predict severe manifestations of SCD later in life (9).

OSTEONECROSIS

Ischemic necrosis of juxta-articular bone arises from thrombosis of the endarterial vessels and often leads to painful destruction of the adjacent joint. The femoral and humeral heads are most often involved. Osteonecrosis of the femoral head may occur in any of the genetic variants of SCD, but is most prevalent in patients with SCD-SS α-thalassemia (10). The mean age at diagnosis varies according

to genotype; patients with SCD-SS α-thalassemia present at 28 years of age, those with SCD-SS present at age 36, and those with SCD-SC present at age 40. The natural history of symtomatic hip disease in SCD patients who are treated conservatively varies with the patient's age. In skeletally immature patients who are 12 years of age or younger, treatment with analgesics, nonsteroidal anti-inflammatory drugs, and protected weight-bearing usually results in healing and remodeling of the involved capital epiphysis, similar to what is observed in Legg-Calve-Perthes disease (1,11). This approach results in preservation of the joint despite the persistence of deformity such as coxa magna and coxa plana (1,12).

In contrast, conservative management of osteonecrosis usually fails in patients in late adolescence and in adulthood. Progressive flattening and collapse of the femoral head results in painful secondary degenerative arthritis. The use of joint-preserving surgical procedures such as core decompression and osteotomy has been reported anecdotally in sickle cell patients who have precollapse femoral head involvement (13). As yet, there have been no prospective, randomized studies in sickle cell patients to critically assess the safety and efficacy of such procedures.

Hip arthroplasty is reserved for patients with advanced disease who are severely symptomatic. Earlier studies have reported high rates of early and late deep sepsis, mechanical loosening of implants, and high reoperation rates (14-18). In these studies, there was a high rate of postoperative events, averaging 10 percent. In more recent reports, patients have been treated with newer surgical techniques, including the use of cementless prostheses, and perioperative medical management has received greater emphasis (19-21). These studies report lower rates of infection, fewer risky reoperations,

and fewer salvage resection arthroplasties. Despite these encouraging recent reports, most orthopedists continue to reserve prosthetic arthroplasty for those patients in whom all other measures have failed to yield relief.

Osteonecrosis of the humeral head occurs commonly in SCD, especially in patients with femoral head involvement (22). The prevalence of humeral head osteonecrosis on radiographs was 28 percent in one population of patients (23); in another study, 48 percent of adults with SCD-SS were found to have radiographic abnormalities suggestive of healed and remodeled osteonecrotic lesions (24). Treatment of symptomatic humeral head osteonecrosis is similar to that described for femoral head osteonecrosis, but because the forces on the shoulder joint are smaller, morbidity is less pronounced (25).

HEMATOGENOUS INFECTION

OSTEOMYELITIS

Blood-borne bacteria may proliferate in the sinusoids of the marrow spaces where flow is sluggish. Previously infarcted bone may provide a protected environment for bacterial infection, and the likelihood of osteomyelitis may be increased further by a diminished immune response in SCD. The prevalence of osteomyelitis may be rare or as high as 61 percent in sickle cell populations (26,27). The predisposition of sickle cell patients to salmonella osteomyelitis is well known.

As noted earlier, acute osteomyelitis must be differentiated from acute bone infarction. Although acute bone "crisis" is much more common, a high index of suspicion for osteomyelitis is warranted. Local tenderness, warmth, and swelling are present in both. Fever is generally high in acute infection. The white blood cell count is often elevated

in patients with SCD and further elevations may be seen with infarcts and infection. A left shift in the differential is usually present in infection, but not in infarction. Positive blood cultures frequently accompany acute osteomyelitis, and a positive culture from local bone aspiration is diagnostic. Radiographs rarely reveal bone changes early on, and the only abnormality may be evidence of soft tissue swelling. Radionuclide bone scans usually do not differentiate infection from infarction in the acute phase (6), but marrow scans may be helpful (28).

Surgical drainage is the primary treatment once the diagnosis is made. Intravenous therapy with antibiotics, chosen according to the sensitivity of the organism, is carried out for 2 to 6 weeks, depending upon the nature and extent of the infection. Protected weight-bearing and bracing are sometimes required when there is significant bone destruction. Chronic undiagnosed infections may involve bone extensively, resulting in the formation of a so-called "bone within a bone" radiographic appearance, reflecting the presence of a shell of periosteal new bone (involucrum) surrounding a core of dead bone (sequestrum).

SEPTIC ARTHRITIS

Septic arthritis, like osteomyelitis, may result from hematogenous spread of bacteria or, alternatively, from direct spread from a contiguous focus of osteomyelitis. Severe pain, tenderness, joint swelling, local warmth, and marked limitation of motion are characteristic findings.

Septic arthritis must be differentiated from other types of arthropathy including synovial infarction, synovitis associated with adjacent osteonecrosis, and nonspecific synovitis, which is usually self-limited and rarely progresses to chondrolysis (29). The use of radiography and

magnetic resonance imaging (MRI) in diagnosis of symptomatic joints is confined to identifying other causes of arthropathy once infection is ruled out by aspiration. Surgical drainage remains the surest means of completely evacuating exudates and breaking up loculations that may predispose to persistent infection and articular cartilage destruction. Intravenous antibiotics are administered, and short-term joint immobilization is carried out, followed by range-of-motion exercises. Re-aspiration of the joint confirms adequate suppression of the infection.

IMAGING MODALITIES IN BONES AND JOINTS

Plain radiography is useful in defining established changes of infection, infarction, and osteomyelitis. However, it is of little or no use in diagnosing acute infection or infarction. Radiography depicts the bone abnormalities associated with marrow hyperplasia and those later adaptive changes that result both from remodeling and from growth disturbances.

Radionuclide bone imaging is nonspecific and therefore of limited value in differentiating infection from infarction. However, radionuclide marrow imaging has been shown to be useful because it has a high likelihood of depicting diminished uptake in infarction and normal uptake in infection (28).

Ultrasound and MRI have been shown to be useful in the diagnosis of acute conditions. Ultrasound can be used in depicting soft tissue conditions such as abscess, particularly when MRI is not available (30). MRI has been shown to depict the early changes of osteonecrosis (31) and acute bone and joint abnormalities in children (32).

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Between 10 and 20 percent of patients with sickle cell disease (SCD) due to a homozygous hemoglobin S (Hb S) genotype (SCD-SS) develop painful, disfiguring, and indolent leg ulcers. The ulcers usually appear between ages 10 and 50 years and are seen more frequently in males than in females. Leg ulcers are rare in individuals with SCD-SC, SCD-S β^+-thalassemia, and patients under 10 years of age, but occur in other hemolytic anemias, such as thalassemia major. In the United States, SCD is the main hemoglobinopathy that causes leg ulcers.

PATHOLOGIC MECHANISMS

The etiology of leg ulcers is unclear. In sickle cell anemia, poorly deformable red cells may cause hypoxia and infarction of distal ankle skin, which can be ameliorated by increased fetal hemoglobin (1). Trauma, infection, severe anemia, and warmer temperatures also may predispose to ulcer formation. Decreased blood flow after the ulcer has healed often results in recurrence.

CLINICAL FINDINGS

Sickle cell ulcers usually begin as small, elevated, crusting sores on the lower third of the leg, over the medial or lateral malleolus of the ankle. Occasionally, ulcers are seen over the tibia 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 loss of subcutaneous fat and hair follicles. These ulcers can be very painful and often are accompanied by reactive cellulitis and regional (inguinal) adenitis.

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 performed to rule out osteomyelitis, which is rare, even though periosteal thickening is common.

TREATMENT

The number of well controlled trials for treatment of leg ulcers is small, the number of patients in most of them is too low, and there have been almost no confirmatory studies. Methods considered to be effective in more common conditions (burns, venous stasis, and diabetic ulcers) have been used, but evidence of efficacy is often absent. In most cases, the patient's history has been used as his control in a condition notorious for unexplained remissions and relapses. Thus, most evidence is relatively weak.

There have been many proposed treatments, including topical honey or topical granulocyte macrophage-colony stimulating factor (GM-CSF), zinc oxide impregnated dressings (Unna boots), various types of natural dressings (such as lyophilized pig skin), synthetic matrices (2)

that foster healing, full-thickness skin flaps attached with microsurgical techniques, parenteral erythropoietin, and intravenous antithrombin III concentrate. Localized infection is an invariant feature (3), and proposed approaches range from acetic acid wet-to-dry dressings to gentle surgical debridement to systemic antibiotics. Anemia is, of course, a problem; most therapeutic regimens involve transfusion to raise the patient's hemoglobin concentration, and some more aggressive programs attempt to dilute sickle cells below some arbitrary limit, as in treatment and prevention of stroke.

There are no published trials of various types of conventional therapy, no reports that assess the efficacy of transfusion, and no reports that compare skin grafting with conventional therapy aside from comparisons of pretreatment and posttreatment courses in individual patients. Particularly when evaluating surgical regimens, it is important to remember that ulcers heal with bed rest alone, and that relatively prolonged bed rest is often part of postgrafting regimens.

Any treatment for a chronic condition that causes many patients to be economically disadvantaged must be practical and cost-effective. Complete bed rest for weeks may be effective, but it is not practical; moderately expensive dressings used for an outpatient might be cost-effective, but inpatient therapy probably is not (4). Issues of cost and practicality are not considered in the following review of several controlled trials, but they underlie any choice of treatment.

Most of the controlled trials were carried out by Serjeant and coworkers in Jamaica (5), where the frequency of ankle ulcers is very high and their etiology is complex. In the first trial, 29 patients received either zinc sulfate or placebo for 6 months in addition to wound

care; 13 cases in the zinc group improved, compared to 8 in the placebo group. No statistical analysis of the difference was reported. Later, topical antibiotic spray was compared to sodium chloride solution in 28 patients (6); 6 of the control patients were taking oral zinc sulfate. For ulcers of the same initial size, those treated with the topical antibiotic were 66 percent smaller (p<0.05) after 8 weeks. A later trial compared Solcoseryl, Duoderm, and conventional therapy (7); patients did not tolerate Duoderm, and results with Solcoseryl were not significantly different from conventional therapy.

Perhaps the most useful but frustrating controlled trial of treatment for ankle ulcers was that of Wethers and coworkers (2). Fifty-five patients with chronic nonhealing ulcers were randomized to treatment with or without a gel composed of an arginine-glycine-aspartate (RGD) peptide (a binding site for integrins on cell surfaces) and sodium hyaluronate for cell attachment. Healing was accelerated in patients treated with the RGD peptide matrix (p=0.0085), and the gel was as effective in ulcers of long duration as it was in those of shorter duration. Although the study appears to have been well designed, the manufacturer of the RGD matrix for clinical use is defunct, and the compound is no longer available.

SUMMARY

Studies to prove the efficacy of treatment of leg ulcers are difficult to perform. One reason is that healing depends on blood circulation, and the cumulative time of bed rest and leg elevation is not easily monitored. In addition, the variable extent of wound debridement is difficult to quantify, and a short period of dependency could erase any gains made in the previous period. Thus, no treatments have been proven to work well or consistently.

Stated differently, the "strength of evidence" that any available treatment except bed rest and wound cleansing is really effective is not good, a conclusion similar to that of a recently published comprehensive review (3).

Since the one apparently effective compound is unavailable, practice is empirical, rather than based on firm evidence. Outpatient treatment is cheaper than hospitalization and can be achieved with intermittent clinic visits for supervision. Some patients will be unable to follow medical advice if they cannot stay off their feet because of employment or domestic duties, afford to buy dressings, or follow instructions on how to change dressings. In such cases, considerable ingenuity on the part of the physician or nurse may be needed. The caregiver can provide encouragement and understanding, which can help the patient accept the long duration of treatment.

RECOMMENDATIONS

Ankle ulcers are painful, and the patient should be given moderately potent analgesics such as oxycodone. Bed rest and elevation of the leg to reduce edema are useful, though not always practical. Wet-to-dry dressings, even if applied only 2 or 3 times a day, can provide gentle debridement; cooperation of patients increases when they are permitted to dampen the dressing slightly before removal, since it is a painful process. Oral zinc sulfate (200 mg 3 times a day) probably does no harm if it does not cause nausea, and may be worth using.

Ankle ulcers are always colonized with pathogenic bacteria, usually *Pseudomonas aeruginosa, Staphylococcus aureus,* and/or *Streptococcus* species (8), and sometimes the ulcers are acutely infected. The infection also can be systemic. In the colonized patient, topical antiseptics (dressings soaked with dilute acetic acid, silver sulfadiazine cream, etc.) may be

helpful, but topical antibiotics invite growth of treatment-resistant strains and should be avoided. In acutely infected patients, vigorous systemic antibiotic therapy is indicated. Periosteal thickening is usually present beneath the ulcer, but osteomyelitis is unusual.

After pain and swelling have subsided, the use of Unna boots can be helpful. Patients can be taught to change the dressing themselves, and must be instructed to remove it promptly if swelling recurs. Patients need to know before a boot is first applied that a shoe may no longer fit when the boot is in place, and a loose sneaker or sandal may fit more easily. If there is much exudate, the boot may need to be changed 2 or 3 times a week; as ulcers improve, weekly changes are sufficient. The ulcer size should be measured at every clinic visit; seeing the dimensions shrink can provide encouragement to the patient.

Some ulcers will not heal. Rigorous studies have not been done to assess the utility of transfusions for treating leg ulcers (see chapter 25, Transfusion, Iron Overload, and Chelation), but the ulcers seem to correlate with degree of anemia, which suggests transfusions may help. They should be considered for recalcitrant or recurrent skin ulcers if conservative therapy fails. If transfusions are used, they probably should be continued for 3 to 6 months. There is no evidence that a specified posttransfusion hemoglobin concentration or percentage of sickle cells is better than another, but a hemoglobin concentration above 10 g/dL with Hb S levels less than 50 percent can be achieved.

More complete bed rest, systemic antibiotics, transfusions, and skin grafts sometimes help. If split thickness or pinch grafts are to be used, preoperative preparation of the ulcer bed is probably quite important. Quantitative bacterial cultures of biopsies of the bed and margin

are advocated by some (9) but not all (10) surgeons as a guide to the time for surgery. Microsurgical attachment of myocutaneous flaps may sometimes succeed when all else fails (11), but this rather heroic procedure is not always successful (12).

Because leg ulcers are less common in patients with high fetal hemoglobin (Hb F) levels, it would seem logical to try to raise Hb F concentrations. Intravenous arginine butyrate infusions have been reported to cause rapid healing of ankle ulcers (13). Hydroxyurea is not a good choice because it appears to cause leg ulcers in patients with myeloproliferative disease (14).

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SPECIAL TOPICS

CONTRACEPTION AND PREGNANCY

In a large multicenter observational study (1), the most common complication during pregnancy for women with sickle cell disease (SCD) was hypertension (table 1). A high percentage of the pregnancies resulted in preterm deliveries and infants that were small for gestational age. Pain episodes were not increased during pregnancy, and of the pregnancies carried to 28 weeks gestation, 99 percent resulted in live deliveries. This study demonstrated that pregnancy is not contraindicated for women with SCD. However, prenatal care for women with SCD should be managed by a multidisciplinary team that includes an obstetrician, nutritionist, primary care physician, and hematologist. The team must decide who will be responsible for each aspect of the patient's care. Close monitoring, combined with prompt diagnosis and aggressive treatment of complications during the prenatal and neonatal period by a multidisciplinary team, will contribute to better outcomes.

CONTRACEPTION

Oral contraceptives, contraceptive agents administered intramuscularly, and barrier methods are all acceptable choices for women with SCD. Few studies have evaluated oral contraceptives in this population; however, there is no evidence of adverse effects (2). Intrauterine devices are not optimal, since they may be associated with uterine bleeding and infection, regardless of the presence of SCD.

IMPACT OF HYDROXYUREA ON PREGNANCY

Women and men who are taking hydroxyurea should use contraceptive methods and discontinue the drug if they plan to conceive a child, since hydroxyurea has been shown to be teratogenic in animal models. If conception accidentally occurs when either partner is taking hydroxurea, the couple should be told that there is a paucity of information on which to determine the effect of hydroxyurea on the fetus. However, in the 14 or 15 cases in which hydroxyurea was taken throughout pregnancy, no fetal malformations occurred (3,4).

MANAGEMENT OF PREGNANCY

PRENATAL CARE

The prenatal assessment visit serves to provide counseling and outline continued care for the duration of the pregnancy. The primary focus is to identify maternal risks for low birth weight, preterm delivery, and genetic risks for fetal abnormalities. At this time, the physician reviews and discusses the behavior and social patterns that place the patient at risk for sexually transmitted diseases, illicit drug use, alcohol and tobacco use, and physical abuse.

A history of previous cesarean section and uterine curettage should be obtained at prenatal evaluation because of the correlation of the occurrence of placenta previa in patients with

Table 1. Complications of Pregnancy in Women With Sickle Cell Disease

Maternal	Incidence (%)	Fetal	Incidence (%)
Preeclampsia	14	Miscarriages	6
Eclampsia	1	Stillbirth	1
Pyelonephritis	<1	Small for gestational age (<10th percentile)	21
Placenta previa	1	Premature (<37 weeks at birth)	27
Rupture of membranes	6		
Premature labor	9		
Acute anemic event (decrease in hemoglobin levels by 30 percent of baseline)	3		
Maternal mortality	0.45		

Data are based on a study of 445 pregnancies in 297 women (predominantly in women with SCD-SS) recorded between 1979 and 1986 at 19 centers participating in the Cooperative Study of Sickle Cell Disease (1).

previous uterine surgery. Adequate nutritional assessment and the avoidance of precipitating factors that cause painful events should be outlined with this initial visit as well as all subsequent visits. The patient's prepregnant weight, height, and optimal weight gain in pregnancy will be recorded. Physical exam should also include determination of splenic size.

Initial comprehensive laboratory studies include complete blood count with a reticulocyte index, hemoglobin electrophoresis, serum iron, total iron binding capacity (TIBC), ferritin levels, liver function tests, urine examination and culture, electrolytes, blood urea nitrogen (BUN), creatinine, blood type and group, red cell antibody screen, and measurement of antibodies to hepatitis A, B, and C, as well as to HIV. Rubella antibody titre,

tuberculin skin test, Pap smear, cervical smear, and gonococcus culture and screening for other sexually transmitted diseases, and bacterial vaginosis also should be performed.

Hepatitis vaccine should be administered when appropriate for patients who are negative for hepatitis B. If asymptomatic bacteriuria is found, the patient should receive antibiotics in order to prevent urinary tract infection and pyelonephritis.

Return visits are recommended 2 weeks after the initial visit. Low-risk patients are scheduled for monthly visits until the second trimester, when they should be seen every two weeks; in the third trimester, they should be seen every week.

RECOGNITION OF PREGNANCY-INDUCED HYPERTENSION AND DIABETES

For women with SCD, preeclampsia and severe anemia have been identified as risk factors for delivering infants that are small for their gestational age (1). In the study summarized in table 1, the incidence of preeclampsia (defined as blood pressure >140/90 mmHg, proteinuria of >300 mg/2 hours, and pathologic edema), and eclampsia (seizures in addition to features of preeclampsia) in pregnant women with SCD was 15 percent (1). The mechanisms for the high incidence of hypertension in this patient population remain unclear; multiple factors such as placental ischemia and endothelial injury have been implicated. Other known risk factors for preeclampsia, even in women without SCD, are nulliparity, a history of renal disease or hypertension, multiple gestation, and diabetes.

Pregnant women with SCD should be observed closely if blood pressure rises above 125/75 mmHg, if the systolic blood pressure increases by 30 mmHg, or diastolic blood pressure increases by 15 mmHg, in association with edema and proteinuria in the second trimester. Preeclampsia, which requires frequent monitoring, can be treated with bed rest at home or in the hospital, if needed. If preeclampsia is worsening, delivery of the fetus may be required if the gestational age is greater than 32 weeks. Expedited delivery is recommended for uncontrolled hypertension.

INDICATIONS FOR BLOOD TRANSFUSION DURING PREGNANCY

The role of prophylactic transfusions in pregnancy is controversial. One randomized trial (5) and a retrospective study (6) concluded that routine prophylactic transfusions from the onset of pregnancy do not alter the outcome for the fetus or mother. However, one additional study, also retrospective in nature, concluded that prophylactic transfusions, if initiated at about 20 weeks, may be beneficial (7). A realistic approach may be to avoid routine prophylactic transfusions for uncomplicated pregnancies but to consider initiation of transfusions for women who have complications such as preeclampsia, severe anemia, or increasing frequency of pain episodes (8). Women who have had previous pregnancy losses or who have multiple gestations may benefit from the early use of transfusions to maintain a hemoglobin level above 9 g/dL (8).

Women should receive leukoreduced packed red blood cells that have been phenotyped for major and minor antigens. If the primary goal of transfusions is to reduce the percent of sickle hemoglobin (Hb S), and the hemoglobin level is high, one approach is to remove 500 mL of whole blood and transfuse 2 units of packed red blood cells. This procedure can be done manually or by automated methods to obtain a posttransfusion hemoglobin level ranging between 10 and 11 g/dL and to reduce the percentage of Hb S to between 30 and 40 percent of the total hemoglobin concentration.

SICKLE CELL-RELATED EVENTS DURING PREGNANCY

The clinical problems of SCD, such as new-onset seizures, hepatopathy, acute anemia, and painful episodes should be evaluated and managed for pregnant women in the same fashion as for women who are not pregnant.

The frequency of previous acute vaso-occlusive painful events is usually predictive of the events during pregnancy, although some patients may experience an increased frequency of pain episodes (9,10). Patients with a chronic pain syndrome should be identified; they may benefit from an individualized care plan.

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 should not be injected because it can cause sickling. Rh-negative women should receive Rh immunoglobulin after therapeutic or spontaneous abortion. Newer methods for medical termination of pregnancy are available, but their use has not been extensively described in women with SCD (11).

LABOR, DELIVERY, POSTPARTUM CARE, AND COUNSELING

Cardiac function can be compromised because of chronic hypoxemia and anemia. During labor, fetal monitoring is useful to detect fetal distress, which can trigger prompt delivery by cesarean section. If surgery appears imminent, simple transfusion or rapid exchange transfusion can be of benefit depending on the baseline hemoglobin levels. The postpartum patient may require transfusion if she has undergone extensive blood loss during parturition. Venous thromboembolism can also complicate the postpartum course. To prevent this, early ambulation is initiated.

Counseling is also an important component of postpartum care. Results of the screen for SCD in the infant should be made available to the mother and father, as well as to the pediatrician. Contraception and plans for future pregnancies also should be discussed. If a woman is considering no future pregnancies, she can receive preliminary counseling about tubal ligation for permanent birth control.

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ANESTHESIA AND SURGERY

Patients with sickle cell disease (SCD) may require surgery for complications such as aseptic necrosis or cholelithiasis, or for conditions unrelated to SCD. Multiple authors (1-5) have reported that the risk of morbidity and mortality in these patients is greater than in the general population because of anemia, the propensity for red blood cells to sickle and obstruct the microvasculature, the presence of chronic organ damage in some patients, the risks of hypoxia, and the effects of asplenia. Risks have been said to be greater for patients with SCD-SS or SCD-S β^o-thalassemia. Various suggestions for risk reduction have been made, including correction of anemia by simple or exchange transfusion, attention to hydration and oxygenation, postoperative respiratory care, and selection of less aggressive or extensive surgical procedures. It also has been suggested (6) that patients undergoing minor surgical procedures (excluding tonsillectomy and adenoidectomy) may not require transfusion if special attention is paid to oxygenation and acid-base status. Several recent reports of larger series have begun to quantify the magnitude of risks and provide some guidance for management (7-9).

SUMMARY OF THE STATE OF THE ART

Two reports published in 1995 and one in 1998 have added greatly to our understanding of the magnitude of risk and the management of surgery in SCD patients. Vichinsky et al. (7) reported on a multicenter randomized

study of aggressive (exchange) versus simple transfusion in SCD-SS patients, with both treatments performed to achieve a hemoglobin level of 10 g/dL. The authors found no difference in complication rates. The protocol specified a minimum of "8 hours of preoperative hydration, with intraoperative monitoring of temperature, blood pressure, electrocardiographic features, and oxygenation." Postoperative care included the administration of oxygen, intravenous hydration, monitoring with pulse oximetry, and respiratory therapy. These guidelines are now generally accepted as the standard of perioperative care.

Koshy et al. (8), reporting for the Cooperative Study of Sickle Cell Disease on 717 patients with SCD-SS, SCD-SC, SCD-S β^o-thalassemia, and SCD-S β^+-thalassemia, reported no deaths in patients under the age of 14 (42 percent of the population was under the age of 20). This nonrandomized study also showed that postoperative complications increased with age, with an "estimated odds ratio 1.3 times increased risk of postoperative complications per ten years of age, p<0.0001." Furthermore, SCD-related complications were more common in those who received regional compared with general anesthesia and preoperative transfusion resulted in a lower complication rate for those undergoing low-risk surgery (p=0.006).

Preoperative transfusions were beneficial for SCD-SC patients undergoing any risk level of surgery (p=0.009) (8). Neumayer et al. (9), reporting on SCD-SC patients in the same

study reported by Vichinsky (7), observed that "in patients undergoing intraabdominal procedures, the incidence of sickle-related complications was significantly higher in those SC patients not transfused prior to their surgery." In this study, 60 percent of the patients transfused underwent exchange transfusion.

Anecdotal data from all three studies suggests that tonsillectomy and adenoidectomy should *not* be considered low-risk procedures. The latter procedure, which is often associated with blood loss, fluid loss, and inability to take oral hydration, appears to be more serious for persons with sickle cell syndromes than for other individuals.

Outcome data from the three studies are summarized in table 1. While some variation exists in the incidence of acute chest syndrome and the infection/fever complications, possibly due to differences in definitions, the incidences of sickle cell pain, cerebrovascular accident, and death are similar, lending validity to the management principles described in the three studies.

RECOMMENDATIONS

- Make sure the operating and anesthesia teams are aware of the diagnosis of a sickle cell syndrome and the need for special attention.

- In patients with SCD-SS and SCD-S β^o-thalassemia, simple transfusion to achieve a hemoglobin of 10 g/dL should be performed before all but the lowest-risk procedures.

- For patients with SCD-SC, exchange transfusions may be needed to avoid complications associated with hyperviscosity.

- Alloimmunization should be minimized by giving antigen-matched blood (matched K, C, E, S, Fy, and Jk antigens).

- Patients with SCD, regardless of genotype, should all receive careful attention, with preoperative monitoring of intake and output, hematocrit, peripheral perfusion, and oxygenation status.

- Intraoperative monitoring of blood pressure, cardiac rhythm and rate, and oxygenation should be conducted for all surgical procedures.

- Postoperative care should include attention to hydration, oxygen administration with careful monitoring, and respiratory therapy.

Table 1. Outcome of Surgery in Patients With Sickle Cell Disease Who Received Perioperative Transfusions

Ref.	Yrs	Hb	Ages	No. of Surgical Procedures	Postoperative Complications (%)				
					ACS	Pain	CVA /Renal	Infection /Fever	Death
Koshy et al. (8)	1978-88	SS*	0-59	650	2.2	3.5	0.15	4.3	0.46
Vichinsky et al. (7)	1988-93	SS*	All	604	10.0	5.0	>2.0	6.0	>0.5
Koshy et al. (8)	1978-88	SC	0-62	81	0.0	2.5	0.0	20.0	0.0
Neumayr et al. (9)	1988-93	SC**	All	92	5.0	3.0	not reported	9.0	2.0**

ACS = acute chest syndrome.
* Data include SCD-S β⁰-thalassemia patients.
** Data include at least one SCD-S β⁺-thalassemia patient.

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ONLINE RESOURCE

Sickle Cell Information Center
(anesthesia and transfusion guidelines)
http://www.emory.edu/PEDS/SICKLE

Transfusion, Iron Overload, and Chelation

Used correctly, transfusion can prevent organ damage and save the lives of sickle cell disease (SCD) patients. Used unwisely, transfusion therapy can result in serious complications. The choice of several methods, such as simple transfusion, partial exchange transfusion, and erythrocytapheresis, depends on the specific requirements of the patient. Except in severe anemia, exchange transfusion offers many benefits and should be made available.

Once a decision is made to transfuse, the type of red cells to be given is specified and goals are set for the final posttransfusion hematocrit and percent sickle hemoglobin (Hb S) desired. In general, phenotypically matched, sickle-negative, leukodepleted packed cells are the blood product of choice, and a posttransfusion hematocrit of 36 percent or less is recommended, since a higher value theoretically causes hyperviscosity, which is dangerous to sickle cell patients. A comprehensive transfusion protocol should include accurate records of the patient's red cell phenotype, alloimmunization history, number of units received, serial Hb S percentages, and results of monitoring for infectious diseases and iron overload.

Transfusions are used to raise the oxygen-carrying capacity of blood and decrease the proportion of sickle red cells. Clinically, they will improve microvascular perfusion of tissues. Transfusions usually fall into two categories: episodic, acute transfusions to stabilize or reverse complications, and long-term, prophylactic transfusions to prevent future complications (1).

EPISODIC TRANSFUSIONS

Management of Severe Anemia

In severely anemic patients, simple transfusions should be used without removal of any blood from the patient. The most common causes of acute anemia are acute splenic sequestration (described in chapter 18, Splenic Sequestration) and transient red cell aplasia (see chapter 12, Transient Red Cell Aplasia). A third form of acute anemia, called hyperhemolysis, is associated with infection (see chapter 11, Infection), acute chest syndrome (see chapter 16, Acute Chest Syndrome and Other Pulmonary Complications), and particularly, malaria.

In patients hospitalized for pain episodes and other events, the Hb concentration may fall well below the admission value. If the patient is stable and the reticulocyte count high (>20 percent or >250,000/μL), transfusions can be deferred. In general, patients should be transfused if there is sufficient physiological derangement to result in heart failure, dyspnea, hypotension, or marked fatigue. Such symptoms tend to occur during an acute illness when hemoglobin falls under 5 g/dL. Patients with an acute event associated with falling hemoglobin can die suddenly from cardiovascular collapse and should be monitored closely.

Management of Sudden Severe Illness

Leading causes of death in SCD, such as acute chest syndrome (see chapter 16, Acute Chest Syndrome and Other Pulmonary Complications), stroke (see chapter 13, Stroke and Central Nervous System Disease), sepsis, and acute multiorgan failure often are accompanied by a falling hemoglobin level. Transfusions can improve tissue oxygenation and perfusion and are indicated in seriously ill patients to potentially limit areas of vaso-occlusion. Controlled clinical trials to evaluate transfusions in most life-threatening situations have not been performed, so medical practice is based mainly on clinical observations. However, limited studies indicate that aggressive transfusion regimens may improve recovery of organ function and survival in instances of acute multiorgan failure (2). In general, the goal is to maintain a Hb S level below 30 percent.

Preparation for General Anesthesia

A multi-institution study recently compared perioperative complications among sickle cell patients undergoing major surgery (e.g., cholecystectomy) (3). Patients were randomized to an aggressive transfusion arm (to decrease Hb S to below 30 percent) or a conservative transfusion arm (with Hb S at about 60 percent, total Hb corrected to 10 g/dL). The groups also were compared to patients who did not receive any perioperative transfusions. Complications occurred in all groups but were substantially more frequent in nontransfused patients. There was no difference between the conservatively and aggressively transfused patients with respect to perioperative complications; however, the latter group had a higher alloimmunization rate.

Thus, there is good evidence to recommend that sickle cell patients be transfused before major surgery. Anemia should be corrected to a Hb concentration of about 10 g/dL and the Hb S level should be approximately 60 percent or lower. Although practice guidelines have not been established, it is generally acceptable to omit preoperative transfusions in healthy SCD-SC patients and stable SCD-SS patients who undergo minor surgery (see chapter 24, Anesthesia and Surgery).

CHRONIC TRANSFUSION THERAPY

Chronic transfusion therapy is indicated when avoidance of potentially serious medical complications justifies the risks of alloimmunization, infection, and iron overload (4,5). The goal is to maintain the Hb S level between 30 and 50 percent, depending on the specific problem. Transfusions are usually repeated every 3 or 4 weeks. While simple transfusions may be used, red cell pheresis or exchange transfusions may help to decrease the risk of iron overload (6).

Chronic transfusion therapy may be warranted for the primary prevention of stroke and prevention of stroke recurrence (see chapter 13, Stroke and Central Nervous System Disease). It may also be used to treat chronic debilitating pain (see chapter 10, Pain), pulmonary hypertension (see chapter 16, Acute Chest Syndrome and Other Pulmonary Complications), and anemia associated with chronic renal failure (see chapter 19, Renal Abnormalities in Sickle Cell Disease). In patients with chronic heart failure, transfusion therapy may assist cardiac treatments and improve quality of life (see chapter 15, Cardiovascular Manifestations).

CONTROVERSIAL INDICATIONS

Transfusions are sometimes suggested for conditions in which efficacy is unproven, but may be considered under extreme circumstances as described in chapter 20, Priapism; chapter 22, Leg Ulcers; and chapter 23, Contraception and Pregnancy.

Preparation for Infusion of Contrast Media

In the past, sickle cell patients were at increased risk of sickling when given hypertonic contrast media for radiographic examinations. To eliminate this problem, transfusion was recommended beforehand, but new agents, such as gadolinium and nonionic contrast media, now lower the risk.

Management of "Silent" Cerebral Infarct and/or Neurocognitive Damage

Subclinical infarcts detected by magnetic resonance technology often are associated with neurocognitive defects. Patients who have subclinical infarcts appear to have a higher incidence of strokes, but the efficacy of preventive transfusion has not been evaluated in these patients. Until rigorous controlled trials are conducted, routine chronic transfusion therapy cannot be recommended.

INAPPROPRIATE INDICATIONS AND CONTRAINDICATIONS

The following conditions alone do not justify transfusion:

- Chronic steady-state anemia. Most patients with SCD are relatively asymptomatic from their anemia and do not require transfusions to improve oxygen delivery.

- Uncomplicated acute pain episodes.

- Infections.

- Minor surgery that does not require prolonged general anesthesia (e.g., myringotomy).

- Aseptic necrosis of the hip or shoulder (except when surgery is required).

- Uncomplicated pregnancies.

TYPES OF BLOOD PRODUCTS TO BE USED

Standard bank blood is appropriate for patients with SCD. 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 for small infants) helps in acute situations requiring immediate correction of oxygen-carrying capacity. All blood should be screened for the absence of sickle hemoglobin; a solubility test is adequate. This eliminates blood with sickle cell trait, which can 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 the phenotyping should be maintained in the blood bank to optimize matching, 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 determination of the proportion of Hb S by quantitative hemoglobin electrophoresis as well as the hemoglobin concentration or hematocrit.

There are several causes of the high prevalence of alloimmunization in SCD, and phenotypic incompatibility between the donor

and recipient is a major factor (7). Limited matching for E, C, and Kell antigens is usually performed, unless patients have antibodies (8).

Prestorage leukodepletion of red cells is standard practice to reduce febrile reactions, platelet refractoriness, infections, and cytokine-induced complications (9). Washed red cells should be reserved for patients who had allergic reactions after prior transfusions. Irradiated blood should be considered in patients likely to be candidates for bone marrow transplantation, but relatives should not be used as blood donors for children who are such candidates. The use of autologous blood transfusions in SCD should be avoided. Red cell substitutes are experimental and generally not indicated.

TRANSFUSION METHODS

Simple transfusions can be used for acute anemia or hypovolemia. Packed red cells are preferred, except when marked volume expansion is needed.

CHRONIC SIMPLE TRANSFUSION

Once a sufficient level of transfused normal cells [60-70 percent normal hemoglobin (Hb A)] is achieved, simple transfusions every 2 to 4 weeks may maintain this proportion of normal cells for years. The level of Hb A must be monitored regularly by quantitative hemoglobin electrophoresis. Significant variation in transfusion requirements for each patient is common, but the pretransfusion hematocrit should be between 25 and 30 percent. The posttransfusion hematocrit should be 36 percent or less to prevent hyperviscosity, especially for initial transfusions.

EXCHANGE TRANSFUSION

Exchange transfusion is used to remove sickle cells and replace them with normal red cells without increasing whole blood viscosity or

chronic iron burden (6,10). The volume of blood needed can be calculated from the patient's weight, initial hematocrit, target hematocrit, and desired percentage of Hb A. An adult exchange usually takes about 6 to 8 units, and children require about 50 to 60 mL/kg of blood. Whole blood or packed cells reconstituted to hematocrits of 30 to 40 percent are used to conserve units, but exchanges will take longer than with packed cells alone. Blood can be removed from the adult patient in 500 mL aliquots, followed by infusion of 500 mL of reconstituted blood, repeated for 6 to 8 cycles, or another schedule can be used. The following is an example:

Step 1. Bleed one unit (500 mL) of blood from 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.

For children, smaller, more precise volumes should be calculated and used in order not to remove or transfuse too much blood at one time. In some patients, whole blood can be taken from one arm at the same time that donor cells are transfused into the other. For adults, this procedure can be performed in 500 mL units, whereas in children, smaller amounts are practical. Automated erythrocytapheresis is safe and is being used fairly often because it prevents iron overload, despite concerns about increased red cell utilization, venous access, and increased cost. When exchange transfusion is performed, the final hemoglobin value should not exceed 10 to 12 g/dL to avoid hyperviscosity, and the percentage of Hb A should meet the goals of therapy.

TRANSFUSION COMPLICATIONS

Transfusion complications, such as alloimmunization, hyperviscosity, and relative hypertension, may be higher for sickle cell patients than for members of the general population (1). Transfusions have precipitated pain episodes, strokes, and acute pulmonary insufficiency.

VOLUME OVERLOAD

This condition occurs when a large volume of blood is transfused too quickly. Congestive heart failure and pulmonary edema tend to occur in patients who have cardiac dysfunction or poor cardiac reserve. Administration of intravenous furosemide, partial removal of red cell supernatant fluid before transfusion, and a slow transfusion rate can help to prevent this problem.

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 (7). This condition causes difficulty in obtaining compatible blood and results in a high incidence of delayed hemolytic transfusion reactions (12,13). Reactions occur 5 to 20 days after transfusion and are due to antibodies undetectable at the time of compatibility testing. More than 30 percent of antibodies disappear with time, but recipients can mount anamnestic responses to further stimulation by transfusion. Delayed hemolytic transfusion reactions may cause severe anemia, painful events, and even death.

ACUTE HEMOLYTIC TRANSFUSION REACTIONS

The causes of acute hemolytic transfusion reactions in sickle cell patients are not different from those in other patients. Major hemolytic reactions occur mainly with major blood group (ABO) mismatches and must be treated aggressively to maintain blood pressure and glomerular filtration. Most reactions can be prevented by avoiding clerical and sample identification errors in the cross-matching and transfer of units from the donor site to the patient. Minor hemolytic reactions occur when the amount of antibody in the patient's serum is limiting and causes the transfused blood to disappear over several days, followed by hyperbilirubinemia. The hematocrit decreases, but no further treatment is needed unless the hematocrit falls greatly.

Any of these reactions, particularly the delayed variety, can initiate a pain episode in patients with SCD. In all cases, a patient's blood should be examined very carefully by immunohematologists to document the antibody or antibodies responsible for the reaction. The patient must be told of the complication and be given a card describing the antibodies found.

Alloimmunization and hemolytic transfusion reactions can be reduced by:

- 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 that cause a subsequent delayed reaction.

■ Diminishing the opportunities for alloimmunization because of a mismatch in the antigens of donors and patients (14). This may be accomplished by:

– Typing the patient before transfusion (if this has not already been done) for Rh and Kell blood group antigens to avoid transfusion of cells with these antigens (particularly E, C, and Kell) if the patient lacks them.

– More extensive antigen matching in patients who are already alloimmunized.

– Increasing the numbers of African-American blood donors because of the similarity of their blood cell antigenic phenotypes. Family members and community groups can assist in accomplishing this objective.

Patients alloimmunized to one red cell antigen are more likely to become alloimmunized to others. Transfusions should be given only for clearcut indications, and care should be taken in the selection of units of blood. Patients should be counseled to advise any new physician of their history of alloimmunization and to carry a card or identification bracelet that lists their red blood cell phenotype and any identified antibodies.

AUTOIMMUNE ANEMIA FOLLOWING ALLOSENSITIZATION

In a highly alloimmunized patient, a syndrome of autoimmune hemolytic anemia may occur. 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. Autoimmune anemia occurs because the recipient produces antibodies against self-antigens, which may persist up to 2 to 3 months before disappearing. Further transfusion is complicated by the autoimmune

antibody and requires special blood bank tests to find the least incompatible units for transfusion. Although transfusion may be necessary in some patients, an alternative course may be to avoid transfusion and to administer corticosteroids, large doses of erythropoietin, and possibly intravenous immune globulin.

ALLOANTIBODIES TO WHITE CELLS, PLATELETS, AND SERUM PROTEINS

Patients who are transfused may become alloimmunized to antigens present on leukocytes or platelets but absent from red blood cells. Such antibodies may cause febrile reactions that can be prevented by the removal of leukocytes by filtration or washing. These antibodies, and those for serum proteins, can cause allergic reactions that can be prevented by prophylaxis with an antihistamine (Benadryl®), leukodepletion, or removal of plasma.

INFECTION

Hepatitis and other transfusion-transmitted viral diseases in blood occur with the same frequency in sickle cell patients as in other patients who receive transfusions. The consequences may be more severe with concurrent SCD, however. Patients who have received multiple transfusions should be monitored serially for hepatitis C and other infections (15,16). Parvovirus occurs in 1 in every 40,000 units, and is associated with acute anemic events and multiple sickle cell complications.

Transfusion-induced bacterial infections are uncommon. Repeatedly transfused hemoglobinopathy patients are particularly vulnerable to *Yersinia* entercolitica and bacteremia from poor skin cleansing before phlebotomy. All patients who develop fever after transfusion need to be assessed immediately for potential bacterial infection.

IRON OVERLOAD AND CHELATION

Iron overload in sickle cell patients is often undetected or not treated. In contrast to thalassemia patients, most patients are iron overloaded because of intermittent transfusions throughout their lives. There is no evidence that SCD patients are spared the fatal consequences of iron overload. Therefore, a comprehensive program to monitor and treat iron overload is necessary.

There is no simple test to determine iron overload. Measurement of serial serum ferritins may help but can be unreliable because ferritin is an acute phase reactant and values are altered by liver disease, inflammation, and vitamin C stores. Liver biopsy is the most accurate test for iron overload and can be performed safely by an experienced physician. The sample should be of adequate size and sent to a reference lab familiar with liver iron quantitation. Some programs recommend liver biopsies at the start of chelation and every 2 years thereafter. As a noninvasive method, the superconducting quantum interference device (SQUID) is acceptable for quantitating liver iron (10). There is progress with MRI and CT, but their clinical use is unproven. The best indication to begin chelation therapy is a rise in liver iron stores to 7 mg/g dry weight. Alternatively, cumulative transfusions of 120 cc of pure red cells per kilogram of body weight can be used (5). Serum ferritin levels above 1,000 ng/mL in the steady state are helpful, but the risk of under- and over-treatment occurs. All iron-overloaded patients should be followed at comprehensive sickle cell centers that can monitor organ toxicity and provide ongoing education and support.

Exchange transfusions and chelation therapy are the only two accepted methods to manage transfusion-related iron overload. Phlebotomy will remove iron in abnormal red cells, which are replaced by normal red cells. The initial dose of the chelator deferoxamine (Desferal™) is 25 mg/kg per day, over 8 hours subcutaneously (17); dose and duration of infusion can be increased, depending on patient age and iron load. Supplementation with vitamin C, 100 to 200 mg per day, may help to increase excretion, especially in those who are vitamin C deficient. New methods of delivery, including twice-daily subcutaneous injections and intravenous home parenteral access, are being studied. Deferoxamine is generally safe, but has been associated with ototoxicity, eye toxicity, allergic reactions, growth failure, unusual infections, and pulmonary hypersensitivity; therefore, patients should be monitored annually for growth and eye toxicity. Iron chelation always should be discontinued during an acute infection. Other chelators are experimental and are not recommended at this time.

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Enhanced concentrations of hemoglobin F (Hb F) can inhibit sickle hemoglobin (Hb S) polymerization and red cell sickling and improve the clinical course of sickle cell disease (SCD). In populations such as Bedouin Arabs from the Saudi peninsula and certain tribes from central India, patients homozygous for SCD have elevated amounts of Hb F and fairly mild clinical manifestations. In a cooperative study of the natural history of patients with sickle cell anemia in the United States, the frequency of pain episodes correlated inversely with the Hb F concentration. Based on these epidemiologic studies and understanding the biophysics of Hb S polymerization, a search was launched for pharmacologic agents that could reverse the switch from γ- to β-globin chain synthesis in erythroid precursors. The first "hemoglobin switching" agent was the nucleoside analog 5-azacytidine (1), which was followed by butyrate derivatives as compounds which increase Hb F gene expression. Other drugs, such as hydroxyurea and erythropoietin, alter maturation of erythroid precursors and promote Hb F production indirectly.

The small amount of Hb F in adults is found in rare erythrocytes called F-cells. Rapid erythropoiesis induces F-cell production, probably due to commitment of early progenitors that contain factors that favor γ-globin expression and faster maturation and release into the circulation. Many cytotoxic drugs induce Hb F expression without gene hypomethylation, and hydroxyurea is one example that supports erythroid regeneration as a mechanism of Hb F induction.

Hydroxyurea is a ribonucleotide reductase inhibitor, which blocks ribonucleoside conversion to deoxyribonucleotides and prevents DNA synthesis. In anemic primates, hydroxyurea increased Hb F levels, and in early studies in two patients with sickle cell anemia, hydroxyurea increased F-reticulocytes and Hb F concentrations. An important pilot trial defined effective dosages, found increased Hb F in most, but not all, compliant patients, and revealed little short-term toxicity.

5-AZACYTIDINE

5-azacytidine is an antineoplastic agent that inhibits methylation of cytosines in DNA. Studies on gene regulation had suggested that methylation resulted in repression of transcription and that hypomethylation was associated with active gene expression. It was observed that the inactive gene becomes methylated during the developmental switch from γ-globin to β-globin production in erythroid cells. The administration of 5-azacytidine caused a marked increase in Hb F in baboons. These results prompted limited clinical trials, which demonstrated significant but less dramatic induction of Hb F in patients with SCD. The antiproliferative activity of this drug may have led to the proposed use of hydroxyurea.

BUTYRATE

Butyrates appear to modulate globin-gene expression by direct binding to transcriptionally active elements, and by inhibition of histone deacetylase, histone hyperacetylation, and changes in chromatin structure. In sickle cell anemia, early trials of butyrate given by continuous infusion over 2 or 3 weeks were inconclusive, but newer studies with pulse butyrate treatment are encouraging. When arginine butyrate was given once or twice monthly, 11 of 15 sickle cell patients responded with a mean rise in Hb F from 7 percent to 21 percent, a level maintained in some people for 1 to 2 years. The studies also suggested butyrate and hydroxyurea are synergistic without cross-resistance; pretreatment with hydroxyurea may select a population of erythroid precursors with active γ-globin genes and make them responsive to butyrate. Butyrate does not seem to be cytotoxic, but its use is experimental.

HYDROXYUREA IN SICKLE CELL ANEMIA

CLINICAL AND HEMATOLOGIC EFFECTS

A pivotal multicenter efficacy trial of hydroxyurea in 299 adults with sickle cell anemia showed that hydroxyurea reduced by nearly half the frequency of hospitalization and the incidence of pain, acute chest syndrome, and blood transfusions (2). In good responders, hemolysis and leukocyte counts fell, and hemoglobin concentrations increased. Hb F increased from a baseline of 5 percent to about 9 percent after 2 years of treatment; Hb F increased to a mean of 18 percent in the top 25 percent of Hb F responders and to 9 percent in the next highest 25 percent, but changed little in the lower half of Hb F responders. These results may not be typical of all patients because the patients in the study had a mean age of about 30 years, had severe disease, and were treated to the brink of myelotoxicity. After treatment, some individuals had improved physical capacity and aerobic cardiovascular fitness. A modest improvement in general perceptions of health and social function and recall of pain was found. Moreover, hydroxyurea was cost-effective and clinically beneficial.

Studies of hydroxyurea in infants, children, and adolescents lag behind adult studies in the appraisal of clinical efficacy. Most patients reported were adolescents or teenagers treated in unblinded pilot studies, although 25 patients with a median age of 9 years were treated in a single-blinded crossover study with drug or placebo. In all trials, Hb F increased from about 5 percent before treatment to about 16 percent after 6 months to a year of treatment.

A trial of 84 children with a mean age of 10 years gave results similar to those in adults (3). Sixty-eight patients reached the maximally tolerated dose, and 52 patients completed a year of treatment. About 20 percent of enrolled patients withdrew from the study, predominantly because of lack of compliance. Baseline Hb F of 6.8 percent increased to 19.8 percent (range, 3.2-32.4 percent). Mean cell volume (MCV) and hemoglobin concentration increased, and the leukocyte count fell. These changes, apparent after 6 months of treatment, were sustained at 24 months. The increment in Hb F was variable, but unlike the adults, the young patients with the highest baseline Hb F concentration had the highest Hb F levels with treatment, and the drop in leukocyte count did not predict the rise in Hb F.

Twenty-nine infants, with a median age of 14 months, were treated with hydroxyurea at a dose of 20 mg/kg for 2 years, escalating to 30 mg/kg thereafter. After 2 years, all parents elected to continue treatment, and 19 children completed a median treatment period of 148 weeks. Changes in hemoglobin concentration, MCV, Hb F, and leukocyte count were compared with the changes observed in a historical control group. Hemoglobin increased from 8.5 to 8.9 g/dL (predicted, 8.2 g/dL), MCV increased from 82 to 93 fL (predicted, 88 fL), and Hb F fell from 21.3 to 19.6 percent (predicted, 12.3 percent). Functional asplenia was found in 24 percent of patients before treatment and in 47 percent after treatment (predicted, 80 percent). Nine patients were dropped from the study because of poor compliance or parental refusal to continue; one child died of splenic sequestration. One patient had a transient ischemic attack, one had a mild stroke, eight had episodes of acute chest syndrome, two had splenic sequestration, and three had episodes of sepsis. Growth was normal. Despite moderate levels of Hb F, acute complications of sickle cell anemia still occurred in these very young patients. Perhaps functional asplenia is delayed by treatment, but risks of splenic sequestration and other complications may persist.

MORTALITY AND MORBIDITY

The best data on the complications of hydroxyurea treatment and its effect on morbidity and mortality come from the followup of patients in the Multicenter Study of Hydroxyurea in Sickle Cell Disease. After 8 years of followup the data strongly suggest that treatment of moderately-to-severely affected adults with sickle cell anemia with hydroxyurea is associated with reduced mortality. Twelve strokes have occured, 9 in patients with more than 1 year of hydroxyurea treatment, 2 in patients with

less than 1 year of drug exposure, and 1 in a patient who never received hydroxyurea. New adverse effects have not been found. Pulmonary disease was the most common cause of death.

We do not know whether hydroxyurea will prevent or reverse organ damage (4). After 1 year of treatment, splenic function in a group of children who averaged 12 years of age did not change. Of 10 patients with sickle cell anemia who received hydroxyurea for 21 months and had an increase in Hb F from 8 to 17 percent, only 1 recovered splenic function. In another prospective study, some patients had partial return of splenic function, possibly related to Hb F levels. Splenic regeneration was reported in 2 adults with sickle cell anemia who had Hb F levels of about 30 percent after hydroxyurea treatment.

Hydroxyurea does not appear to prevent the cerebrovascular complications of SCD. However, in children ages 5 to 15 years without a history of overt CVA and with more than three painful episodes yearly, hydroxyurea maintained cognitive performance comparable to sibling controls. Performance was found to deteriorate in untreated patients.

ADVERSE EVENTS

Long-term effects of hydroxyurea are still poorly defined. The multicenter trial had power to detect only 100-fold increases in the incidence of leukemia or cancer. Hydroxyurea has been given to 64 children with cyanotic congenital heart disease for a mean duration of more than 5 years without any reports of malignancies. In myeloproliferative disorders, however, the drug may have helped to transform premalignant conditions into acute leukemia in about 10 percent of patients. There are at least three patients with SCD treated with hydroxyurea who developed

leukemia, two after 6 and 8 years of treatment. Cellular changes that may precede neoplastic transformation, such as increases in chromosome breakage, recombination, and mutations, have not been reported in hydroxyurea-treated sickle cell patients.

Adverse effects on growth and development have not been reported. Whether continuous drug exposure at a very young age will be especially hazardous or beneficial is not known. Contraception should be practiced by both women and men on hydroxyurea, and the uncertain outcome of an unplanned pregnancy should be discussed frankly. Pregnancy resulting in infants without malformaions has been reported in at least 15 women receiving hydroxyurea; most mothers had myeloproliferative disorders, but 6 had sickle cell anemia.

TREATMENT PROTOCOL

Table 1 summarizes the treatment protocol and points that should be considered when using hydroxyurea as a treatment for patients with sickle cell anemia.

COMBINATIONS OF HB F INDUCERS

When both hydroxyurea and erythropoietin were given to patients with sickle cell anemia, an increment in Hb F concentration beyond that seen with hydroxyurea alone occurred (5). It is conceivable that combination therapy with butyrate and hydroxyurea and/or erythropoietin may provide additive effects on Hb F production, although verification of this conclusion must await the results of appropriate clinical trials.

CONCLUSION

Hydroxyurea is a valuable adjunct in the treatment of severe SCD, although its clinical effectiveness for individuals with SCD has not yet been reported. Meanwhile, it must be used carefully with full appreciation of its toxicity and possible long-term adverse effects. Many questions about its use and effects remain unanswered. Hydroxyurea is not the final solution in the pharmacologic therapy of SCD, but it is a promising start.

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Table 1. Hydroxyurea in Sickle Cell Anemia

Indications for Treatment

Adults, adolescents, or children (after consultation with parents and expert pediatricians) with sickle cell anemia or SCD-S β^o-thalassemia and frequent pain episodes, history of acute chest syndrome, other severe vaso-occlusive events, or severe symptomatic anemia. Initial high levels of Hb F (e.g., >10 percent) do not preclude favorable responses to therapy.

Baseline Evaluation

Blood counts, red cell indices, percent Hb F, serum chemistries, pregnancy test, willingness to follow treatment recommendations, nonparticipation in a chronic transfusion program.

Initiation of Treatment

Hydroxyurea, 10-15 mg/kg/day in a single daily dose for 6-8 weeks; CBC every 2 weeks; percent Hb F every 6-8 weeks; serum chemistries every 2-4 weeks.

Continuation of Treatment

If no major toxicity, escalate dose every 6-8 weeks until the desired endpoint is reached.

Treatment Endpoints

Less pain, increase in Hb F to 15-20 percent, increased hemoglobin level if severely anemic, improved well-being, acceptable myelotoxicity.

Failure of Hb F (or MCV) To Increase

Consider biological inability to respond to treatment or poor compliance with treatment. Increase dose very cautiously to a maximum dose of 35 mg/kg/day. In the absence of transfusion support or concurrent illness suppressing erythropoiesis, a trial period of 6-12 months is probably adequate.

Cautions

Special caution should be taken in patients with compromised renal or hepatic function. Contraception should be practiced by both men and women since hydroxyurea is a teratogen and its effects during pregnancy are unknown. After a stable, nontoxic dose of hydroxyurea is reached, blood counts may be done at 4-8 week intervals. Granulocytes should be ≥ 2,500/μL, platelets ≥ 95,000/μL.

Hematopoietic Cell Transplantation

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Hematopoietic cell transplantation (HCT) has curative potential for a broad spectrum of genetic disorders, including sickle cell disease (SCD) (1). The goal is to eliminate the sickle erythrocyte and its cellular progenitors and replace them with donor hematopoietic pluripotent stem cells that give rise to erythrocytes that express no sickle hemoglobin (Hb S), thereby reducing Hb S levels to those associated with the trait condition. The possibility of preventing serious complications from SCD, which can cause extensive morbidity and early death, is balanced by the risk of severe adverse events after transplantation. The first case reports of successful outcomes after transplantation have been extended by several multicenter investigations (table 1). To date, nearly all transplants have utilized HLA-identical sibling donors, which has limited the number of eligible sickle cell patients. Thus, there are no randomized, controlled studies that support this therapeutic option for SCD. However, with the development of new therapies that prevent and treat graft-versus-host and host-versus-graft reactions, it is likely that transplantation will take on added importance for selected patients with SCD.

INDICATIONS FOR HCT

The first published reports of HCT for SCD involved patients who had other hematological or genetic disorders that were the primary indication for transplantation (2,3). From this initial experience it was learned that engraftment of donor cells was associated with elimi-nation of SCD. In the decade and longer that followed, there was considerable discussion about who should be considered and when they should be referred for transplantation (13-15). The first limited series of patients who underwent transplantation because they had SCD comprised a group of families from Africa living at the time in Belgium (4). Based in part on the very good outcome experienced by these initial patients, several multicenter phase II studies for children with symptomatic SCD were conducted in North America and Europe (7,9). It was reasoned that children might have a superior outcome compared to adult patients because of children's lower risk of transplant-related complications such as graft-versus-host disease (GvHD) and because of a presumed lower burden of sickle-related organ damage. The inclusion and exclusion criteria for enrollment adapted from one multicenter study (7) are summarized in table 2.

RESULTS OF HCT FROM HLA-IDENTICAL SIBLING DONORS

Approximately 150 patients have undergone HCT from HLA-identical siblings worldwide (9,10,16,17). The combined results of three studies have demonstrated that transplant-related mortality is about 5 percent, and that more than 90 percent of patients survive. Approximately 85 percent survive free from SCD after transplantation with a period of followup that extends to 11 years, but about 10 percent of patients experience recurrence

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Table 1. Supporting Evidence for HCT for Sickle Cell Disease

Study Description	References
Case reports	Johnson et al. (2), Milpied et al. (3)
Patient series	Vermylen et al. (4,5)
Proposal of HCT trial	Thomas (6)
Collaborative HCT trial	Walters et al. (7)
Collaborative HCT trial in Europe	Vermylen and Cornu (8)
Long-term impact of HCT	Vermylen et al. (9), Walters et al. (10)
UCB report	Brichard et al. (11), Minero et al. (12)

Table 2. Eligibility Criteria for HCT for Sickle Cell Disease

Inclusions

Patients < 16 years of age with sickle cell anemia (SCD-SS or SCD-S β^o-thalassemia)

One or more of the following complications:
Stroke or central nervous system (CNS) event lasting longer than 24 hours
Impaired neuropsychologic function and abnormal cerebral magnetic resonance imaging (MRI) scan
Recurrent acute chest syndrome or Stage I or II sickle lung disease
Recurrent vaso-occlusive painful episodes
Sickle nephropathy [glomular filtration rate (GFR) 30-50 percent of predicted normal]
Osteonecrosis of multiple joints

Exclusions

Patients >16 years of age

HLA-non-identical donor

One or more of the following conditions:
Lansky performance score <70 percent
Acute hepatitis or biopsy evidence of cirrhosis
Renal impairment (GFR <30 percent predicted normal)
Stage III or IV sickle lung disease

of SCD. Neurologic complications, such as seizures, occurred frequently after transplantation, leading to the development of preventive measures (18-20).

Among patients who had stable engraftment of donor cells, there were no subsequent sickle cell-related clinical events, and there was stabilization of preexisting sickle cell-related organ damage (9,10,21). There was also recovery of splenic function (22). Some patients developed mixed donor-host hematopoietic chimerism after transplantation that was stable (23). Of interest, these patients also had no symptoms from SCD.

About 5 percent of patients developed Grade III acute or extensive chronic GvHD; the others had no graft-vs-host response or mild GvHD. Primary and secondary amenorrhea were common among females after transplantation and it is likely that most patients will be infertile (9,10). The risk of secondary cancers after HCT remains uncertain, but it is estimated to be less than 5 percent (24). Linear growth was normal or accelerated after transplantation in the majority of patients (9,10).

ALTERNATIVE SOURCES OF STEM CELLS

Umbilical cord blood (UCB) and hematopoietic cells from volunteer donors represent alternative sources of hematopoietic stem cells that might increase the number of donors for SCD patients. Successful hematological reconstitution has been observed after UCB transplantation for SCD (11). However, there are no published reports of transplantation to treat SCD using UCB from volunteer, unrelated donors.

There is evidence to suggest that the incidence of GvHD is lower after UCB transplantation than after bone marrow transplantation (25).

This advantage is balanced by somewhat lengthier periods for hematopoietic engraftment and perhaps a higher rate of graft rejection, especially when nonidentical donors are used and when cell doses are low (26). Strategies for transplantation from unrelated volunteer stem cell donors will need to overcome histocompatibility barriers associated with higher rates of GvHD and graft rejection. There are no established protocols for transplantation from alternative sources of stem cells; however, pilot clinical investigations are being designed.

HCT FOR ADULTS

There is very limited information about the outcome after HCT among adult patients. However, they might have a higher risk of dying due, in part, to the increased frequency of GvHD in adults (27). Compared to younger patients with β-thalassemia major, adult patients had an increased risk of dying after HLA-identical bone marrow transplantation (28), but ethnic factors might have contributed to the risk. The use of nonmyeloablative preparation before HCT may lower the risk of complications (29). The intent is to establish stable donor-host hematopoietic chimerism after transplantation, which might provide a significant clinical benefit. If successful, the nonmyeloablative approach might improve the safety profile of HCT for older individuals who have advanced organ damage from SCD. Several investigations have been initiated to test this hypothesis.

SUMMARY OF THE STATE OF THE ART

Currently, HCT is the only therapy for SCD that has curative potential. The results of transplantation are best when performed in children with a sibling donor who is

HLA-identical. While there appears to be a considerable benefit to those who survive with stable engraftment of donor cells, there are also significant health risks associated with this treatment. Thus, careful discussions with families by health care professionals experienced in the care of patients with SCD and with HCT should be conducted to establish informed consent for this procedure.

HCT is reserved for those patients who have experienced significant complications caused by SCD, such as stroke and recurrent episodes of acute chest syndrome or pain. In the future, identification of clinical or genetic markers that reliably predict an adverse outcome may permit the application of HCT before significant clinical complications occur. Efforts are ongoing to expand donor availability by overcoming graft-versus-host and host-versus-graft reactions and to diminish the toxicity of HCT by using nonmyeloablative preparations to establish stable donor-host hematopoietic chimerism. If successful, these efforts could expand the role of HCT in treating patients with SCD.

RECOMMENDATIONS

Children with SCD who experience significant, noninfectious complications caused by vaso-occlusion should be considered for HCT, and if full siblings are available, HLA typing should be performed. Families should be counseled about the collection of UCB from prospective siblings (30). For severely affected children who have HLA-identical sibling donors, families should be informed about the benefits, risks, and treatment alternatives such as HCT. There are no comparative studies that would permit clinicians to recommend one intervention, such as chronic red blood cell transfusions or hydroxyurea treatment, over another.

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GENETIC MODULATION OF PHENOTYPE BY EPISTATIC GENES

A unique mutation is responsible for sickle hemoglobin (Hb S), but sickle cell disease (SCD) is clinically pleiotropic and can be considered a multigene disease. Polymerization of Hb S can injure red cells and cause a cascade of pleiotropic effects that determines the clinical picture (1,2). Some patients are always sick, and others infrequently ill. What is the basis of this variability? An environmental effect on the course of SCD is dramatically apparent in tropical Africa. Provided there is good access to medical care, survival to adulthood and a decent quality of life is possible. Still, SCD in Africa remains a childhood disease since premature death, often from malaria, is common.

Most of the pleiotropic effects result from the activity of other genes—which also may be polymorphic—that differ among patients. These epistatic (or modifier) genes may account for the interindividual variation that characterizes SCD. Another source of genetic variation in SCD derives from the multicentric origin of the Hb S gene. Because it arose more than once, the gene had the opportunity to interact with different (polymorphic) linked genes, particularly the two γ-globin genes that ameliorate SCD through expression of fetal hemoglobin (Hb F).

The two best understood genetic factors that influence the clinical expression of the Hb S mutation are 1) those linked to the synthesis of fetal hemoglobin (Hb F) (gender, β-globin

gene cluster haplotypes, chromosome 6 locus), and 2) the copresence of α-thalassemia. These known factors explain only a small fraction of the diversity of sickle cell anemia, however. Other epistatic genes must exist, and based on our knowledge of the pathophysiology of SCD, candidate genes have been suggested (3).

FETAL HEMOGLOBIN MODULATION OF SICKLE CELL ANEMIA

THE β-GLOBIN GENE CLUSTER AND GLOBIN GENE SWITCHING

Hb F levels in sickle cell anemia vary over two orders of magnitude. Initially only very high levels of Hb F were considered capable of influencing the phenotype of sickle cell anemia (4,5), but any increment in Hb F appears to be clinically and perhaps therapeutically important (6).

Hemoglobin gene switching is the process of sequential globin gene activation and inactivation. It involves complex interactions of stage-specific transcription factors, chromosomal gene order, gene proximity to the β-globin locus control region (LCR), cis-acting sequences that positively and negatively regulate transcription, and erythroid-specific and ubiquitous trans-acting factors (7). By interacting with promoters of the β-like globin genes, the LCR plays a critical role in gene expression; polymorphisms in some of their sequences

are considered vital elements of γ-globin gene regulation in sickle cell anemia. Nevertheless, the full picture of this process is not known.

β-GLOBIN GENE CLUSTER HAPLOTYPES—EFFECTS ON HB F LEVELS, HEMATOLOGY, AND CLINICAL COURSE

Four β-globin gene cluster haplotypes are linked with the independent emergence of four $β^s$ genes in Africa. The three most common are the Senegal haplotype in Atlantic West Africa, the Benin haplotype in central West Africa, and the Bantu haplotype in all Bantu-speaking African societies (equatorial and southern Africa) (8). The Arab-Indian haplotype is found in the Middle East and India.

Although β-globin gene cluster haplotypes are convenient markers for genetic regulators of γ-globin gene expression, most polymorphic endonuclease restriction sites used to assign a haplotype have no known role in the differential transcription and temporal regulation of these genes. An exception is the Xmn I site that is 5' to the $^Gγ$-globin gene in the Senegal and Arab-India haplotypes (9-11). This site is strongly associated with high expression of the $^Gγ$-globin gene compared with the $^Aγ$-globin gene. In adults and neonates lacking the Hb S gene, this polymorphism is associated with small but significant increases in the synthesis of Hb F and $^Gγ$-globin chains. More recently, twin studies have implicated it as a major factor in defining the level of Hb F expression (see below).

Considerable variation also exists among patients who have Senegal or Arab-India haplotypes, although they tend to have higher Hb F levels than those who have Benin and Bantu haplotypes. A patient's sex, in addition to his or her haplotype, also may modulate Hb F production (12).

Most of the detailed and larger studies of the clinical and hematological effects of haplotype in sickle cell anemia have been in regions where the Hb S gene arrived by gene flow. After many years of miscegenation, patients are commonly haplotype heterozygotes, complicating the interpretation of potential associations of haplotype with phenotype. Therefore, reports of the clinical and hematological effects of haplotype in sickle cell anemia should be interpreted carefully. Often too few patients are studied, the patients' ages differ among series, clinical events are not sharply defined, age-dependence of their phenotype is not considered, and the distinction between haplotype homozygotes and heterozygotes is not clearly drawn.

In longitudinal studies from the United States, the Senegal haplotype was associated with fewer hospitalizations and painful episodes. The relationship between the Senegal haplotype and reduced frequency of acute chest syndrome was of marginal significance. The Bantu haplotype was associated with the highest incidence of organ damage and was strongly associated with renal failure in a study that used robust statistics and a large number of patients (13-15). Most work suggests that the Arab-India haplotype is associated with milder disease, although vaso-occlusive events are not rare. In India the almost fixed (approaching 100 percent) haplotype frequency of α-thalassemia adds considerably to the benign picture of SCD (16).

Hᴃ F Modulation Unlinked to the β-Globin Gene Cluster: Gender Effects and Role of Chromosomal Sites Other than Chromosome 11

Hb F is restricted to a subset of red cells, called F-cells, whose numbers are determined genetically, although exactly how is unknown. There are likely to be genetic determinants of Hb F level not linked to the β-globin gene cluster that influence Hb F concentrations in sickle cell anemia. The Hb F level in sickle cell anemia is set by the number of F-cells, the amount of Hb F per F-cell, and the differential survival of F-cells and non-F-cells (17). Family studies have shown that this considerable variation is inherited, but the number of genes involved and the mode of inheritance are largely unknown. Identical-twin studies showed that the heritability of F-cell numbers is very high and that gender, age, and the -158 T-to-C mutation 5' to the $^G\gamma$-globin gene account for close to 40 percent of the variance.

Other trans-acting autosomal loci, termed quantitative trait loci (QTL), also appear to influence the amounts of Hb F in F-cells (18). Two such QTLs have been mapped by linkage analysis, one to chromosome 6q23 (19). Genetic studies originally localized this QTL to a region approximately 4 Mb or 11 cM between markers D6S408 and D6S292. More recently, novel polymorphic markers plus existing markers have further localized the QTL within an interval of 0.8-1 Mb between D6S270 and D61626 (20). Further analysis suggests an additional QTL on chromosome 8q (20). It is clear that further QTLs affecting the expression of Hb F will be found in the future.

The second possible F-cell production locus (FCP) is X-chromosome-linked and has been localized between DXS143 and DXS16 within the short arm of chromosome X (Xp22.3-22.20) (21). The FCP locus may account,

in part, for the higher Hb F levels in females compared to males, an observation found in both the normal population and in patients with sickle cell anemia. More recent multi-point linkage analysis with seven polymorphic markers has further localized the FCP within 2 to 3 cM between DXS452 and APXL, with a maximum LOD score of 3.3.

α-THALASSEMIA

α-thalassemia in individuals of African descent is usually a result of the deletion of one or two α-globin genes. Missing even two of the normal complement of four α-globin genes is not clinically significant in normal individuals. About a third of African Americans carry an α-globin gene deletion, and this prevalence is even higher in some populations, so α-thalassemia and sickle cell anemia frequently coexist (22).

The hematological and clinical consequences of interactions between these two disorders have been studied intensively. The presence of α-thalassemia with sickle cell anemia is associated with less hemolysis, higher hemoglobin concentration, lower mean corpuscular volume (MCV), and lower reticulocyte count, when compared to individuals with normal α-globin gene numbers. α-thalassemia does not appear to modify the effect of haplotype on Hb F levels in sickle cell anemia despite an early report to the contrary, but it can further ameliorate the disease. Therefore, it is unlikely that any clinical benefit α-thalassemia confers upon sickle cell anemia is mediated through its effect on Hb F level.

α-thalassemia has a strong effect upon the phenotype of sickle cell anemia by reducing the erythrocyte Hb S concentration. Hb S polymerization depends on hemoglobin concentration, so concurrent α-thalassemia should diminish the polymerization potential

of sickle hemoglobin in sickle cell anemia. When these conditions coexist, there is less hemolysis, and anemia is less severe. Clinically, the copresence of α-thalassemia and sickle cell anemia is a paradoxical outcome. Vaso-occlusive events appear undiminished in SCD with α-thalassemia, and in some studies, even appeared to be increased. Fewer dense and poorly deformable cells as a result of α-thalassemia raise the packed cell volume (PCV), and because the cells contain Hb S, blood viscosity is increased. Raising the number of sickle cells, as occurs with α-thalassemia, might promote vaso-occlusion since younger sickle cells are more adherent (a critical phenomenon in painful episodes) (23). On the other hand, a higher PCV may have beneficial effects in some organs, so that skin ulcers of the leg, childhood stroke, and retinal vascular disease may be less common in carriers of α-thalassemia and sickle cell anemia. The effect of α-thalassemia on cellular, hematological, and clinical aspects of sickle cell anemia have been reviewed recently (22).

Some but not all studies suggest that the combination of α-thalassemia and sickle cell anemia may increase survival (24). A recent followup study of the age-dependency of α-globin gene frequency is compatible with the following interpretation: as medical care improves, the advantage of α-thalassemia on survival disappears, a phenomenon that could explain the contradiction in the available data.

INTERACTIONS OF β-GLOBIN GENE HAPLOTYPE AND α-THALASSEMIA

Some studies have examined how α-thalassemia interacts with different β-globin gene haplotypes to modify the hematological and clinical

picture of sickle cell anemia (12,25,26). Most often there is little interaction besides minor reductions in MCV and reticulocyte count and increases in PCV. One exception was a study of two western Indian populations with high Hb F levels in which the coexistence of α-thalassemia was associated with milder disease (16).

HEMOGLOBIN A₂

Hb A_2, the tetramer of α- and δ-globin chains, impairs the polymerization of Hb S to the same extent as the γ-globin chain of Hb F. When Hb A_2 and Hb F levels are high, the combination of these two hemoglobins may potentially modulate SCD and cause a mild phenotype.

ERYTHROCYTE G-6-PD DEFICIENCY

Glucose-6-phosphate dehydrogenase (G-6-PD) deficiency is common in sickle cell anemia. In a study of 800 males over age 2 with SCD, G-6-PD deficiency was not associated with differential survival, reduced hemoglobin levels, increased hemolysis, more pain episodes, septic episodes, or a higher incidence of acute anemia episodes (27,28). It now seems clear that there is little, if any, modulation of the phenotype of sickle cell anemia by coincident G-6-PD deficiency, particularly in males where the expression of this X-linked trait is most apparent.

INHERITED DISORDERS OF THROMBOSIS

Some have postulated that thrombosis and hemostasis could play roles in the pathophysiology of SCD. Coincidental mutations that favor blood coagulation or thrombosis could influence disease phenotype (29), particularly the occurance of SCD-related stroke.

Recent studies attempting to relate the presence of mutations in genes for factor V, platelet glycoprotein IIIa, and 5,10 methylenetetrahydrofolate reductase (MTHFR) to the pathogenesis of specific complications of SCD have had disparate results. In one report, a C→T mutation at position 677 of the MTHFR gene that is associated with enzyme thermolability and a putative hypercoagulabile state due to hyperhomocystenemia was found in 36 percent of 45 adults with SCD and osteonecrosis but in only 13 percent of 62 SCD patients without osteonecrosis—a significant difference (30). However, smaller studies reported that the same mutation was not associated with vascular complications of SCD, including osteonecrosis and stroke (31-33). Studies of the platelet glycoprotein IIIa gene have not found a link between a C→T mutation at position 1565 (which is associated with premature coronary artery disease) and osteonecrosis. Factor V Leiden, a common cause of thrombosis in Caucasians, is rare in African Americans; limited studies have not linked this mutation to stroke in SCD.

High levels of antiphospholipid antibodies were found in patients with SCD and individuals with sickle cell trait (33), but no relationship to disease complications was noted. Clearly, further work is needed to resolve the role of genetic risk factors for thrombosis, many of which have been examined only in pilot studies or reported in abstract.

The potential genetic contribution to stroke risk in SCD can be estimated from clinical stroke risk observed in sibling pairs with SCD. In 210 pairs among 2,353 patients with SCD, 167 pairs had no history of stroke, 33 pairs had a stroke in one sib, and 10 pairs had history of stroke in both sibs (34).

A case-control candidate gene association study involving patients with SCD and ischemic stroke suggested an association with ischemic stroke and angiotensinogen repeat alleles 3 and 4 ($p<0.05$) and plasminogen activator inhibitor (PAI-I) 4/4 alleles ($p<0.01$) (35).

GENETIC PREDICTION OF PHENOTYPE IN SICKLE CELL ANEMIA

As with other diseases, the sickle cell diseases are variable in their presentation due to differences in the genetic makeup and the environmental exposure of the affected individual. Although the exact genes have yet to be identified, extensive advances in understanding the pathophysiology of SCD suggest that genes involved in numerous mechanisms might have epistatic potential in SCD. These include:

1. Genes involved in the adhesion of young sickle cells to the vascular endothelium (e.g., genes related to integrin and other adhesive molecules).

2. Genes that affect the density of sickle cells, including transporter genes such as those involved in Ca-dependent K efflux, K:Cl cotransport, Na/H exchange.

3. Genes involved in thrombosis, particularly in sickle cell stroke.

4. Genes involved in angiogenesis, particularly in sickle cell retinopathy.

5. Genes involved in hemopoiesis, particularly marrow response to anemia.

6. Genes involved in vascular reactivity, particularly genes involved in the effects of endothelin and NO.

Eventually, researchers may develop a reliable method of predicting severity of disease. This would allow better grounds for decisions pertaining to termination of pregnancy in the context of prenatal diagnosis and the establishment of risk/benefit ratios when contemplating bone marrow transplantation, chemotherapeutic manipulation of Hb F level, and even gene therapy, all of which have potentially serious complications.

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Many of the observational studies and therapeutic trials that have contributed to the understanding of syndromes associated with sickle cell disease (SCD) have been federally funded. This chapter highlights some of the research funded by the National Heart, Lung, and Blood Institute (NHLBI) that has led to a clearer understanding of the clinical course of SCD and appropriate interventions to reduce morbidity. Specifically, it describes a large multi-year observational study, known as the Cooperative Study of Sickle Cell Disease (CSSCD), as well as several interventional clinical trials. The discussions are not inclusive but rather highlight successful efforts in the study and treatment of the disorder.

COOPERATIVE STUDY OF SICKLE CELL DISEASE—EPIDEMIOLOGY COHORT STUDY

The CSSCD, started in 1979 after years of planning, was a large multi-institutional prospective study of the clinical course of SCD (1). The recruitment goals included individuals with major phenotypes of sickle cell disease (SCD-SS, SCD-SC, and SCD-S $\beta^{+/o}$ thalassemia); 3,200 subjects, with an SCD-SS sample of 2100; individuals from different geographic areas (including rural areas); and inclusion of individuals at all stages of life (including newborns and pregnant women). The CSSCD completed its third phase in 1999; it followed the newborn cohort of 694 children who were identified through screening programs. The CSSCD has identified the

risk factors responsible for the increased morbidity and early mortality of SCD (table 1). Below are just a few of the findings from the CSSCD studies, which have resulted in 39 papers (1-39).

LABORATORY REFERENCE VALUES

The CSSCD described reference values and hematologic changes from birth to 5 years of age (2). Anemia was observed by 10 weeks of age in infants with SCD-SS and was associated with a rising reticulocyte count, exceeding 12 percent by 5 years of age. The fetal hemoglobin (Hb F) concentration in SCD-SS infants declined more gradually than did that of infants with SCD-SC. Infants with SCD-SS had evidence of abnormal splenic function after 6 months of age, and by 1 year, 28 percent of SCD-SS infants had evidence of poor splenic function. By the time the children had reached 3 years of age, this percentage had increased to 78 percent for SCD-SS children and 32 percent for those with SCD-SC. Children with SCD-SC were mildly affected, and displayed mild anemia (10.5 g/dL), slightly elevated mean reticulocyte counts (3 percent), and fetal hemoglobin levels (3 percent) during early childhood.

PAINFUL EVENTS

One of the major accomplishments of the CSSCD was an analysis of the epidemiology of pain episodes (3). The natural history of 3,578 individuals ranging in age from newborns to 66 years was evaluated. The average pain rate was 0.8 episode per person-year in

Table 1. Risk Factors for Major Organ Dysfunction or Event (Results from the CSSCD)

Condition (Reference)	Associated Risk Factors*
Painful events (3)	↓ Hb F ↑ hematocrit (Hct)
Premature death (3)	↑ painful event rate
Leg ulcers (4)	↓ Hb F concentration
Splenic sequestration (12)	↓ Hb F concentration
Osteonecrosis, femoral head (13)	↑ painful episodes ↑ Hct ↓ mean cell volume (MCV)
Infarctive stroke (17)	acute chest syndrome prior transient ischemic attack (TIA) ↓ Hb concentration ↑ systolic blood pressure
Hemorrhagic stroke (17)	↓ Hb concentration ↑ white blood cell count (WBC)
Silent infarct (18)	↓ Hb concentration ↑ WBC ↓ splenic function Senegal globin haplotype
Acute chest syndrome (19)	↓ Hb concentration ↓ Hb F concentraion ↑ steady state WBC
Sickle cardiomyopathy (21)	↓ Hb concentration ↑ age

* ↓=decreased, ↑=increased

sickle cell anemia (SCD-SS), 1.0 episode per person-year in SCD-S β^o-thalassemia, and 0.4 episode per person-year in SCD-SC β^+-thalassemia and SCD-SS β^+-thalassemia.

The rates varied widely within each of these four groups. Thirty-nine percent of persons with sickle cell anemia had no episodes of pain, and 1 percent had more than six episodes per year. The 5.2 percent of persons with 3 to 10 episodes per year had 32.9 percent of

all episodes. Among persons over the age of 20, those with high pain rates tended to die earlier than did those with low pain rates. High pain rates were associated with high hematocrit and low Hb F levels, and α-thalassemia had no effect on pain rates apart from its association with an increased hematocrit. The data indicated that the Hb F level was predictive of the pain rate, prompting attempts to increase Hb F levels with pharmacologic agents such as hydroxyurea.

MAJOR ORGAN DYSFUNCTION

Leg Ulcers

The incidence of leg ulcers was evaluated at study entry in 2,075 persons 10 years and older between 1979 and 1986 (4). Leg ulcers were most prevalent in persons with SCD-SS and SCD-SS α-thalassemia. Prevalence rates per 100 persons were: SCD-SS (4-5 α genes) = 4.97; SCD-SS (2-3 α genes) = 3.9; SCD-SS unmapped = 1.5; SCD-S β°-thalassemia = 0.9. Individuals with SCD-SC and SCD-S β⁺-thalassemia did not have leg ulcers at entry. The incidence rates of leg ulceration among males were significantly higher than among females (15 versus 5 per 100 person-years). Persons who had SCD-SS experienced a sharp increase in incidence of leg ulcers after the second decade of life. At any given total hemoglobin concentration, rates were lower in individuals with fetal hemoglobin (Hb F) levels greater than 5 percent.

Osteonecrosis of the Humeral Head

Osteonecrosis of the humeral head was determined in a study of 2,524 persons in the CSSCD cohort (5). At entry, 5.6 percent had radiologic evidence of osteonecrosis in one or both shoulders. The highest age adjusted incidence rates were observed in SCD-SS persons with concomitant α-thalassemia (4.9 per 100 person-years), followed by SCD-S β°-thalassemia (4.8 per 100 person-years), SCD-SS without α-thalassemia (2.5 per 100 person-years), and SCD-SC (1.7 per 100 person-years). Most were asymptomatic, with 20.9 percent reporting pain or limited range of motion at time of diagnosis.

ALLOIMMUNIZATION RISKS OF TRANSFUSION

In 1,814 persons with SCD who had been transfused, the rate of alloimmunization to erythrocyte antigens was 18.6 percent (6). The rate of alloimmunization increased exponentially with increasing numbers of transfusions. However, the rate of alloimmunization in persons whose first transfusion occurred at less than 10 years of age was less than expected based on the number of transfusions administered.

DEMOGRAPHICS

An analysis of socioeconomic status of 3,538 African-American SCD persons enrolled in the CSSCD revealed the following: there were fewer two-parent families than in the total United States black population (USBP) (40 percent versus 54 percent); twice as many persons of both sexes with SCD worked in white-collar positions; a higher percentage of SCD persons were unemployed and disabled (compared to the USBP); and men with SCD patients had lower median incomes than all black males in the United States (7). The percentage of high school graduates was similar (71 percent SCD versus 75 percent USBP), and female heads of household employed full time earned about the same salary as USBP females.

CLINICAL TRIALS IN SICKLE CELL DISEASE

Interventional trials grew partly from needs and observations related to the CSSCD. Examples of clinical trials funded by the NHLBI are described below and are summarized in table 2.

Prophylactic Penicillin Studies I & II (PROPS I & PROPS II)

The Prophylactic Penicillin Study (PROPS I), one of the first multicenter clinical trials, was initiated in 1983 to test the effectiveness of prophylactic oral penicillin in the prevention of severe pneumococcal infections in young children under 3 years of age with SCD (8,9). The multicenter randomized double-blind placebo-controlled trial demonstrated an 84 percent reduction in the incidence of infection in children who received oral penicillin twice daily, compared to the placebo group. It indicated that all neonates should be screened for sickle hemoglobinopathies, and those with sickle cell anemia should be placed on prophylactic penicillin by 4 months of age.

Penicillin Prophylaxis in Sickle Cell Disease II (PROPS II) demonstrated that penicillin prophylaxis can be stopped safely after age 5 because no significant benefit was found in comparing the placebo and penicillin groups (40).

Hydroxyurea Phase II Trial

Based on the findings that persons with poorer prognoses often had lower fetal hemoglobins (table 1), a multicenter safety and dosing study of hydroxyurea was undertaken in adults to determine responsiveness of fetal hemoglobin levels and toxicity (41). Forty-nine persons were enrolled, and 32 of them were still receiving therapy at the end of the study. Eighteen persons were treated for 24 months or longer, and 11 completed 16 weeks of therapy at a maximally tolerated dose (MTD). Hb F levels ranged from 1.9 percent to 26.3 percent, with the most significant predictors of Hb F levels being last plasma hydroxyurea level, initial white blood cell count, and initial Hb F level. No serious toxicities were observed, significant bone marrow depression was avoided, and chromosome abnormalities after 2

years of treatment were no greater than those observed before treatment. Hemoglobin concentrations increased, as did body weight. There was a suggestion of clinical benefit, although the study was uncontrolled and open-label and therefore was not designed to test therapeutic efficacy. This study was followed by the Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH Trial), the first randomized double-blind trial to test the efficacy of an agent in decreasing the rate of painful events.

Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH Trial)

The randomized, double-blind, placebo controlled MSH Trial conducted at 21 clinic centers (42,43) found that hydroxyurea decreased painful sickle cell episodes or crises, hospitalizations for painful episodes, acute chest syndrome, and total number of units of blood transfused by approximately 50 percent. In 1998, as a result of this trial, hydroxyurea became the first agent to be approved by the Food and Drug Administration for the prevention of painful episodes in adults with sickle cell anemia.

A contract to follow the MSH patient cohort, a phase IV study, began in February 1996. Only persons involved in the MSH Trial were recruited for this study, and they are being followed for long-term morbidity and mortality in association with long-term hydroxyurea usage.

Ancillary studies in the MSH Trial have explored factors responsible for genetic modulation of γ-globin gene expression (44) and effects of hydroxyurea administration on body weight and exercise performance (45). An analysis of the cost-effectiveness of hydroxyurea has shown that individuals with SCD who

received the drug had an average yearly lower cost of health care than did those originally randomized to receive placebo (46). Other areas being explored by the MSH investigators include effects of hydroxyurea usage on quality of life and the effect of hydroxyurea on analgesia use.

PHASE I/II STUDY OF HYDROXYUREA IN CHILDREN (PED HUG)

Children between the ages of 5 and 15 years with sickle cell anemia were entered into a multicenter safety and dosing study of hydroxyurea in 1994 (47). A total of 84 children were enrolled, 68 reached MTD, and 52 were treated at MTD for 1 year. This study demonstrated significant increases in hemoglobin concentration, Hb F levels, and decreases in white blood cell, neutrophil, platelet, and reticulocyte counts. Laboratory toxicities were transient and were reversible with cessation of hydroxyurea, as had been seen in adults. This study set the stage for the design of phase III trials of hydroxyurea in even younger children to determine whether hydroxyurea can prevent chronic end-organ damage.

PERIOPERATIVE TRANSFUSION STUDY

Perioperative transfusions are used frequently to prevent morbidity in patients with sickle cell anemia. A prospective multicenter study that ran from 1988 to 1993 randomly assigned 692 patients to receive either exchange transfusions to decrease their Hb S levels below 30 percent or simple transfusions to increase their hemoglobin levels to 10 g/dL (48). The conservative transfusion regimen was as effective as exchange transfusion in preventing perioperative complications, and the conservative regimen was associated with a much lower rate of transfusion-associated complications. In addition to decreasing morbidity for patients undergoing surgical procedures, simple transfusions are associated with significant cost savings.

STROKE PREVENTION TRIAL IN SICKLE CELL ANEMIA (STOP TRIAL)

Stroke is the second leading cause of death in children with SCD. In the STOP trial, an investigator-initiated multicentered trial funded by the NHLBI, children between the ages of 2 and 16 who were at risk for first-time stroke, as determined by having transcranial Doppler velocity greater than 200 cm/sec, were randomized to receive either periodic transfusions to maintain the Hb S level below 30 percent or standard supportive care (49). An interim analysis demonstrated that periodic transfusions were efficacious in preventing first-time stroke in the children randomized to the transfusion arm. At the end of the trial, all participants were offered periodic transfusion therapy. The main side effects of the transfusion therapy were iron accumulation and alloimmunization, although the rate of occurrence was low. A new trial, known as STOP II, is now in place to determine whether transfusions need to be continued indefinitely or if they can be stopped after some period of time when risk of stroke has diminished.

SUMMARY

The trials discussed are examples of only some of the major clinical efforts in SCD research. The NHLBI funds 10 Comprehensive Sickle Cell Centers, whose mission is to perform basic research in SCD, conduct clinical studies, and provide community outreach and education. It also supports a variety of other endeavors.

Table 2. NHLBI-Sponsored Clinical Trials in Sickle Cell Disease

Trial	Therapy Tested (Type of Trial)	Outcome (Reference)
PROPS I	Prophylactic penicillin in infants (Phase III)	Pneumococcal sepsis prevented in infants (8)
PROPS II	Prophylactic penicillin in children (Phase III)	Penicillin prophylaxis can be safely stopped at age 5 (40)
Hydroxyurea Phase II Trial	Hydroxyurea in adults (Phase II)	Hydroxyurea can be safely given to adults with SCD-SS (41)
MSH Trial	Hydroxyurea in adults with severe sickle cell anemia (Phase III)	Hydroxyurea lowered rate of painful events, blood transfusions, acute chest syndrome, and hospitalizations by 50 percent (42,43)
PED HUG (HUG KIDS)	Hydroxyurea in children (Phase II)	Hydroxyurea can be safely given to children between the ages of 5 and 15 (47)
Perioperative Transfusion Trial	Simple blood transfusions to raise the total Hb level to 10 g/dL regardless of Hb S concentration, compared to aggressive blood transfusions to suppress Hb S level to below 30 percent at time of surgery in children and adults (Phase III)	Simple blood transfusions can be safely given during the perioperative period to raise Hb concentration to 10 g/dL (48)
STOP Trial	Blood transfusions to prevent stroke in children (Phase III)	First-time stroke can be prevented in children found to be at risk by periodic blood transfusions to suppress Hb S concentraion to less than 30 percent (49)

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