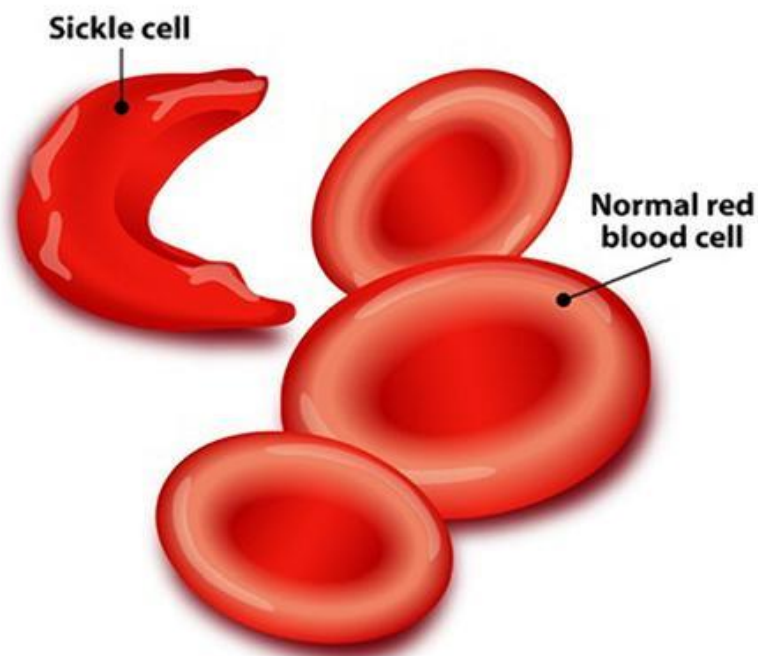


State of Louisiana Standards for Care of Patients with Sickle Cell Disease



*Renee V. Gardner, MD and the
Louisiana Sickle Cell Commission*

*Renee V. Gardner, MD, Professor,
Pediatrics/ Pediatric Hematology/Oncology;
Louisiana State University Health Sciences Center, New Orleans, LA*

Table of Contents

1. Newborn Screening and Followup	2
2. The First Visit	3
3. Health Care Maintenance for Children and Adolescents with Sickle Cell Disease	10
4. Prevention of Infection	14
5. Immunizations	15
6. Treatment of Pain	18
7. Acute Chest Syndrome	22
8. Aplastic Crisis	24
9. Sequestration Crisis	26
10. Stroke and Other Neurologic Event(s)	29
11. Transfusions	33
12. Iron Overload	37
13. The Child with Sickle Cell Disease and Surgery	38
14. Priapism	41
15. Leg Ulcers	46
16. Pulmonary Hypertension	48
17. Pulmonary Complications	51
18. Retinopathy	53
19. Renal Functional Impairment	54
20. Hepatobiliary Complications	57
21. Growth and Metabolic Disturbances	59
22. References	64

Newborn Screening and Follow-up

The state of Louisiana has instituted universal hemoglobinopathy screening in the newborn period. Regardless of race or ethnicity, all children are screened for the presence of abnormal hemoglobins, with the goal of identifying disorders at the earliest possible time of the child's life. Such an approach allows education of patients regarding their child's disorder and aims at prevention of complications associated with hemoglobinopathies.

If sickle (S) hemoglobin is present on the newborn screen, the primary care physician and Newborn Screening Program coordinator are notified; subsequently the child is referred to a hematologist/oncologist in a nearby clinic or practice. This referral should take place within the first two months of life. The hematologist/oncologist will then perform confirmatory testing via hemoglobin separation (using hemoglobin electrophoresis*, isoelectric focusing and/or HPLC or DNA analysis) in an appropriate laboratory. A complete blood count (CBC) with reticulocyte count will be obtained concurrently. Parents may also request that they themselves be tested, as well, to determine their own status as carriers (or individuals with trait) or as having the disease. Such testing would entail obtaining a CBC and hemoglobin electrophoresis (or other methods of hemoglobin separation as noted above). Solubility testing, i.e. Sickledex, Sickleprep, Sicklequik, should not be utilized since it is inadequate for hemoglobinopathy screening.

Outcomes of screening are shown below in the accompanying Table (Table 1).

Probable Diagnosis	Screening Results	Hemoglobin Separation after 2 years
Homozygous sickle cell disease (HbSS)	FS	75-95% HbS 2-25% Hb F <3.5% HbA2
Sickle –beta ⁰ thalassemia	FS	0% Hb A 80-92% Hb S 2-15% Hb F 3.5-7% Hb A2
Sickle –beta ⁺ Thalassemia	FSA or FS	5-30% Hb A 65-90% HbS 2-10% HbF 3.5-6% Hb A2
Sickle hemoglobin C disease	FSC	0% Hb A 45-50% Hb S 1-5% Hb F 45-50% Hb C
Sickle Cell Trait	FAS	50-60% Hb A 35-45% Hb S <2% Hb F <3.5% Hb A2
Normal	FA or AF	95-98% HbA <2% Hb F <3.5% Hb A2

*Used at Children's Hospital of New Orleans and in the reference lab at Mayo Clinic

First Visit: Informing Parents of the Diagnosis

Parents are informed upon coming to the hematologist/oncologist's office or clinic that the initial hemoglobin screening results are *suggestive* of diagnoses in some cases (SF) and diagnostic in others, e.g. FSC (or SC Disease). They are informed that since the production of adult forms of hemoglobin does not begin in earnest until 6 months of age, at which time the production of hemoglobin F begins to be turned off, one cannot determine with any definitiveness the hemoglobin phenotype of the child until he/she is 18 to 24 months of age. Accordingly, the final diagnostic sampling will be performed when the child is 18-24 months of age. Further confirmation of diagnosis may be sought by sending blood sample to a reference laboratory (e.g., Mayo Clinic Laboratories) to perform other testing that would further define the child's illness, e.g., through the performance of alpha or beta chain analysis if sickle-thalassemia states are suspected. Other tests that may be necessary may include also a Kleihauer-Betke stain which may allow distinction of the persistence of Hemoglobin F as in S-HPFH (sickle cell disease with hereditary persistence of fetal hemoglobin). Although most counseling is performed adequately by the hematologist/oncologist and his/her staff, Genetics personnel can be consulted for more in-depth counseling, if necessary. In addition to formal education conducted by the hematologist/oncologist carried out at the first visit, reading material on the disorder will be given to the parents of the referred child. At times, parents do not follow through on keeping appointments for their scheduled education/counseling session. In that event, social services will be notified of the failure of the family to bring the child to the clinic and every effort will be made to make sure that the child is seen by the hematologist/oncologist in a timely manner.

First Visit: Counseling

Patients will be informed of the following information upon presenting themselves and their child to the hematology/oncology clinic:

1. The possible hemoglobin phenotype indicated by the patient's initial hemoglobin electrophoresis will be discussed, although definitive identification of the child's phenotype will not be possible until the second year of life.
2. Start of penicillin prophylaxis should be confirmed or prophylaxis initiated (an explanation of why it is important should be given and confirmation of its having been prescribed by the child's primary care physician should be made; if it has not already been prescribed, it is the job of the hematologist to insure that the child starts this medication on the first visit.)
3. The pathophysiology of sickle cell disease will be discussed in simplified version with the family.
4. The genetics of the disorder will be discussed with the family, as well. This is especially important because occasionally misconceptions concerning the origin and the inheritance of sickle cell disease arise. An example would be the idea held by a family member that the disorder is of infectious nature and can be contracted through sexual or other intimate contact.
5. The signs and symptoms of the disorder, should be outlined, in order to have the caregiver of the child recognize illness in the child and to instruct them as to what are emergent situations and

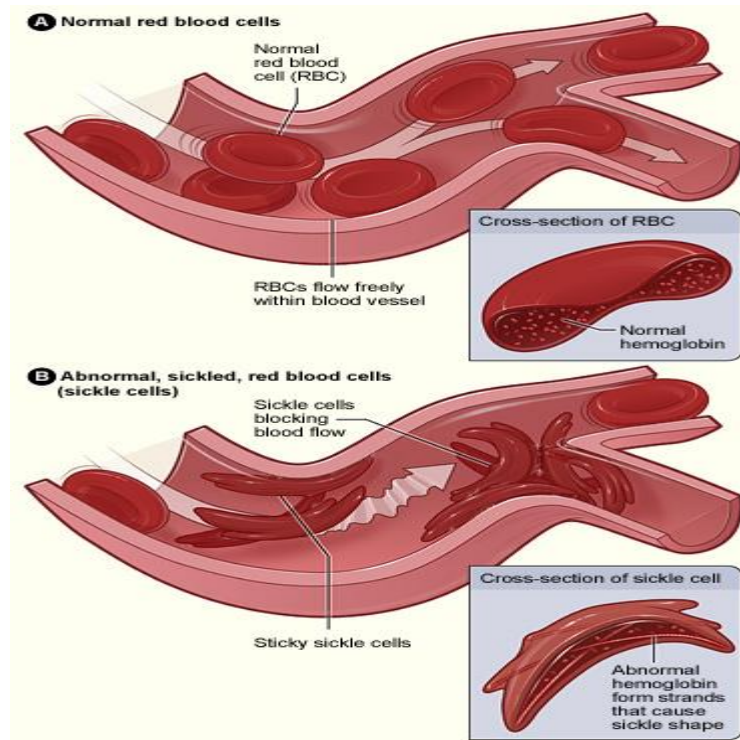
what measures need to be taken by him/her if such circumstances occur. Conditions that are to be elaborated upon include: splenic sequestration, painful crisis, aplastic crisis, and fever. These problems will be discussed at length in sections below.

6. Parents will also be taught how to palpate the spleen as the complication of splenic sequestration is discussed.
7. Laboratory evaluation will consist of:
 - a. A repeat hemoglobin electrophoresis to confirm the state laboratory findings.
 - b. A complete blood count with reticulocyte count should be obtained. However, the child's baseline may not become immediately evident due to the expected physiologic nadir of hemoglobin that will take place at 8-12 weeks of age. Several months after the nadir has taken place, the child's baseline hemoglobin can be established by following serial CBCs.

Pathophysiology of sickle cell disease

The pathophysiology is presented in a simplified, clear manner. While we now know that sickle cell disease is a complex process, in which elements of vasoocclusion, inflammation, altered adhesive state, heightened cytokine response, etc. work together to produce the disease state,¹⁻³ we emphasize primarily the vasoocclusive nature of the disease and outline those triggers that may lead to vasoocclusion and subsequent cellular injury. Such triggers may include: 1. temperature extremes; 2. hypoxia; 3. Stress; 4. dehydration; and 5. excessive exercise among others.

A diagram such as is shown below is drawn for the families with an explanation of the transformation of the red cell into a sickle-shaped cell which now has the capacity to slow blood flow and oxygen delivery to cells that subsequently become injured or die due to that oxygen deprivation. The most common manifestation of such injury is pain crisis.



Pain crisis usually is not present in the neonatal period because of the presence of elevated fetal hemoglobin levels at birth. As noted, fetal hemoglobin production lessens after the age of 6 months. It is therefore at that time that painful episodes may begin to be seen. (There may be individual variation, of course, with some infants manifesting pain crisis at a slightly earlier age or not at all.) The first manifestation of these episodes can be painful swelling of the hands and feet, known as dactylitis. The baby, unable to indicate pain, may then give behavioral clues such as failure to crawl or pull to a stand, demonstrating withdrawal response, and displaying irritability and inconsolable crying, among other responses. The involved body part will be swollen, warm, and tender to touch. This situation must be viewed as a medical “emergency” and dictates that the family member brings the child to the emergency room immediately. There, the child should be evaluated by emergency room staff. (More specifics regarding the treatment of pain crisis will be given below.) Intravenous fluids should be administered. The child should be monitored for the presence of fever. Analgesic should be administered. The choice of analgesic should be left to the discretion of the admitting physician but the use of morphine may be suitable, if given as a continuous low-dose infusion by PCA pump (this mode of analgesic administration may be appropriate in an infant, in whom gauging the severity of pain may be difficult; oral narcotic such as Tylenol with codeine could be used, but may be inadequate for pain relief. Again the choice of analgesic is left to the physician’s discretion). The use of a narcotic analgesic will necessitate continuous pulse oximetry monitoring and close supervision by the nursing and medical staff. Parents should be made to understand that such a practice, i.e. giving narcotic analgesic, is indicated in order to alleviate pain and has no significant addictive potential in most circumstances. Alternatively, if the child’s pain is assessed

as being mild, an analgesic such as Tylenol can be given, providing that temperature elevation is not present.

Discussion with Parents of Genetics of Sickle Cell Disease

Sickle Cell disease is the most common genetic disorder in the United States, with about 100,000 Americans thought to be living with sickle cell disease; each year about 1000 babies are born with the disorder.^{4, 5} Worldwide it may affect more than 500,000 babies a year. About 2 million Americans are carriers (have the trait). Common misconceptions held by parents about the disorder are: (1) It is a uniformly fatal disorder; (2) it is contagious, akin to an infectious disease; and (3) one may grow out of it as one enters adolescence and adulthood. Our counseling is geared to disabuse individuals of these erroneous conceptions about sickle cell disease.

What follows is a sample discourse regarding the genetics of sickle cell, geared to the non-physician/parent of a child with sickle cell disease: Education on the genetics of sickle cell disease begins with the knowledge that genes dictate everything about the human body, e.g., hair and eye color, propensity towards certain diseases, height and weight, etc. People also inherit a pair of genes that regulate hemoglobin, an essential molecule or protein that carries oxygen and is contained within red blood cells. Genes dictate how the hemoglobin molecule will be structured, where “building blocks”, i.e. amino acids are ordered. The substitution of a single amino acid leads to an abnormal hemoglobin (HbS) that now behaves abnormally when the red cell encounters a state in which there is lack of oxygen or excessive acid build-up, among other conditions. The red cell then may assume an abnormal shape, --- that of a sickle, making the cell more inflexible and incapable of passage through small blood vessels called capillaries. Eventually, blood flow slows to the organ involved, making oxygen delivery impossible or lessened, with the end result being organ damage and/or cellular death.

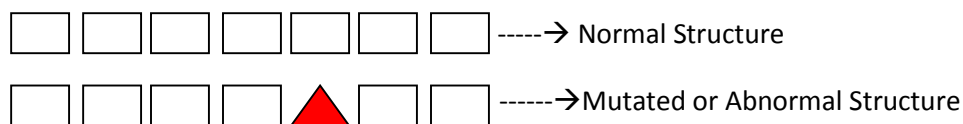


Diagram of how gene may mutate.

The HbS gene is inherited. In the United States, it is seen primarily in African-Americans with a gene frequency of 1:500-1:600. However, it must be stressed that sickle cell disease is a worldwide disorder that is not restricted solely to those of African descent. This is especially important in an age in which emigration is the rule and people travel to all corners of the world.⁶ It should be understood that sickle cell disease can be seen in those from Latin America, the Caribbean, the Middle East and Mediterranean countries such as Greece and Italy, as well as India. This is important since our impression is that follow-up is often less than optimal among non-African Americans who may feel inordinately stigmatized by the diagnosis of sickle cell disease.

To say that one has the homozygous disease, SS, means that both parents carry the HbS gene and that a copy of the gene has been passed from each parent to the child, who will subsequently carry 2 sickle hemoglobin genes. This form of disease is generally the most severe, with the child having greater likelihood of multiple complications of the disease. If one normal hemoglobin gene and one sickle cell

gene are inherited, the child will have sickle cell trait. These individuals should be asymptomatic and have no manifestations of sickle cell like pain or stroke, for example. They, however, will be “carriers” who can pass the HbS gene to their children. About one in 10-12 African-Americans has sickle cell trait. Individuals with sickle cell trait should be made aware of their status, especially when they become of child-bearing age, so that they can make intelligent choices regarding a mate and, at least, query a prospective mate about his/her sickle cell status. The parents should, however, be made aware of the fact that individuals with sickle trait can experience problems such as sickling and pain if they are placed in extreme circumstances. In recent years, there have been reports of sudden death associated with sickle cell trait in those participating in competitive athletics or other exertional activities.⁷⁻⁹ Such instances are rare and have included individuals who have performed very vigorous exercise, e.g. army recruit or high school athlete, in very hot climates or high altitude or being in a depressurized airplane cabin. For instance, a 30-fold increased risk of sudden death in black Army recruits with sickle trait has been reported, with an absolute risk of sudden unexplained death of 32.2 per 100,000 individuals with sickle cell trait.^{10, 11} However, with greater attention to the need of such individuals for better hydration/re-hydration, such occurrences have been exceptional. (Please note that the American Academy of Pediatrics has not endorsed a policy of screening for sickle cell trait “unless the results have clear health benefits.”⁹ The recommendations coming out of the US Department of Health and Human Services also indicated that genetic testing “should not be a prerequisite for participation in sports unless deemed medically necessary.” Neither was screening necessary for enlistment in the armed services nor for participation in professional or amateur sport.⁹)

Another problem that may sometimes be experienced by individuals with trait would include kidney complications such as hematuria.^{12, 13} Hematuria is a rare complication of sickle cell trait, a result of renal papillary necrosis. In one paper, it has been cited that the admission rate for hematuria was 4% for patients with sickle cell trait, double that of patients with normal hemoglobin.¹³ Still, the presence of hematuria should necessitate examination of the patient for other causes of hematuria besides sickle cell trait. Such differential diagnoses would include renal stones, urinary tract infection, and renal neoplasm, just as such a work-up would be carried out in any other individual without the heterozygous or homozygous sickle condition.

Similarly, another renal complication of sickle cell trait is renal medullary carcinoma that presents with hematuria, flank pain, and abdominal mass.¹³ It has been almost exclusively associated with individuals with sickle cell trait; interestingly, those with actual sickle cell disease have a relatively low prevalence of this malignancy, which is in almost all cases fatal.

For the most part, however, we emphasize that most individuals with sickle trait will have overall healthy and symptomless lives, and would be expected to have normal lifespans. They should be encouraged, as should all individuals whether with carrier status, diagnosed hemoglobinopathy, or normal hemoglobin state, to maintain good health practices and routinely see a physician for health surveillance, at any age.

At times, the HbS gene may be paired with other abnormal genes. This would include Hemoglobin C, a hemoglobin that is determined by a gene that again results from a single amino acid substitution or change. Hemoglobin C is found predominantly among those of African descent, although it too can be

found in individuals whose ancestors came from Italy, Greece, and Latin America.¹⁴ About 1 out of every 40 African-Americans has hemoglobin C trait. Again it should be emphasized to parents that this is an inherited condition. Individuals can have one normal hemoglobin gene, with the other gene being the C gene. In that event, the child will have C trait. He/She should then be asymptomatic, having only microcytosis ("small cells") that can sometimes cause confusion, with misdiagnoses such as thalassemia or iron deficiency anemia being the result. Alternately, an individual could have two aberrant genes, those of HbS and of HbC, that have been inherited. In that case, they will manifest a disorder called SC Disease that generally is milder than homozygous SS disease. Individuals with SC disease are found to have hemoglobin concentration in the red cells that is usually higher (~9-11 gm%) than that seen in those with homozygous disease (~6-8.5 gm%). While they can have pain crises, acute chest syndrome, sequestration and other complications of sickle cell disease, these problems occur much less frequently, if at all. A recent clinical study of patients with SC disease found that there was a prevalence of 36%, 20%, and 20% respectively for pain crisis, acute chest syndrome, and priapism.¹⁵ Parents should be made aware of the fact that children with SC disease may be more likely to experience problems with their eyes (sickle retinopathy with a prevalence as high as 70%), or sensorineural otological disorders (prevalence 29%). The prevalence of hypertension, strokes or leg ulcers, as well as nephropathy was relatively low. Therefore, although appearing to be healthier and perhaps seeming to not need regular care from the hematologist, these individuals should periodically visit the hematologist for regular maintenance visits, e.g., every 6 months.

Similarly, those with HbS-beta thalassemia, whether beta-zero or beta-plus, bear two abnormal genes, one for the HbS gene and the other for the beta thalassemia gene. Parents should be made aware that there are differences between the two forms of beta thalassemia. Those having the S-beta-zero phenotype (meaning that they express no normal or A hemoglobin) may behave similarly to those with homozygous SS disease and suffer multiple complications of disease, including frequent painful episodes, sequestration, and stroke. However, those with S-beta-plus thalassemia only rarely present with pain crises or other complications of disease. Their hemoglobin is likely to be normal (11-12%) and if they are hospitalized during early childhood, it is usually for problems such as fever or sequestration.

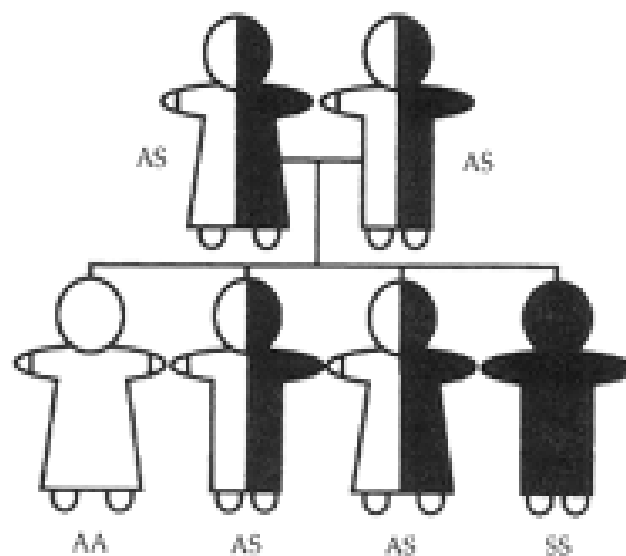
There is also a condition in which individuals may bear two copies of the hemoglobin S gene but also have a relatively mild phenotype of the disease: individuals with SS with hereditary persistence of fetal hemoglobin (HPFH). Hemoglobin S does not assume the sickle form to the same extent as it otherwise would when hemoglobin F is present in the cell since the presence of hemoglobin F inhibits polymerization of the S hemoglobin molecule. The presence of fetal hemoglobin (HbF) in conjunction with hemoglobin S has an ameliorating effect on the disease¹⁶ and it is known that percentages of HbF of >8.6% are beneficial.¹⁶ However, having SS-HPFH means that during infancy, the Hemoglobin F levels range from 50-90%; decreasing within the first few years of life, Hemoglobin F declines to ~30% between ages 3 and 5 years.^{17,18} Patients 5 years and older, usually have a mean hemoglobin F of $31 \pm 3\%$. Their average hemoglobin concentration is about 13 gm% and the MCV is 75 ± 4 gL. Individuals with high levels of HbF have far fewer episodes of pain, acute chest syndrome, priapism, or other complications. The gene for continued presence of HbF is also inherited. The diagnosis of SS-HPFH is then primarily made on the basis of hemoglobin F percentage. This diagnosis can be confirmed in specialized laboratories (such as

ARUP) by means of genetic testing. This is not widely utilized due to cost. However, one means of confirmatory testing can be the use of the Kleihauer-Betke stain which allows identification of red blood cells containing fetal hemoglobin. This test has several other applications. However, the demonstration of a pancellular or homocellular (meaning uniform distribution) pattern is suggestive of the condition of HPFH. Alternatively, it may be possible to perform flow cytometry to demonstrate the same characterization of the red cells but not every institution may have the capacity to perform such an analysis.

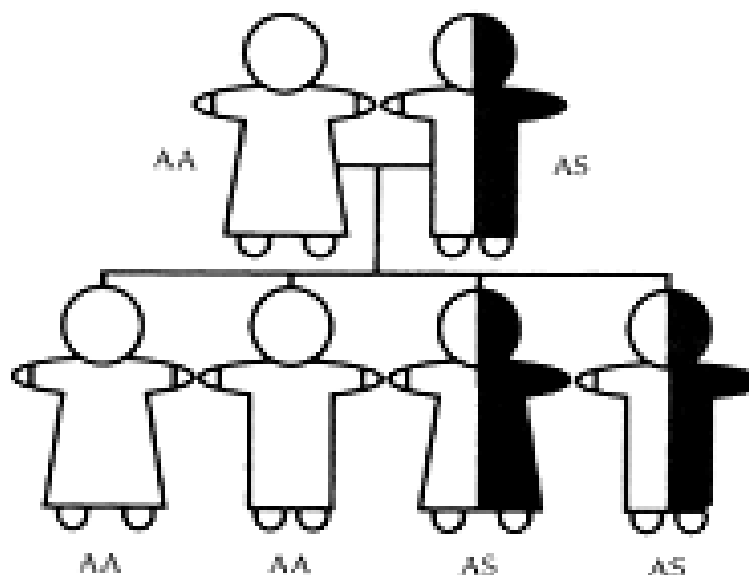
In fact, both SS-HPFH and S-beta plus-thalassemia may have such mild symptoms associated with them (or none at all) that both of these conditions have been debated as being “non-diseases” and not meriting regular follow-up by the hematologist. At Children’s Hospital, however, we have seen individuals with both these forms of hemoglobinopathy who have required hospitalization for splenic sequestration and pain crises and we have urged families to continue regular follow-up (once or twice a year) even if the child appears to be having no overt problems.

Risk of Inheritance

1. If both parents have sickle cell trait (one normal hemoglobin gene and one sickle cell gene, AS) (see diagram below), then the parents should be informed that a child coming from their union would have a 50% chance of inheriting sickle cell trait (as noted, asymptomatic), a 25% chance of being homozygous for the disease (two copies of the abnormal sickle cell gene and manifestations of disease), and a 25% chance of having two copies of the normal hemoglobin gene A (AA, neither trait or disease, but normal hemoglobin).



2. If one parent has the sickle trait and the other parent has two copies of the normal hemoglobin gene A (see diagram), the child has a 50% chance of inheriting sickle cell trait and a 50% chance of having two normal gene copies, with neither trait nor disease.



3. If one parent has sickle cell disease (two sickle cell genes) and the other parent has sickle cell trait, then the child has a 50% chance of inheriting sickle cell trait and a 50% chance of inheriting sickle cell disease.
4. If one parent has sickle cell disease and the other parent has two copies of the normal hemoglobin gene, the child has a 100% chance of being a carrier or having the trait.
5. If both parents have sickle cell disease (homozygous SS Disease), the child has a 100% chance of inheriting the disease.
6. If one parent has Hemoglobin C trait (one normal gene and one abnormal gene, expressing C Hemoglobin, AC), and the other has sickle cell trait (AS), then there is a 25% chance of having a child with C trait (AC), a 25% chance of having a child with sickle trait (AS), a 25% chance of having a child with SC Disease and a 25% chance of having a child who is neither trait nor disease, i.e., normal hemoglobin (AA).

Note that a child may, at times, present with two genes for hemoglobin C, inherited from each parent, for instance, with hemoglobin C trait. In that event, the child will have a disorder called CC Disease.¹⁹ Individuals with this disorder generally have a mild anemia that sometimes may be exacerbated by viral illness. Such exacerbation is characterized by a drop in hemoglobin concentration, pallor, excessive fatigue, and sometimes jaundice and dark urine. Anemia exacerbation may be the result of either virally-induced transient aplasia or increased hemolysis. This occurs very rarely and most individuals will be asymptomatic or mildly symptomatic, and occasionally will be found to have mild splenic enlargement.

Parents may occasionally request genetic counseling. This can be made available to them through referral to the Geneticists. Prenatal diagnosis is available through amniocentesis (sampling of amniotic fluid). For such screening, parents should be advised to consult their Obstetrician.

Health Care Maintenance for Children and Adolescents with Sickle Cell Disease

Febrile Precautions (and Immunizations)

Infection is the most common cause of death in sickle cell disease.^{20,21} The risk of sepsis is markedly greater for children with the disorder than for normal children, especially for pneumococcal disease (400 times greater).²²⁻²⁴ It is recognized that individuals with sickle cell are at greatest risk during the first 5 years of life. This is due to “functional asplenia”.

Upon initial presentation and with each subsequent visit, parents are informed of the importance of the symptom of fever as a possible indicator of serious and even life-threatening infection. The parents are educated regarding the reasons for the child’s increased susceptibility to infection with encapsulated organisms such as pneumococcus, meningococcus, Haemophilus influenza, and salmonella (See accompanying Table for organisms that have been isolated in sickle cell disease with fever):

Table 2. Bacteremia in children with SSD taken from a cohort of 694 children with Sickle hemoglobinopathy

Organism	Patient	Total No. Cases
Streptococcus pneumonia	SS	62
	SC	12
Haemophilus influenza	SS	10
	SC	4
Staphylococcus aureus	SS	5
	SC	1
Viridans streptococci	SS	5
	SC	1
Escherichia coli	SS	5
	SC	2
Salmonella species	SS	3
	SC	2
Other	SS	2
	SC	0

Adapted from *Nathan and Oski, Hematology*²⁵ Data on Bacteremia in Cohort of 694 Children with Sickle Cell Anemia (SS) and SC Disease Monitored Prospectively from Infancy (Gill FM, Sleeper LA, et al., Blood 1995)

The spleen is an important element in our immune response to infection. Because of infarction (cell death of the splenic cells caused by sickling) of the spleen, the child with sickle cell becomes increasingly vulnerable to infection with these organisms. In children with homozygous disease (SS), the process of splenic infarction begins at 2-3 months of age after the onset of the decline of fetal hemoglobin and, in most infants, is evident by 9-10 months of age and is usually completed by the age of 5 years. It is not exactly known when splenic infarction begins to take place or when it is completed in those with SC or S-beta-thalassemia. Some studies have demonstrated complete infarction of the spleen by age 10 years in individuals with SC disease. Yet we have seen those with sickle-beta thalassemia or SC disease who present with sequestration in late adolescence, e.g., 16-18 years.²⁶ This indicates that there may be considerable variability in the course of disease in individuals with these disorders. Also, there is uncertainty as to whether the spleen in these individuals, even if present, maintains normal immune function or not. We have seen demonstrable splenic function in patients, 16-18 years of age, through performance of liver-spleen scans and red cell pitting assays. However, due to this uncertainty, it has

been our practice to treat these patients with the same caution we would have with any child with sickle disease, whether homozygous or not.

- Parents are to be told to bring their child with sickle cell disease to the hospital or doctor's office if fever of 101°F (38.3°C) or greater is noted, regardless of age. Even in an age of vaccination and penicillin prophylaxis, these instructions are necessary since there are children who will not have received full immunization and there has also been development of antibiotic-resistance. Risk of infection by encapsulated organisms also may lessen but is never absent, even in older children and adults. Parents should be made aware of the fact that although the child may appear to have nothing more than a viral illness, such an appearance may be misleading. Fever alone may be the symptom signaling sepsis or blood-stream infection. The febrile child with sickle cell should be triaged quickly once he/she comes to the Emergency Room. Emergency Room staff should be educated as to the measures that need to be taken by them when confronted with the febrile sickle cell patient. They should then be examined carefully and a CBC performed. Blood cultures should be drawn, along with urinalysis, urine culture, chest X-ray (especially if respiratory symptoms are present), and throat culture, if indicated. Broad-spectrum antibiotic such as ceftriaxone (Rocephin) should then be administered, even if there are no signs or symptoms consistent with bacterial sepsis or disease. Toxic patients are considered those who appear ill, and/or have a temperature greater than 39.5°C (103.1°F). They should be automatically admitted after receiving as quickly as possible antibiotics in the Emergency Room. Children who do not appear toxic and have a temperature of less than 103.1°F but who have infiltrate on chest X-ray, should also be admitted to the hospital for the administration of parenteral antibiotics and observation. Additional factors that would dictate that a child be admitted include a WBC greater than 30,000/mm³ or lower than 500/mm³, a platelet count less than 100,000/mm³, hemoglobin below 5 gm%, or history of prior sepsis, and age 2 years and under.
- If the child has signs of meningitis, such as stiff neck, photophobia, headache, vomiting, etc., that child should undergo a lumbar puncture. Cerebrospinal fluid will be sent for cultures, cell count, and chemistries.
- An effort should be made, if the child comprehends the instructions to do so, to obtain a sputum culture, if there is an infiltrate on chest X-ray.
- If diarrhea is present, the patient may have Salmonella; a stool culture that is positive for Salmonella, however, may be the only evidence of Salmonella pneumonia or bacteremia.
- In most cases, a bacterial organism will not be isolated and the patient should receive antibiotics for a length of time that depends upon their clinical symptomatology. For instance, if an infiltrate is present on chest X-ray, even in the absence of proven bacterial infection, antibiotic should be continued for 7-10 days (a switch to oral antibiotic can be

contemplated once the child improves after a sufficient course of intravenous antibiotic). A suitable antibiotic choice for oral usage might be Augmentin or an oral cephalosporin.

- If the child is proven to have specific bacterial source of infection, then the antibiotic choice should be tailored to the sensitivities of that organism. If the child is, on the other hand, culture-negative and afebrile for 24-48 hours, then antibiotics can be discontinued. Again, documented sepsis should be treated for 7-10 days with intravenous antibiotics. Similarly, bacterial meningitis is treated for a minimum of 10 days from the time of negative cultures with parenteral antibiotic.
- Symptoms consistent with osteomyelitis such as bone pain and fever that is persistent or higher than 101F, accompanied by swelling of the affected area, warmth and indication of fluid accumulation, may indicate the need for needle aspiration and culture of the lesion. Antibiotics with efficacy against Salmonella and Staphylococcus aureus should be considered.
- If this has been a compliant patient (parent) and, importantly, the child does not appear toxic or have any of the above-listed factors, then the physician may have the option of obtaining a sepsis work-up and then empirically administering antibiotic (Rocephin, which has a half-life of 7-10 hours and should have adequate levels 12-24 hours later, to offer antibacterial protection) and sending the patient home. If cultures are positive, the family will be called back and the child admitted. This option can only be a reasonable one **IF** there is a reliable way to contact the family to notify them of the culture results or of the need for the child to be hospitalized; **IF** the family does not live a far distance from the hospital or clinic; **IF** the family has reliable transportation; and **IF** the parents have previously demonstrated reliability and have a clear understanding of the issues involved.
- Antipyretics can be given to a child with sickle cell disease, but we advise that they should be administered only after the child's temperature is documented. We should emphasize to the child's parents that improper use of antipyretics can mask fever, making it more difficult to assess the child. If fever is present, it should be emphasized, the treatment does NOT consist of antipyretic therapy but the proper course is to bring the child to the ER or physician's office, where cultures can be obtained and the child given parenteral antibiotics.
- Cooling blankets or ice packs should not be used for a child with sickle cell disease.

Please note that the choice of Rocephin depends upon the hospital's sensitivity profile. If there is a history of organisms that have been identified as resistant to cephalosporin, then one should consider the addition up front of an antibiotic such as Vancomycin. Also, if the child appears toxic, the addition of Vancomycin is indicated.

At Children's Hospital of New Orleans, we have taken the step to have preprinted orders for admission to the hospital that include antibiotic choice and sepsis workup instructions. Additionally, such orders are included on the EDM for the Emergency Room usage. Physicians should consult their hospital antibiogram to determine what the sensitivities of isolated organisms have been; if there is a pattern of resistance, this information will be used as a guide to antibiotic selection.

Patients who are allergic to cephalosporin (this should be proven allergy, e.g. history of urticaria/rash, bronchospasm, anaphylaxis, etc.) may be given clindamycin but it must be remembered that clindamycin does not cross the blood-brain barrier. If this is a concern, then a specialist in Infectious Diseases should be consulted to help with the choice of suitable antibiotic(s).

Discharge of the patient admitted with fever should be considered only if:

1. The patient has negative culture for 24-48 hours and the patient has remained afebrile for at least 24 hours.
2. The child is taking adequate oral fluids and is able to take oral antibiotic, if this is indicated.
3. There has been resolution of any pulmonary symptoms that have been present and there is indication of adequate oxygenation on room air as measured by pulse oximetry.
4. The patient has demonstrated a stable hemoglobin, with no evidence of aplastic or sequestration crisis.
5. Adequate follow-up has been arranged and there is assurance of compliance regarding follow-up.

Measures Aimed at Prevention of Infection

It is imperative then that the baby presenting to the hematology/oncology office or the pediatrician's office be started on penicillin prophylaxis.²⁷ Prophylaxis should begin optimally by 6-8 weeks of age. The dose for these infants is 125 mg po BID Penicillin VK. This dose will be continued until the child is 3 years of age. At that time, the dose of penicillin VK will be increased to 250 mg po BID. The most recent guidelines for antibiotic prophylaxis are:

1. Continuation of penicillin in children until they are 6 years and above.^{28,29} It is felt that the risk of pneumococcal sepsis after this age is small and the patient can then have the antibiotic stopped. It is recognized that there may be some children who may still contract pneumococcal disease (that the risk of sepsis or invasive pneumococcal disease is not zero),³⁰⁻³⁴ but issues such as development of resistance to penicillin are of concern.
2. This rule will not stand for those who have undergone surgical splenectomy (who continue to be at increased risk for pneumococcal and meningococcal sepsis); or for those who have a history of non-compliance; or who have a history of invasive pneumococcal disease or sepsis. These individuals should be continued on penicillin prophylaxis for their lifetime.

3. If patients have a proven allergy to penicillin(s), e.g., have had in the past demonstrable urticaria, rash, or anaphylaxis after exposure to penicillin(s), erythromycin ethyl succinate (dose 10 mg/kg orally twice daily), or clarithromycin should be given.
4. Parents should be reminded of the signs of infection, with instructions to come to the Emergency Room or physician's office immediately if fever ($\geq 101^{\circ}\text{F}$) is present. Parents should also be taught that temperature taken under the arm (axillary) is actually higher than that recorded by the thermometer (e.g., temperature of 99.8°F taken as an axillary temperature is actually 100.8°F).³³

It must be remembered that while the risk of serious infection is greatest in early childhood, as discussed earlier, infection also can pose a risk for older children and adults with sickle cell disease. In this group of patients, pneumonia, kidney infections, and osteomyelitis are often seen, with a different spectrum of causative agents. The organisms that would now be of importance in the older sickle cell patients include *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*, and gram negative bacteria. Antibiotic coverage should be chosen with these differences in mind and patients should be reminded to come to the physician's office or ER if there is fever.

Immunizations

Parents are urged to comply with the childhood or pediatric immunization schedule as established by the CDC and American Academy of Pediatrics and published in January 2014.³⁵ Of particular importance to the patient with sickle cell disease are vaccines against pneumococcal antigens, hepatitis A and B, and *Haemophilus influenza*. These vaccines would be routinely administered to **all** children during the first 2 years of life. The schedule that is followed is shown in Table 3 below. Infants may miss having shots given at the recommended time for various reasons. Nevertheless, any dose, "if not administered at the recommended age should be administered at a subsequent visit, when indicated and feasible." Please note the following recommendations which have been summarized from the CDC guidelines on immunization schedules:

Hepatitis Vaccines

Infants should receive monovalent HepB vaccine before discharge from the neonatal nursery and at 1-2 months of age. If an infant does not receive a birth dose, he/she should receive 3 doses of HepB-containing vaccine on a schedule of 0, 1-2 months and at 6 months.

Hepatitis A vaccine should be given as a 2-dose series beginning at 12 months and continuing through 23 months. The 2 doses should be separated by 6-18 months. If the child is over 2 years of age and has not already received the HepA vaccine series, 2 doses of HepA vaccine should be separated by 6-18 months. For catch-up vaccination involving HepA, the minimum interval between the two doses is 6 months.

Influenza Vaccine

Influenza vaccine should be given to all children beginning at age 6 months. For those who are receiving the vaccine for the first time, 2 doses separated by at least 4 weeks should be administered. For those individuals 9 years and older, 1 dose should suffice.

Haemophilus Influenzae Vaccine

Hib conjugate vaccine for prevention of Haemophilus influenza type b infection can be given at a minimum age of 6 weeks, but the primary series with PedvaxHib or COMVAX consists of 2 doses and should be given at 2 and 4 months of age. One booster dose (dose 3 or 4 depending on vaccine use in the primary series) should be administered at ages 12 through 15 months. Children with sickle cell disease who are ages 12 through 59 months are at increased risk for Hib infection. These children should receive 2 additional doses of Hib vaccine 8 weeks apart if they have received either no doses or only 1 dose of Hib vaccine before 12 months of age; if they have received two or more doses of Hib vaccine before 12 months of age they should receive 1 additional dose.

Meningococcal Vaccination

Although the incidence of meningococcal disease has declined in recent years and had done so even before the advent of vaccine-derived protection, its virulence and rapid development dictate the need for meningococcal vaccination, especially for those at increased risk of infection. Meningococcal disease in children has two peak incidences, children <5 years, and adolescence and early adulthood, ages 16 -21 years; the highest incidence during the first 5 years of life takes place among infants ages 0-5 months of age.³⁶ For children with sickle cell disease, Meningococcal conjugate vaccine such as MenHibrix or Menveo should be administered to those less than 19 months of age at 2, 4, 6, and 12 through 15 months of age. If the child is ages 19 through 23 months and has not completed a series of MenHibrix or Menveo, 2 primary doses of Menveo should be given 3 months apart. If the child is 24 months or older, and has not received a complete series of MenHibrix or Menveo or Menactra, then 2 primary doses of either Menactra or Menveo should be administered at 2 months apart. If Menactra is administered to a child with sickle cell disease, Menactra should not be administered until 2 years of age and at least 4 weeks after completion of all PCV13 doses. (Please note that most infants seen by us have not received MenHibrix or Menveo as a part of their routine immunization schedule. As a result, Menactra is usually the vaccine of choice for us and we administer the vaccine at 2 years of age.)

It should be noted that after vaccination against meningococcus, serologic studies conducted for infants and young children showed that there was a decline over the years in the protection afforded by the vaccine.³⁵⁻³⁸ Antibody titers in a significant proportion of the immunized population fell to non-protective levels. As stated in the *Morbidity and Mortality Weekly Report (MMWR)* published in March 2013, the duration of protection after the prescribed booster dose in adolescents, given at ages 16 through 18 years, is not known although protection is expected through at least age 21 years.³⁴ This is especially crucial since asplenic persons have a mortality rate of 40-70% when infected with *N. meningitidis*, the organism responsible for meningococcal disease.³⁹ Individuals with asplenia generally have lower antibody titers against meningococcus after vaccination than would be seen in a healthy individual.⁴⁰ Meningococcal vaccine is therefore recommended routinely for all persons ages 11 through 18 years. However, in those

with functional or anatomic asplenia, e.g., those who have undergone surgical splenectomy, a booster dose should be administered every 5 years; if the child has received the primary series before his/her seventh birthday, he/she should receive the first booster dose in 3 years and subsequent doses every 5 years (<http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6202a1.htm>).

Pneumococcal Vaccination

The four dose series of PCV 13 vaccine should be administered at ages 2, 4, and 6 months of age and again at age 12 through 15 months. If the child has received an age-appropriate series of the 7-valent PCV (PCV7), then a single supplemental dose of 13-valent PCV (PCV13) will be sufficient.

In addition to PCV13 vaccine, PPSV23, the 23-valent vaccine against polysaccharide antigen, is administered at 2 years of age and usually at least 8 weeks after the receipt of PCV (either 7 or 13) vaccine. While previously the PPSV23 vaccine was given at 2 years, 5 years, and again every 5 years thereafter, it is now recommended that a single revaccination with PPSV23 should be administered 5 years after the first dose in children with sickle cell disease and then not again until the age of 65 years. However, it may be necessary to consider separately as an especially compromised group those who have had pneumococcal disease in the past, as these individuals may require a periodic check of their anti-pneumococcal antibodies to ascertain whether they have adequate, protective titers against serotypes of pneumococcus. It is not known if surgical splenectomy so predisposes one to infection with encapsulated organisms that revaccination or administration of booster shot might be necessary.

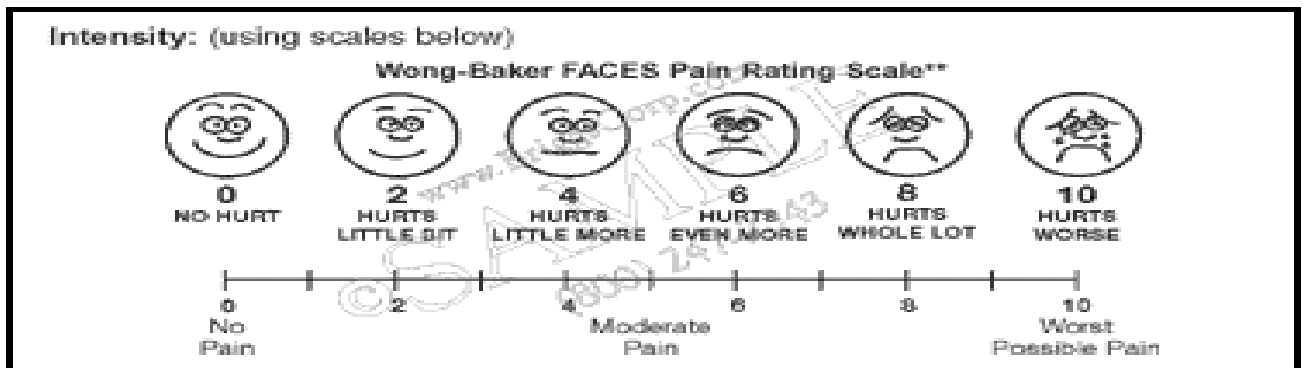
Vaccination

Vaccine	Birth to 2 years	2 years	5-7 years	10 years	15 years	20 years
Hep A/B*						
H Infl						
PCV13						
PPV23						
Influenza						
Meningococcal						

Treatment of Pain

Pain (sickle cell crisis or vasoocclusive crisis) is the hallmark of sickle cell disease. Pain can be induced by a number of factors. These include hypoxia, febrile illness, physical or even emotional stress, temperature extremes or abrupt changes in temperature, dehydration, or being at high altitudes. Many times, however, a specific trigger cannot be identified. Although the pain may occur at any time, it appears to preferentially come at night. Its duration is variable but the average length of a pain crisis is 7 to 10 days. Pain can be intense. However, especially in older individuals---adolescents and adults---, chronic pain may sometimes supersede that of acute vasoocclusive episodes and become the predominant complaint. Teaching a patient to differentiate between pain that is chronic and that which is more acute may be necessary to enable the individual to live more easily and productively, in the face of the chronicity of their discomfort. Most patients remain pain-free between episodes.

When confronted with the child who presents with pain, the physician must determine the nature of the pain, as well as its location and severity. Obviously, measurement of severity is subjective. However, it is necessary to ask the patient, when the child can communicate clearly with medical staff, how he/she might rate the severity of pain. Seeking some consistency in this rating process, we utilize the Wong-Baker Faces Scale,^{41, 42} and allow the child to



indicate what the level of pain might be. Another question that must be asked of the parent or child is the length of time the patient has had pain and what analgesics have already been used. It is particularly important to ask whether the analgesic employed was narcotic or non-narcotic and when the last dose might have been given. One must know whether there are associated symptoms, such as fever or evidence of dehydration and what analgesic the patient had been given previously during past admissions for pain, and whether it was effective or was associated with adverse side-effects. Giving patients a choice of pain medication, if such choice is reasonable, allows a sense of empowerment and also of involvement in one's own care.

The physical exam should focus on the vital signs, the state of hydration, degree of pallor, evidence of infection, spleen size and the presence of any neurologic or priapic signs. Laboratory data that will be necessary for proper evaluation of the patient should include a CBC with differential and platelets, as well as reticulocyte count that can be compared with the patient's baseline values; comprehensive metabolic profile; urinalysis; and, if fever is present, cultures as presented above. Radiographic studies should be obtained only if there is indication of respiratory symptoms or possibly bone infection. Similarly, an abdominal ultrasound could be obtained if the patient has right upper quadrant or epigastric pain, since such pain might be a sign of cholelithiasis or, worse, cholecystitis.

Emergency Room Care and Assessment. If pain is mild or moderate, treatment could conceivably be rendered solely in the Emergency Room. The pediatric hematologist should be notified of the presence of the patient in the Emergency Room and that individual will advise on treatment. Treatment should begin within 30 minutes of triage or within 60 minutes of registration.⁴³ The patient should be started on intravenous fluids, e.g. D51/2 NS with 10 meq/L KCL, at 1x maintenance fluid rate. If the patient is deemed dehydrated, then a fluid bolus of 10 ml/kg D5NS can be given. The patient's pain should be rated using the Wong-Baker Faces scale. Intravenous morphine or dilaudid (according to the patient's expressed preference or based on prior record of efficacy) should be administered at a dose of 0.1-0.15 mg/kg (morphine) or 0.015-0.02 mg/kg (Dilaudid). The patient should be assessed carefully and often (e.g., every 15-30 minutes) thereafter for response to the analgesic. The dose of narcotic analgesic can be then repeated within 1-2 hours. If the physician's

assessment is that the dose of analgesic may have been insufficient to achieve pain relief, escalation of the dose by 25% can be made until pain is controlled. Demerol (meperidine) should be avoided as it is known to lower the threshold for seizures in children.^{44,45} An initial pulse oximetry reading should be performed. O₂ saturation should be maintained at $\geq 92\%$. Hypoxia will indicate the need for oxygen by nasal cannula or face mask. If hypoxia is present, it is imperative that a chest X-ray be obtained to determine if there is pulmonary pathology present. If pain relief has not been achieved after two doses of morphine, the patient should be hospitalized for IV fluids and narcotic analgesia.

In-patient Care and Assessment. Once the patient becomes in-patient, vital signs should be monitored closely and the patient should be continued on IV fluids. The presence of fever will indicate the need for a sepsis workup and empiric antibiotics. If the hemoglobin of the patient is 1.5-2.0 g% lower than baseline or if there is hypoxia or signs of respiratory distress such as might be seen with Acute Chest Syndrome, transfusion of prbcs may be necessary.

Treatment measures consist of the following:

1. If the child is 6 years or older, they may be sophisticated enough to understand the mechanics of a patient-controlled analgesic (PCA) pump. There is significant individual variation, however, as to the ability of a child to understand the workings of the machine and there may be younger children who can also operate the pump without any difficulties. The PCA pump allows the patient some autonomy with regards to administration of his analgesic and allows a less uneven level of drug in the bloodstream of the patient, while making it unnecessary to wait for longer periods of time for a nurse to administer pain medication. Some patients will aver that they prefer bolus administration on a prn or even scheduled basis. We have tended to discourage this since the use of intermittent prn dosing is associated with too much waxing and waning of levels of analgesic, making pain control less optimal.⁴⁶ This mode of narcotic administration has also occasionally been associated with the achievement of a "high" and narcotic dependence.
2. Morphine sulfate is the usual drug chosen by most of the physicians treating patients with sickle crisis. Please see the accompanying PCA morphine order sheet for an example of how the medication can be ordered. A similar order sheet is also included for hydromorphone (Dilaudid). Many patients have been previously admitted for multiple episodes of pain crisis. Some of them have also been prescribed narcotics for home use. For this reason, they may have developed a tolerance for narcotics and starting doses may need to be higher than those that would be used in individuals with no history of prior narcotic exposure. We have therefore asked physicians admitting these individuals to the ward to familiarize themselves with the patient's previous admissions for pain crisis and use a starting dose for narcotic that was the highest dosage level achieved and yielding success in alleviating pain during that prior admission. The medication dose can then be lowered or weaned as tolerated and dictated by the patient's clinical course. Alternatively, Dilaudid may be the drug of choice for the patient. As stated previously, patients should be questioned about their pain medication of choice and, if appropriate, given that medication.
3. Ketorolac (Toradol) is a nonsteroidal anti-inflammatory drug that is often given in conjunction with the opioid analgesic at a dose of 0.5 mg/kg /dose (30 mg maximum dose) IV q6-8 hours. The

patient should have no evidence of gastritis or ulcer, bleeding disorder, dehydration, or renal impairment. Ibuprofen should not be used together with Toradol due to concerns about overlapping or additive toxicities.

4. Ibuprofen can be used at a dose of 10 mg/kg/dose po q 6-8 hours. (However, again, this drug also should not be used if there is a history of gastritis, ulcer, bleeding disorder, or renal dysfunction).
5. Oxygen delivery by nasal cannula or face mask may be necessary to keep the patient with adequate oxygen saturation; pulse oximetry should be performed (continuously if PCA is used) and baseline capillary blood gas should be obtained. Oxygen may be requested by some patients who are not hypoxic but they may feel that it is a “comfort” measure.
6. Heating pads or heat packs may be offered since they are frequently felt by the patient to ameliorate pain.
7. Once opioid analgesic has been started, care should be taken by the medical team to relieve or prevent narcotic-induced constipation and to relieve associated nausea or pruritus. Colace, lactulose, or Miralax may be used to treat or prevent constipation, while patients may utilize Benadryl or Atarax to counter the itching. Ondansetron (Zofran) is employed for treatment of nausea.
8. Pain control should be assessed on an on-going basis by the staff. Special attention should be paid to possible side-effects such as oversedation, hallucinations, or allergic manifestations, among others. As noted, analgesics should be weaned as tolerated, by decreasing progressively the doses of either bolus or basal opioid, as tolerated by the patient.
9. It is important to remember that addiction is not a common problem experienced by patients with sickle cell, especially among children. Often, in adults, there may be the impression of addiction or drug-seeking behavior, even of drug-hoarding. However, the majority of individuals with sickle cell disease do not develop addiction⁴⁸ and their behavior may often be influenced by the attitude and insensitivity of some caregivers that, at times, may border on typecasting or stereotyping or appear to the patient as callousness.
10. Careful and continuous monitoring for hypoventilation is imperative while the patient is on the PCA pump. If any patient becomes oversedated while on the drugs, the infusion of the narcotic should be halted and narcan given to reverse the narcotic effect. Subsequent doses should be reduced and the patient monitored closely to avoid recurrence of respiratory or sensorial depression.
11. The patient should be encouraged to ambulate or engage in activities that will get him/her mobilized. This is done to minimize the chances of the patient’s incurring Acute Chest Syndrome, since immobilization can lead to the development of atelectasis and predispose to localized pulmonic hypooxygenation and subsequent sickling or vasoocclusion within the lungs. Incentive spirometry is also utilized to prevent atelectasis and should be performed at least every two hours while the patient is awake (or with each commercial break during television programming).
12. Occasionally, the physician may request the assistance of psychologists and/or social workers if there appears to be a psychosocial component to the pain experienced by the patient. Please note that the patient is always given the benefit of the doubt regarding attestation of pain. However, the child may sometimes derive benefit from the use of biofeedback techniques or psychological counseling. Alternative therapies have not been used often but have rarely been

used to bring about relief of pain in the patients. These have included acupuncture and massage therapy, as well as use of TENS (transcutaneous electrical nerve stimulation) units for treatment of pain that might be of a more chronic nature.

13. We have also encountered children and young adolescents whose pain may be somewhat atypical and therefore different from their usual pain crisis. A patient may state that they are having “pain all over.” If the pain appears to be more chronic or indolent, we have at times requested a consult from the Rheumatology team. A diagnosis of alternate etiologies such as fibromyalgia has, at times, been made and patients having been placed on medications such as amitriptyline, lexapro or neurontin as indicated, may achieve relief or, at least, better control of their pain.

Acute Chest Syndrome

Acute Chest Syndrome (ACS) is a leading cause of morbidity and mortality in patients with sickle cell disease.⁴⁹⁻⁵⁴ It is defined as the acute onset of respiratory decompensation, characterized by chest pain, fever, cough, shortness of breath, and development of respiratory distress. Patients must have a new segmental infiltrate on Chest X-ray, usually basilar but not always so, with at least one of the following findings:

- Fever
- Tachypnea
- Cough
- New-onset hypoxia
- Increased work of breathing (retractions, use of accessory muscles including abdominal musculature, nasal flaring), and chest pain.

Pain may not have been originally or presently confined to the chest but may have started in the extremities or abdomen. Fever is seen without an obvious source. The patient may have a normal lung examination initially and there may be no initial radiographic findings to suggest disease. The evolution of infiltrate may instead lag behind the clinical deterioration.

Individuals complaining of substernal, rib, or upper vertebral pain may be especially prone to developing ACS. Pain may prevent adequate expansion of the lungs and atelectasis will then result. Incentive spirometry may help in preventing such segmental atelectasis and it is vital to get the patient to understand the importance of cooperating with any respiratory therapy that is ordered, including spirometry. The patient is asked to use the spirometer every 2 hours while he/she is awake or with each commercial break while watching television. But it is also equally critical to adequately treat pain that is experienced by the patient since alleviation of pain may allow the desired cooperation and respiratory effort that is needed. Careful monitoring of oxygen saturation must take place since the onset of unexplained hypoxia may augur the onset of pulmonary infiltrate and development of ACS. Hypoxia should be an indication for transfusion of the patient with packed red blood cells (prbcs) with the intent to raise the patient’s hemoglobin to 10-11 gm%.

Etiologies for ACS include infection, fat embolism, atelectasis or pulmonary edema, although most of the time the etiology is unknown. Documentation of a bacterial etiology is rare. In those in whom a bacterial association was found, the organism most often associated with ACS was *S. pneumoniae*. Prior to immunization with H. Flu vaccine, H. influenza was also seen as a possible causative agent. However, most infections that might lead to acute chest syndrome are either viral or due to atypical organisms such as *Chlamydia* and *Mycoplasma*. Because of the occasional presence of bacterial pneumonia with ACS, antibiotics are administered routinely to patients with this complication. The antibiotics chosen are similar to those employed for the treatment of febrile illness. Broad-spectrum coverage with ceftriaxone and the inclusion of macrolide therapy, usually azithromycin, must be instituted as quickly as possible. If there is no improvement in the patient's status within 24-48 hours, Vancomycin can be added to the antibiotic regimen.

Care should be taken to avoid overhydration or fluid overload and patients should be hydrated with ½- to 2/3 maintenance IV fluids. Intake and output should be measured carefully and attention should be paid to the patient's vital signs, in particular respiratory rate.

As noted, simple blood transfusion can be given to those with SS Disease to achieve a hemoglobin of ~10 gm%. (However, if the patient's baseline hemoglobin is ≥ 9 gm%, simple transfusion may result in the patient's blood becoming hyperviscous, a state that will be counterproductive, since hyperviscosity may impede proper oxygenation. For that reason, those with SC disease or S- β^+ -thalassemia will require exchange transfusion because of their higher baseline hemoglobin and the concerns had about causing hyperviscosity once transfusion is given.) Units of blood should be requested that are leukocyte-poor and, importantly, sickle cell-free (so as to avoid risk of further sickling). If clinical deterioration of the patient is seen, despite recent simple transfusion, exchange transfusion may be necessary. In that event, the Transfusion Medicine specialist/Director of the Blood Bank must be notified and arrangements made for exchange transfusion with the intent of reducing the patient's hemoglobin S to <50% (or ideally <30%) and achieving a hemoglobin again of about 9-10 gm%.

Please note that exchange transfusion should be performed in the Intensive Care Unit after the placement of a pheresis catheter, to permit free flow of blood during the exchange. [Randomized trials to investigate the comparative efficacy of exchange transfusion vs. simple transfusion have not been performed. A comparative study of 20 simple transfusion patients and 20 exchanged patients showed no significant difference in efficacy in the treatment regimen for ACS.⁵⁵] During the exchange, careful monitoring of platelet numbers and calcium (and magnesium) is warranted and calcium and magnesium replacement may be necessary during the procedure. The femoral or central venous catheter that is placed should be removed as soon as possible to reduce the risk of thrombosis in the blood vessel that has been used.

Chest X-rays should be monitored on a daily or every other day basis, although one should remember that there is often a lag between radiographic progression (or improvement) and the patient's clinical state.

Bronchodilator therapy, usually in the form of albuterol, should be given along with oxygen therapy, especially if the patient has a history of reactive airway disease or wheezing on exam. Chest physical therapy may not be tolerated by the patient with ACS due to the preexistent pain in chest or ribs.

However, supervision by individuals from the Respiratory Therapy team will be crucial in the care of patients with this disorder. Oxygen saturation will, of course, be watched closely. However, the regular performance of blood gases is necessary, to determine when dangerous levels of carbon dioxide have accumulated, raising the risk of respiratory failure and indicating the need for intubation and ventilator support. Other parameters that may tell us that the patient is in need of ventilatory support include an increasing work of breathing, increased oxygen requirement with inability to raise the oxygen saturation to $\geq 90\%$, rise in carbon dioxide, and fatigue observed in the patient as he struggles to breathe.

If there are signs of fluid overload, then the patient can be given furosemide (Lasix) to induce diuresis. The role of steroids is not known.

Recurrence of ACS is relatively common and can result in significant lung dysfunction either immediately after an episode or over time. Adults who had experienced recurrent ACS were left with lower median forced vital capacity, and total lung capacity.⁵⁶ It is therefore suggested that individuals who have experienced ACS be offered either hydroxyurea or chronic blood transfusion (or sometimes, both) with the intent of prevention of future episodes.

Aplastic Crisis

Sickle cell disease is characterized by a shortened red cell life with a red cell survival of 15-50 days,⁵⁷ as opposed to the approximately 120 days of a normal red cell. Because of this decrease in red cell survival, the bone marrow usually responds by increasing marrow output 6-8 times the rate seen in a normal individual. Aplastic crisis refers to an exacerbation of anemia seen usually after a viral or, at times, bacterial illness and caused by a temporary cessation of bone marrow activity. Without compensatory reticulocytosis, the hemoglobin/hematocrit may fall as much as 10-15% per day. Parents are then instructed to call the physician or hematologist if they notice easy fatigability (more than would be seen in the child normally) and pallor. Jaundice is not ordinarily seen as a manifestation of this complication. Splenic enlargement should not be observed. A CBC can be obtained by the child's physician, hematologist, or Emergency Room staff member. The hemoglobin will be below the child's baseline and the reticulocyte count will be markedly depressed. (it is therefore essential that there is a record of the child's baseline hemoglobin and reticulocyte values that can be readily accessed by medical personnel; equally important is emphasizing the importance of these values to the child's family so that they can easily relay such information to individuals who may not be familiar with their child or have no such information access.)

Treatment of aplastic crisis and Instructions to Parents

1. Parents and patients should be instructed on the symptoms of aplastic crisis: fever, pallor, fatigue, malaise, shortness of breath, and/or syncope.
2. If such symptoms are present, then the parents should call the physician immediately and come to the Emergency Room
3. One should question the patient or family about duration of pallor; recent onset of lethargy, shortness of breath, rapid breathing, or high heart rate, as well as decreased exercise

- tolerance, presence of recent or current infection, rash, or fever, and exposure to sick contacts
4. Exclude presence of spleen and liver enlargement (they may sometimes be coexistent). Physical findings may include pallor, tachycardia, tachypnea, lethargy. With extremely low hemoglobin values, the patient may be in actual heart failure.
 5. Obtain CBC, differential, platelet count with reticulocyte count. (This testing should be repeated daily.)
 - a. Patients should be admitted to the hospital for a significant decrease in their baseline hemoglobin >1.5 - 2 gm% and a low reticulocyte count. Remember that knowledge of the child's baseline reticulocyte count is critical here, since a child's baseline might be $>21\%$ and the presenting reticulocyte value, while high, e.g. 11% , still represents a decline from the child's normal reticulocytosis.
 6. Type and screen/crossmatch blood. If the child appears stable and does not have clinical signs that signal possible development of congestive failure (tachycardia, rales, gallop), and if the hemoglobin is not significantly below baseline, it may be possible to monitor the patient, even as an outpatient, and avoid prbc transfusion. However, if the hemoglobin has dropped >1.5 - 2 gm% or if it is <5 g% with no evidence of erythroid recovery, admission will be necessary and preparations should be made to transfuse the child. Similarly, if the patient shows signs of cardiovascular compromise or appears toxic or unstable, then transfusion of packed red blood cells should be given. It is understood that the child may require continuous cardiopulmonary monitoring, such that cannot be performed on the regular ward; this would necessitate transfer to the PICU.

The amount of blood in the aliquot that will be given will depend upon the patient's presenting hemoglobin level. As an example, if the patient is tachycardic and showing signs of incipient or actual decompensation, and has a hemoglobin of 3 gm% upon presentation, one would elect to place the patient in the Intensive Care Unit where he can be continuously monitored. The patient would then begin with a small aliquot of leukocyte-poor and sickle-free blood at an initial rate of 3 cc/kg to be given over 3-4 hours. This procedure could be repeated in 1-2 hours and then the hemoglobin would be measured. Depending on the subsequent hemoglobin measurement, transfusion could be repeated with the administration of blood at ≥ 5 cc/kg again over 3-4 hours until the patient's hemoglobin concentration measured 7-8 gm%.

7. A chest X-ray should be obtained to search for signs of respiratory illness or cardiovascular compromise. If anemia is severe, oxygen may be indicated. IV fluids should not be given above maintenance and generally if used, would be given at a rate that is no greater than $\frac{1}{2}$ maintenance between aliquots of blood, to avoid fluid overload.
8. While other viruses also are capable of causing marrow suppression, parvovirus B19 infection has been linked most often with this problem.⁵⁸ IgM and IgG titers for parvovirus should be ordered. (PCR for Parvovirus, of course, can be ordered instead and will be more sensitive but more costly.) They may be negative but if so, should be repeated 6 weeks later to check convalescent titers that then may have become positive.

9. Patients may sometimes be discharged before they have recovered their baseline hemoglobin or reticulocyte level. It is extremely important that adequate follow-up be arranged with the primary care physician or the hematologist after discharge. This follow-up should take place within a week of discharge so that the CBC and reticulocyte count can be checked. This testing will continue sequentially until the patient's counts have returned to his/her norm.
10. One should also use isolation during the hospitalization of these patients since they may be infectious. Spread of the virus occurs through either direct contact with feces, via droplet transmission, and also through blood or blood products. (Dogs can sometimes be a source of infection as they also may contract Parvovirus infection.) Surveillance of those who have been in contact with the infected individual should be considered, especially for those in contact but having immunocompromise, or for those who are pregnant. Other individuals in the home may have been exposed as well and it should be suggested to their primary physicians that those children/adults be followed and possibly have complete blood counts checked.

Sequestration Crisis

Splenic sequestration is a leading cause of death in children with sickle cell disease.⁵⁹ Symptoms of anemia are accompanied by abdominal distension and tenderness to palpation often of the left upper quadrant, and most importantly, enlargement of the spleen that is, at times, massive. The child, when seen in the Emergency Room, may be hypotensive and, if the hemoglobin has dropped enough, have evidence of congestive heart failure. The hemoglobin level is usually at least 2 gm% lower than baseline and is accompanied by a brisk reticulocytosis. Thrombocytopenia may be present since these cells can also be sequestered. This complication can be seen as early as 8 weeks of age. Recurrences are frequently seen and can be associated with high mortality rate.*

1. Parents should be taught on their initial clinic visit how to palpate the spleen of the child.^{60, 61} This training should be reinforced on subsequent visits. Parents are instructed to contact the hematologist or primary care physician if the child has developed abdominal distention and/or discomfort, irritability, increased pallor, lethargy or fatigue. They should be reminded that fatigue may entail more frequent and prolonged naps, excessive sleepiness, decreased suck or falling asleep before the prescribed bottle has been finished. If the spleen is palpated, then parents should reference what the child's splenic size is so that size can be followed.
2. Once the physician has been informed of a potential sequestration episode, the Emergency Room physicians should be notified of the child's imminent arrival. The patient should be triaged immediately and emergently.
3. Questions to be asked include: Duration of symptoms; associated symptoms such as fever; previous spleen size; baseline CBC and reticulocyte values; prior episodes of splenic sequestration.
4. The patient should be assessed for spleen and liver size. Vital signs should be obtained with a special eye to identifying hypotension, threadiness of pulse and other evidence of shock. Evidence of cardiovascular or cardiopulmonary decompensation should be looked for and the child's neurologic status should also be assessed.

5. Laboratory data that is required include: CBC, differential, platelet count, and reticulocyte count; type and crossmatch (if there is cardiovascular instability that does not permit performance of a type and crossmatch, then O-negative blood should be utilized for transfusion). If possible, use minor-antigen-matched, sickle-negative, leukocyte-poor packed red blood cells.
6. As would be expected and as outlined in the section above on “Febrile Illness”, if fever is present, then a sepsis workup should be performed and is to include blood cultures, urinalysis, and urine culture. If there are respiratory signs present, then a chest X-ray will be obtained. Antibiotics will be administered, as outlined above.
7. Patients who have been assessed to have cardiovascular decompensation should be placed in the Intensive Care Unit where continuous monitoring of vital signs can take place. The patient should be placed on continuous pulse oximetry monitoring. Transfusion should be initiated as soon as possible. Again, the rate of infusion of the blood will depend on the degree to which the patient is anemic and also upon his cardiovascular status. However, take the example of a 15 kg child who presents with a hemoglobin of 2 gm%. This child must be viewed as at extreme risk for going into or being in heart failure or cardiopulmonary decompensation. This child should be sent immediately to the PICU. There with continuous monitoring, the patient might be, if in shock, transfused with say, 5 cc/kg prbc. The hemoglobin should be checked within ½ hour of the transfusion’s completion. A second transfusion could then be performed.
8. It is important to remember that fluid resuscitation for patients with hemodynamic compromise must be cautiously administered. The administration of blood is the prescribed treatment for this emergency, rather than vigorous and rapid administration of intravenous fluids. If fluids must be given while one is waiting for blood to be delivered for the child, then they should be given carefully with continuous monitoring of the child for the onset of hemodynamic instability.
9. With transfusion of red cells and the arrival at a higher hemoglobin, as well as resolution of cardiovascular instability, autotransfusion, i.e. the release from the spleen of trapped red cells and platelets occurs; the spleen decreases in size; and there is often an overshoot of hemoglobin values to a level that is higher than expected. Accordingly, the goal of transfusion should not exceed 8 gm% hemoglobin.
10. The administration of oxygen may be necessary in those with extremely low hemoglobin values or cardiovascular instability.
11. Fever will exacerbate cardiovascular compromise in the face of severe anemia and should be controlled. As noted, an attempt should be made to identify a source of fever, and antibiotics should be initiated immediately. Patients should be treated with acetaminophen at a dose of 15 mg/kg orally q4 hours. Alternatively or additively, ibuprofen can also be given for fever at a dose of 10 mg/kg po q6-8 hours.
12. Once hemoglobin and spleen size have been stable for 24 hours and the patient is taking fluids and medications well, he/she may be discharged. The patient should have been afebrile for at least 24 hours and there should be no culture-positivity. Most importantly,

there should be a clear follow-up plan outlined to the parents with the patient returning to the clinic or office within 1 week of discharge.

13. It has been our practice to recommend surgical splenectomy in any child who has had one life-threatening episode or 2 episodes of sequestration.⁺ When surgical splenectomy has been contemplated for the child who has had multiple episodes but has not yet reached the age where he/she can receive his/her first meningococcal or PPSV23 vaccination (at two years of age), prbc transfusion may be administered monthly until the child has reached the second birthday. Allowing the child to reach this age may mean preservation of splenic immunity until the child can be immunized against pneumococcus and meningococcus.
14. If splenectomy is planned, there should be proof that the patient has received pneumococcal, meningococcal and H. influenza vaccines. If such proof does not exist, then the patient should be immunized at least 6-8 weeks before splenectomy is to be performed.^{62, 63}
15. Sequestration can occur in the liver as well. This is important to remember, as the individual who has undergone splenectomy, whether auto- or surgical, can present with tender, enlarged liver, increased anemia, reticulocytosis, and hyperbilirubinemia. Usually, sequestration in the liver is not associated with cardiovascular collapse, due to the lesser distensibility of the liver but its treatment (transfusion) is the same as that for splenic sequestration.

*Educating parents on the technique of palpating the spleen and also instructing them to seek medical attention for their child if they suspect splenic sequestration has been largely successful in bringing about a decrease in the fatality rate incurred with splenic sequestration.⁶⁴

+Some have instituted guidelines that dictate that elective splenectomy should be performed after one episode of sequestration. This may be a correct approach since recurrence was found in 67% of patients in one cohort.⁵⁹

Stroke and Other Neurologic Event(s)

Sickle Cell is a vasculopathy (i.e., disorder in which vascular abnormalities are a key feature of disease).⁶⁵ Sickle Cell Disease is the second most common cause of stroke in children.⁶⁶ The underlying lesion is most commonly disease of large vessels (in the child),[^] in particular of arterial vessels, such as the internal carotid, and middle or anterior cerebral arteries. The lumen of the vessel may be narrowed or completely obliterated due to intimal hypertrophy. This complication occurs in 6-12% of patients and causes significant mortality and morbidity in these children. Not only must parents be educated about the risk of this complication in children with sickle cell disease, but physicians in the general medical community must also be taught about the signs and symptoms of this problem, since our experience has told us that the symptoms of stroke may be missed or misassigned to other less serious disorders. Occasionally, patients will present with symptoms of unilateral weakness, dysarthria, drooling, facial palsy, and dysphagia. These symptoms may resolve by the time the child is seen in the Emergency Room or physician's office. This event, however transient, may augur the later

development of stroke and is evidently a transient ischemic attack (TIA). TIAs are focal neurologic deficits that persist <48 hours (<24 hours for internal carotid, anterior, or middle cerebral arteries and <48 hours for vertebral or basilar arteries). The child will be left with no permanent or residual deficit after a TIA. The presence of these symptoms, or of gait disturbance, other speech defects, focal seizures, and hemiparesis are the most common signs of stroke. Infarction is usually seen segmentally on MRI. The performance of MR angiography (MRA) is required to demonstrate narrowing or complete occlusion of the vessels in the Circle of Willis.

Treatment of stroke is outlined:

1. Parents should be told to call the hematologist and come to the Emergency Room immediately if any changes in the child's neurologic status are noted. These include
 - numbness of extremities or face
 - weakness and inability to use one's limb(s)
 - confusion
 - somnolence
 - seizures
 - slurring of speech
 - difficulty swallowing
 - severe headache.

The Emergency Room should be notified of the child's imminent arrival at the hospital.

2. Once the child has arrived in the Emergency Room, he/she should be carefully evaluated for the presence of neurologic sequelae that indicate the presence of stroke. A complete neurologic assessment should be performed. Prior history of trauma, duration of symptoms, and results of any previous CNS imaging studies should be recorded.
3. Diagnostic imaging should then be obtained. A non-contrast CT scan may not be positive for infarction in the first 6 hours of ischemia but it should allow visualization of hemorrhage or nonischemic causes. However, MRI will give the best visualization of areas of ischemia and will do so within minutes of the brain injury. (TCD is not a tool for assessment of acute stroke.)
4. Once stroke has been confirmed, the patient should then be transferred to the Intensive Care Unit, where he/she can be stabilized and monitored continuously. A femoral or central venous catheter should be placed by surgical or intensive care personnel.
5. The following labs should be obtained:
 - CBC, diff, platelets and reticulocyte count (it is best to have a record of the patient's baseline values to allow comparison)
 - Coagulation profile. While the patient most likely does not have an underlying coagulopathy, it should be remembered that patients with sickle cell disease are, on average, hypercoagulable. Although it is not absolutely necessary to perform a hypercoagulable workup in everyone, the screening for such an underlying state should be considered if the patient's history so dictates or there are other risk factors present.
 - Electrolytes (should be repeated daily)

- Type and crossmatch for exchange transfusion
 - If patient is febrile, then cultures of blood and urine should be obtained. Also consider CSF culture; performance of LP should proceed if the patient is stable enough to undergo this procedure and there is no clinical or radiographic (MRI) evidence of increased intracranial pressure
6. Contact the director of the blood bank and notify them of the intent to perform erythrocytapheresis or exchange transfusion. While simple transfusion of prbc to achieve a hemoglobin of 10 gm% may at times suffice as treatment of acute stroke, erythrocytapheresis is the treatment of choice. Remember that blood should be sickle-cell free and leukocyte-depleted. Most patients will undergo exchange transfusion with the goal of achieving a hemoglobin of ~10 gm% and a HbS percentage of $\leq 30\%$, as verified by hemoglobin electrophoresis after the procedure.
 7. Consult neurology. The neurologist should be aware of the child's condition and assist in the evaluation of the child's neurologic deficit, whether acute or residual. Also, if there is any indication that there is elevation of intracranial pressure or hemorrhage, the Neurosurgeon should be asked to see the child. If there is increased intracranial pressure, then the child should be treated accordingly.
 8. If seizures are present, place the patient on anticonvulsant therapy.
 9. IV fluids should be given at a rate of $\leq 1X$ maintenance.
 10. The intravenous catheter used for exchange should be removed as soon as possible to avoid risk of thrombotic complications.
 11. Maintain O_2 saturation $\geq 92\%$.
 12. At Children's Hospital, Neuro-Rehabilitation will be arranged by neurology staff once the patient has stabilized and is deemed ready for such therapy. Once the child is placed on the Neuro-Rehab unit, he/she will be assessed by Physical Therapy, Occupational Therapy, Speech and Hearing, and Psychology. Therapies will be established according to the child's needs.
 13. Psychometric testing should also be performed to assess the patient's intellectual functioning. This should be performed at some point after stabilization of the child's neurologic status. Parents should be informed of the results of the testing and of any deficits that might subsequently worsen; they should also be informed if the child's condition suggests that there is a plateauing of the patient's neurologic status, i.e. improvement is unlikely thereafter. In that event, the parents of the child should receive assistance or guidance in seeking special needs assessment, 504c accommodations, or other educational adaptations that may be necessary to allow reentry into school.

1^o Stroke Prevention

Transcranial Doppler (TCD) Ultrasound screening is now widely used for the prevention of stroke in children with sickle cell disease, after this methodology, adopted in the 1990's and substantiated as a valid preventive technique through the STOP study, was proven to identify those individuals with sickle cell disease having vasculopathic changes in the Circle of Willis.⁶⁷ Several studies have since been published

that appear to validate the efficacy of TCD in preventing stroke in this population of patients.⁶⁸⁻⁷¹ They include a study from California that was performed retrospectively, in which the rate of stroke in children diagnosed with sickle cell disease declined from 0.44/100 person years to 0.19/100 person years.⁷¹ A prospective study examining the efficacy of TCD⁷² was subsequently performed; after the institution of TCD screening, the cumulative risk of overt stroke by 18 years of age was 1.9%, a rate significantly reduced from that of 11% reported earlier by the Cooperative Study of Sickle Cell Disease (CSSCD).⁷³

The guidelines that have evolved are as follows:

- As recommended by the American Heart Association, TCD should be performed annually for stroke prevention in all children, 2-16 years, who have homozygous SSD. We have also screened those having S-beta⁰-thalassemia and those with SS-HPFH or high F. Those diagnosed with SC disease or S-beta⁺-thalassemia are excluded from study due to their very low risk of incurring stroke.

Mean TCD velocities are measured in the internal carotid artery or middle cerebral artery. Interpretation of mean velocities in these vessels is shown in the Table below:

Mean TCD Velocity	Interpretation	Action
<170 cm/sec	Low Risk (normal)	Repeat TCD annually
170-199 cm/sec	Borderline(intermediate or conditional)	Repeat in 3-6 weeks; if no change in results, then repeat in 3 months; if no change then, continue every 6 months
>200 cm/sec	High Risk (Abnormal)	Repeat in 3-6 weeks; if no change, then get MRI/MRA; if MRA abnormal, then repeat TCD in 8 weeks. If still abnormal, transfuse. If <200 cm/sec and MRA normal, then repeat TCD in 4 months
<70 cm/sec	Low Flow	Perform MRI/MRA. This result is usually not indicative of high risk for stroke but does merit performance of MRI/MRA

Please note that in normal children, 5-15 years old, the mean TCD velocity in the MCA should be 79+/-13.

To summarize: Individuals considered at low risk for stroke will have TCD monitoring annually.

- Those with conditional interpretations are scanned again in 3-6 weeks. If the scan is then normal, we have monitored them again in 3-6 months. The management of these children has not been clearly mandated. We, however, would continue to monitor such children every 6 months with TCD.
- Abnormal results (i.e., velocities >200 cm/sec) must be repeated, usually in 3-6 weeks. Substantiation of narrowing using the MRI/MRA has been performed by us for those individuals having velocities >200 cm/sec. This allows us to see clearly the stenoses and other vasculopathic

changes in the vasculature, as well as the infarctive changes in the gray matter. These scan results will then serve as a baseline assessment for future comparison.

- Those children found to have abnormal TCDs are then started on chronic transfusion therapy with the goal of maintaining the hemoglobin S percentage below 30%. Maintenance of the hemoglobin at this level was sufficient to reduce the incidence of first stroke in these children. The STOP II study showed that once transfusions were halted in individuals for whom TCDs normalized after transfusion, 34% of these individuals developed high-risk TCD velocities again. An additional 5% of the children suffered stroke.⁷⁴ Nevertheless, hydroxyurea was shown to slow the progression of cerebral vasculopathy in very young children; it was therefore proposed as a substitute for chronic transfusion for stroke prevention. Until recently, however, data had not shown hydroxyurea to be equivalent to transfusion as a means of stroke prevention and it was understood that chronic transfusions needed to be continued indefinitely.⁷⁵ More recent data has countered that prevailing wisdom and more recently hydroxyurea has now been proven to be equivalent to chronic transfusion as a means of maintaining TCD velocities and helping prevent primary stroke.^{75b} In those undergoing transfusion therapy, hydroxyurea should be implemented where possible by continuing red cell transfusion for a period of at least 6 months while adjusting the hydroxyurea dose to its maximally effective level.
- Children undergoing TCD should never be sedated as sedation will alter results of the screening.
- Tests should not be performed during acute illness. If they are, they should be repeated once the patient has recuperated.

Family Refusal to Allow Transfusion

Families may refuse to comply with recommendations to proceed with chronic transfusion. In that event, document clearly that parents have refused to allow the child to be transfused. Explain to parents that the child should be monitored very closely for progressive neurologic deficit and persistent risk of stroke. They should be informed that transfusion therapy is the standard of care for a child shown to be at increased risk for stroke by TCD. Although hydroxyurea has thus far been shown to be inferior to blood transfusion in individuals with abnormal TCD for stroke prevention, in such an instance as this it might be considered as a viable alternative.

2^o Stroke Prevention

Once stroke has been diagnosed, the patient is at increased risk for recurrence of stroke. His risk is quite high; Powars, for instance, reported a recurrence rate within 9 years of 67%, but temporal clustering of recurrence occurred, with 80%-90% of subsequent strokes seen within 36 months.⁷⁶ The sickle cell patient who has suffered a stroke should therefore be placed on chronic transfusion (to be discussed in the section below.) Placement of patients on a chronic transfusion program was demonstrated to reduce the risk of recurrent stroke. Yet, even with transfusion, there was a risk of recurrent stroke of 1.9 per 100 patient-years.⁷⁷

Transfusions

One of the most important principles to be remembered by the physician in encountering low hemoglobin values is that one does not necessarily treat a number but rather an individual. One should be mindful of the symptomatology exhibited by that person; knowledge of the patient's diagnosis and baseline values for hemoglobin, hematocrit, and reticulocyte count; need for determination of length of time the patient has possibly had the "low" value; and one should have an understanding of the patient's underlying condition. It should be remembered that most individuals with sickle cell disease will adapt hemodynamically to low, customary levels of hemoglobin through their increased oxygen-hemoglobin affinity, increased stroke volume and cardiac output, and increased O₂ extraction from the blood, as well by increasing 2,3-DPG in the red cells.⁷⁸⁻⁸¹ They can usually tolerate their anemia reasonably well, unless stressed by increased activity demands or illness. In the sickle cell patient, transfusion is generally performed to replace blood volume, e.g., as in splenic sequestration, or to improve oxygen-carrying capacity, e.g., as in aplastic crisis, or to dilute and replace sickle cells with normal red blood cells, e.g., as in exchange transfusion for treatment of acute stroke or prevention of recurrent stroke.

In the patient with sickle cell disease, the indications for transfusion are not always evidence-based but can be based on physicians' preferential practices or even "tradition". However, those indications that are generally agreed upon and that have good support through evidence-based medicine are listed below:^{82, 83}

Chronic transfusions are typically administered every 3-4 weeks, depending upon the patient's HbS and hemoglobin levels. For instance, if one wishes to achieve a HbS level of <30% as primary stroke prevention, but you note that the patient's HbS level is 60% after transfusion every 4 weeks or is 60% just prior to the next transfusion, this indicates that your strategy of reducing HbS has not been successful and you may then need to transfuse the patient every 3 weeks instead or possibly transfuse a larger aliquot than you have used before. **Strong Indications** for chronic transfusions are:

- Treatment of stroke
 - Treatment of acute stroke
 - Primary stroke prevention
 - Transient ischemic attack (TIA)
 - Abnormal TCD (>200 cm/sec with MRA documentation of vascular abnormality)
- Recurrent acute chest syndrome
- Older or adult patients with sickle cell disease (these patients may require transfusions to maintain hemoglobin levels >6-7 gm%)
- Recurrent, intractable or debilitating pain
- Severe chronic anemia with high-output cardiac failure
- Chronic organ failure, e.g. heart failure

Strong indications for repeated transfusions with limited duration include:

- **Complicated** pregnancy
- Prolonged hematuria
- Recurrent splenic sequestration*

*With recurrent splenic sequestration, transfusion may be given over a limited duration, and is intended to prevent recurrent sequestration until the spleen can be removed, usually when the child is 2-5 years old.

Strong indications for episodic transfusion (simple or exchange): generally used to treat acute complications of SCD

- Severe ACS
- Aplastic crisis
- Splenic sequestration
- Hepatic sequestration
- Priapism **unresponsive to medical therapy**
- Perioperative preparation of patient for surgery^{84, 85} (It is recommended that all patients with sickle cell disease who are expected to undergo **major** surgery should be prepared in advance through transfusion, to achieve a hemoglobin of about 10 gm/dl . Aggressive transfusion has been used by some to achieve a hemoglobin S percentage of about <30%. However, comparison of the more conservative regimen with this more aggressive approach found the conservative regimen to be as effective in preventing perioperative complications with fewer transfusion-associated adverse effects.⁸⁶ Healthy SC disease patients may not require preoperative transfusion therapy.⁸⁷ If, however, they are to go for extensive surgery e.g., orthopedic surgery especially with use of a tourniquet, or surgery expected to extend for $\geq$ 2 hours, then we have performed exchange transfusion to avoid hyperviscosity and to allow achievement of a HbS percentage of <30%.)

Equivocal indications for transfusion are as follows:

- Management of acute priapism (Note here that the acute management of priapism is medical and will involve the combined interventions of urologist and hematologist (To be discussed below).)
- Preparation for infusion of contrast media
- Uncomplicated pregnancy
- “Silent” cerebral infarct (Patients with silent infarcts are at increased risk of suffering an overt stroke in the future.^{88, 89} Until recently, it was not known whether preventive use of transfusions could prevent progression of disease and stroke occurrence. However, recently the results of a controlled trial examining the use of chronic transfusion in individuals with silent cerebral infarction were published.⁹⁰ DeBaun and others showed that regular transfusions led to a significant reduction in cerebral infarction. However, these results have been felt by others to be inconclusive,⁹¹ although discontinuation of prophylactic transfusions were associated with an increase in the risk of silent brain infarction, as demonstrated from a previous study (although uncontrolled).⁹² **At Children’s Hospital, we have taken the approach that these individuals are at increased risk for this future event and should be transfused.** We have not transfused those individuals who have had neurocognitive defect alone; we have then made every attempt to identify an actual neurologic defect on MRI/MRA or TCD prior to the placement of an individual on transfusion therapy.)
- Leg ulcers (These can be notoriously difficult to treat since the skin of the lower leg, particularly over the medial malleolus, is poorly supplied with blood. The ulcers appear to correlate with degree of anemia and transfusion appears to aid in healing. Again, there has been no rigorous clinical trial that validates the practice. At Children’s Hospital, we have transfused those

individuals who have presented with non-healing leg ulcers and have combined this therapy with the physical therapy service's wound-healing protocol(s).)

Nonindications:

- Chronic steady-state anemia
- Uncomplicated acute pain crisis
- Infection
- Minor surgery not requiring prolonged general anesthesia (e.g., dental surgery, myringotomy)
- Aseptic necrosis of the hip or shoulder (unless surgery is planned)

Episodic transfusions are either simple or exchange. The physician may deem that a simple transfusion may be sufficient to treat patients with stroke or acute chest syndrome. This is strictly a judgment call, based upon the severity of the complication for which the patient will be transfused. Simple transfusion may very well be sufficient treatment in some instances. However, if a simple transfusion is to be chosen as a therapeutic regimen, the baseline hemoglobin level should not be greater than 8-9 gm% since transfusion might lead to a state of hyperviscosity, a situation that could even impede recovery.

Exchange Transfusion

If the complication for which transfusion will be used is deemed by the physician to be life-threatening, or if rapid reduction of the HbS concentration to <30% is necessary, and/or the patient is at risk for irreversible tissue damage, then exchange transfusion may be necessary. The performance of exchange transfusion may be performed without risk of hyperviscosity or too rapid expansion of the blood volume or excessive strain on the cardiovascular system. This can be manual or automated. If the child is felt to be able to tolerate the performance of the automated exchange (erythrocytapheresis), then the head of the Blood Bank should be notified immediately, along with the surgeon and intensivist, either of whom should place a pheresis catheter or central line (e.g, Vortex, with double-lumen) through which the procedure can be performed. The patient should be placed in the intensive care unit where he/she can be continuously monitored and replacement of calcium/magnesium/platelets can be performed as needed.

Single volume exchanges should be expected to replace about 65% of the patient's cells whereas a double volume exchange will replace about 85%. In our experience, the HbS level usually has been <30% after a single rbc exchange.

We have relied upon the Pathologist who is a specialist in Transfusion Medicine to help us determine the volume of blood that is needed for exchange and also to help with the coordination of the performance of the exchange which more often than not nowadays is performed via automation (apheresis machine) rather than manually. However, calculation of the volume of blood needed can be made as outlined in The ASH Handbook of 2006:^{92, 93}

Partial Exchange Transfusion

Partial exchange transfusion entails the removal of blood from a central venous line or peripherally from one arm as normal packed red cells are infused in the other arm. The volume of blood volume needed for manual partial exchange in mL is calculated as follows: $(\text{desired HCT} - \text{initial HCT}) \times \text{TBV}$ (60 mL/kg for adult women, 70 mL/kg for adult men, 80 mL/kg in children, 100 mL/kg for infants) / $(\text{HCT of replacement packed RBC [usually 55-60\%]} - [(\text{initial HCT} + \text{desired HCT}) / 2])$.⁹⁴ Generally, we have removed blood in the amount of 5 cc/kg while transfusing the individual with blood in the amount of 10 cc/kg. This approach is generally taken to avoid excessive iron load, especially in those who have evidence of transfusion-associated hemosiderosis. It is generally acknowledged to be less efficient than erythrocytapheresis with adequate chelation in reducing or preventing iron load, but can be elected as a means to effectively reduce Hbs percentage while at least slowing the rate of accumulation of iron.⁹⁵⁻⁹⁷

Tests that need to be performed prior to the initiation of a transfusion program include:

- Complete blood count with reticulocyte count (to be performed prior to each transfusion)
- Type and screen [Blood type with phenotype] (and performed prior to each transfusion)
- Screen for alloantibodies
- Hemoglobin electrophoresis (and performed prior to and after each transfusion)
- Ferritin (every 1-3 months; this may not be the most reliable measure of iron overload but has been utilized by most, including us at Children's Hospital, to monitor iron overload status. We have also at our disposal T2-weighted imaging by MRI which can be utilized for the screening of hepatic iron. Finally, if there are questions re. the accuracy of the ferritin measurement, then consult the GI service so that a liver biopsy can be performed to assess hepatic iron content.)
- Hepatitis panel (A, B, and C)--- to be performed at least yearly
- Verify immunization status for hepatitis A and B. If there is no indication of adequate protective titers, then plan to immunize against the specified virus
- HIV testing (and to be repeated annually)
- EBV and CMV antibodies
- Liver enzymes
- Consider audiometric and eye exam
- ECG/ECHO (yearly and before chelation is started)
- H/H after each transfusion

Blood used for transfusion of sickle cell patients should be leukocyte-reduced (leukopoor) to avoid the risk of allosensitization. It should also be sickle cell-free (i.e., blood from those having the carrier status or trait should be avoided). The blood received by patients with sickle cell disease should be antigen-matched beyond ABO and D to include C, E, and Kell to reduce the risk of sensitization.

The amount to be given with each transfusion should be 10-15 ml/kg)

Preadminister an antihistamine (usually Benadryl) and acetaminophen 20-30 minutes before the transfusion (We have elected to do this routinely although one can elect to give pretreatment only if there is a prior documented history of allergic reaction.)

The transfusion should be administered over 3-4 hours with monitoring of vital signs (using the hospital's customary standard vital sign monitoring).

Notify the blood bank of any possible transfusion reaction, whether fever, urticaria, rash, or evidence of bronchospasm or anaphylaxis. Be sure to send the specimen back to the Blood Bank so that proper testing can be performed, if reaction is suspected.

Iron overload

Iron overload is usually seen after a cumulative volume of transfused blood of 120 ml/kg. Serial ferritin measurements should be performed to determine iron load. Ferritin is, however, an acute phase reactant that may become elevated in times of stress or inflammation or acute illness.

Chelation therapy should begin when the serum ferritin is ≥ 1000 ng/ml. Alternatively, MRI can be requested with T2-weighted imaging. This will allow a look at hepatic iron concentration and is fairly accurate as a means of detecting iron overload in that organ. (Remember that in sickle cell disease iron accumulates in the liver preferentially and before the development of iron overload in the heart; cardiomyopathy secondary to iron overload is usually a later manifestation.)

Once iron overload is suspected, there are several alternatives for chelation therapy. They include:

Desferrioxamine (Desferal) (subcutaneous administration): Desferal should be given SC utilizing a portable pump for mini-infusion over 10-12 hours (therefore it is administered at night) at a usual dose of 20-40 mg/kg/day to a maximum of 2 gm/day for 5 days

Desferal (intravenous administration): This is primarily intended for those individuals whose compliance with home chelation methods has been suboptimal. Desferal may then be given on a weekly basis, usually over a 10-12 hour period with the patient being admitted for the duration of the infusion. High-dose intravenous desferal was shown by Kalpathi et al⁹⁸ to be effective in reducing iron overload in sicklers. A dose of 15 mg/kg/hr IV was given for 48 hours every 2-4 weeks and brought about a significant reduction in liver iron burden. We have instead given a lesser dose, 10 mg/kg/hr, for about 10 hours on a weekly, or at times monthly, basis to hospitalized patients. The dosage should not exceed 15 mg/kg/hour for 12 hours.

Individuals who should be considered for IV desferal weekly include:

- those who have been noncompliant, with ferritin >2500 with persistent liver enzyme elevation
- those with ferritin >5000 ng/ml
- those with cardiac arrhythmia or evidence of congestive heart failure
- those with progressive iron overload despite subcutaneous treatment
- those who cannot tolerate subcutaneous desferal treatment.

Exjade (deferasirox): Exjade is an oral chelator that comes in tablet form, requiring dispersion of the tablet in liquid. A starting dose of 10 mg/kg can be selected but efficacy has been shown to improve with higher doses in the range of 25 mg/kg/day to 35 mg/kg/day. It has been used in children as young as 2 years of age. It should be taken on an empty stomach and at least 30 minutes before food. As noted, it comes in tablet form and must be crushed prior to mixing with water, apple juice, or orange juice. It must NOT be chewed or crushed or swallowed whole. It SHOULD NOT be used with milk or carbonated beverages. Parents should also be instructed NOT to mix the medication the night before as efficacy of the drug is lessened if it is not mixed fresh. The medication should be stored at room temperature and protected from light and moisture.

Exjade should also not be used in those with creatinine clearance less than 60 ml/minute or in those with a preexisting low platelet count ($<50,000/\text{mm}^3$).

JadeNu is an alternative form of deferasirox that has recently come on the market. It has the advantage of being in tablet form but does not require dispersion in water. For many children, Exjade's granular consistency, and purported taste are unpleasant and the medication has also been associated with nausea or gastric upset. These associated characteristics/side effects have led to noncompliance in taking the medication (Exjade). JadeNu is then an attractive alternative to its sister medication with a starting dose of 14 mg/kg given once a day. The dose can be increased as needed by 3.5-7 mg/kg every 3-6 months to a maximum daily dose of 28 mg/kg/day.

Deferiprone (Ferriprox)

Deferiprone is also an oral chelator. The recommended starting dose of deferiprone is 25 mg/kg/dose orally three times a day for a total dose of 75 mg/kg/day (max. dose is 33 mg/kg/dose). Of course, a drawback to this medication is the three times daily dosing, a problem if noncompliance is an issue. Myelosuppression with neutropenia has been seen with this drug⁹⁹ and counts must be monitored very closely while the patient is on this medication. A study is currently being conducted that will look at twice daily dosing but current recommendations are based on the three time daily dosing schedule.

The Child with Sickle Cell Disease and Surgery

Surgery that requires general anesthesia is associated with an increased risk of postoperative complications in sickle cell disease.¹⁰⁰⁻¹⁰² Such complications include vasoocclusive crisis and acute chest syndrome. Data from a prospective, multi-institutional study published in 1996 suggested that preoperative transfusion, whether simple or exchange, should be given to those individuals scheduled to undergo surgery.¹⁰³ The goal was to raise the preoperative hemoglobin level to 10 gm% and, if possible, reduce the HbS to $\leq 30\%$. Elective procedures should allow ample preparation prior to any anticipated procedure. The patient can be transfused 2-3 weeks in advance, the hemoglobin concentration checked, and the patient can be transfused a second time if the hemoglobin level (and/or HbS percentage) has failed to reach the targeted goal. Such a transfusion strategy should be communicated to the surgeon. If the procedure is urgent, the pediatric hematologist/oncologist should be involved in the preoperative management and planning for the patient, from the time of initial contact with the patient.

The patient should be carefully evaluated preoperatively. This will include the following assessments:

1. Detailed history re. diagnosis, coexistent disease, and organ damage, as well as baseline CBC and retic count
2. Review the transfusion history (how many prior transfusions, transfusion reactions, antibodies, and regimen of chronic transfusions)
3. Check for fever, pain, dehydration, or infection and treat accordingly
4. Laboratory Testing needed:
 - Baseline CBC, retic count
 - CMP and indication of renal or hepatic compromise

Chest X-ray, especially in those with history of previous pulmonary complication
Consider ECG/ECHOCardiogram in those with history of chronic iron overload
Baseline pulse oximetry
Type and crossmatch
Hemoglobin electrophoresis, before and after transfusion

Simple transfusion, partial exchange transfusion, or serial simple transfusion:

The goal of the simple transfusion is to increase the hemoglobin to ~10 gm% (see guidelines for transfusion as noted above). However, the goal of a partial exchange transfusion or serial simple transfusion is to achieve not only a hemoglobin of 10-11 gm% but also in some circumstances, e.g., transfusion of a child with previous history of splenic sequestration over a period of months prior to splenectomy, to reach a HbS percentage of 30% or less. Again, the hemoglobin should not exceed 12 gm% in order to avoid problems with hyperviscosity. Note that a patient who is being prepared for non-elective or emergent surgery may require transfusion over a short period of time and will not reach the stated goal of HbS level of 30% or less; nevertheless, they should be transfused to reach a goal of 10gm% hemoglobin prior to surgery.

In patients whose surgery is anticipated to be prolonged, e.g. femoral revascularization or hip replacement or CNS surgery, if time permits, we may wish to opt for erythrocytapheresis as a way to significantly reduce the HbS percentage (usually to <20%).

If major surgery is planned and the patient is known to have had severe sickle cell disease or to have had a past history of pulmonary or other complications, a decision can be made to admit the patient the night before the date of surgery. The patient should then be given intravenous hydration at 1X maintenance prior to surgery.

Intraoperative Management

An oxygen saturation of $\geq 92\%$ should be maintained during surgery. The patient should be given a minimum of 50% O₂ during the surgery. Continuous monitoring should be performed.

The patient should not be allowed to become chilled but should be kept warm (ambient temperature for the operating room should be warmer than usual.)

In surgeries where prolonged use of tourniquet is planned, .eg. orthopedic procedures, one should consider performance of erythrocytapheresis beforehand to minimize the percentage of hemoglobin S on electrophoresis and also of intra- or postoperative sickling.

Blood loss should be monitored closely and blood that is sickle-free and leukopoor should be given intraoperatively as needed.

Care should also be taken to avoid fluid overload. The sometimes used practice of the surgeon's opening the IV to drip as fast or freely as possible should be discouraged, as allowing overload may predispose the patient to the subsequent development of acute chest syndrome in the post-operative period.

Postoperative Management

We would recommend that most sickle cell disease patients who undergo major surgery be observed at least overnight postoperatively. After minor procedures that do not require general anesthesia or that require only brief general anesthesia, e.g., 30 minutes (simple dental procedures or PE tube placement), it might be possible to discharge the patient after a short postoperative observation period, if the patient appears to be stable.

Pulse oximetry should be monitored during the postop period to ensure that the patient is not experiencing hypoxia. O₂ should be administered if necessary to keep the saturation >95%. If the patient has had thoracic or abdominal surgery, it should be anticipated that there may be some difficulty with respiratory effort and the patient should be given O₂ but also should be instructed to perform incentive spirometry. If the patient is too young to understand the workings of the incentive spirometer, then he/she should be instructed on how to do bubble therapy. These procedures should be repeated every 2 hours while the patient is awake. (Or the patient can be asked to perform spirometry with each commercial break while watching TV.) Ambulation should also be encouraged to prevent atelectasis.

Hydration should be administered at a rate of 1 to 1-1/2 times maintenance. Overhydration can result, as noted above, in congestive heart failure and acute chest syndrome. If the patient is dehydrated or if the patient has increased insensible losses, then the fluids should be adjusted accordingly. However, extremely close monitoring of the patient's I/O's should be maintained for any sign of overload. If fluid is retained or there is clinical evidence of overload, then lasix should be administered.

Give analgesics (See section on Pain Control) as needed. This usually involves the use of narcotic analgesia and in those capable of understanding its usage, the Patient-controlled analgesic (PCA) pump

Prevent constipation, especially when using narcotic analgesic; Miralax, Senna, docusate, or lactulose can be chosen for use.

Priapism

Priapism is an unwanted and sustained penile erection that is not associated with sexual activity and that lasts for more than 2 hours. Its prevalence among sickle cell patients ranges

from 6% to 45%¹⁰⁴⁻¹⁰⁷ It can occur in children as young as 2-3 years of age, and can be precipitated by a variety of factors, including fever, cold, nocturnal tumescence during REM sleep, dehydration, full bladder, drug use (cocaine, alcohol, marijuana, testosterone, or sildenafil). There are basically two types, stuttering (multiple, repeated, short episodes) and severe, prolonged (up to >24 hours). Priapism can also be either high flow (arterial) or low flow (ischemic or venoocclusive). The former is rarely seen in Sickle Cell disease while the latter is most often represented in individuals with the disorder and is due to stasis, acidosis, and hypoxia, with resultant sickling within the venous sinusoids of the corpus cavernosa. **After 24 to 48 hours, irreversible changes will occur to the cavernosal smooth muscle and endothelial cells and fibrosis of the corpus cavernosa will take place with resultant erectile dysfunction.**^{108, 109} **Because of this risk, it is imperative that the presence of priapism be greeted with a sense of urgency and prompt management that should be aimed at nonsurgical interventions. Also, patients who presented for medical care within 12 hours of becoming priapic were able to retain normal erectile function.**¹¹⁰

Acute priapism that is limited to short periods of time may be treated at home most of the time. Patients may be instructed to

- Void frequently
- Exercise
- Increase fluid intake
- Soak in a warm bath
- Take analgesics
- Use warm compresses

If the episode has not resolved within 1 hour, the patient should present to the Emergency Room for intravenous fluids and analgesics and admission. The urologist should be consulted immediately.

Upon the patient's presentation to the Emergency Room, he should be asked about:

- How long symptoms have been present
- Has he had previous episodes of priapism, including details of previous hospitalizations and in-patient treatment, home treatments, and what measures, if any, may have already been taken by him to alleviate symptoms or bring the present episode to a halt
- History of transfusion
- History of trauma
- Degree of pain
- Medications taken
- Possibility of sleep apnea. If there is a possibility of this complication, a sleep study should be considered. Once obstructive sleep apnea is documented, a referral should be made to an ENT specialist for further workup and treatment (e.g., T&A).

Although there is no standard of care for priapism, the following measures are generally accepted by most clinicians in the treatment of priapism:¹⁰⁴⁻¹⁰⁷

- Fluids. Administration of Intravenous fluids at 1 to 1-1/2 times maintenance
- Pain management. Give analgesics. These should be parenterally administered narcotics, either via PCA or as intermittently administered boluses as needed.
- Aspiration and irrigation (This is felt to be the first-line therapy for priapism):¹¹¹ Aspiration and irrigation of the corpus cavernosum with saline or α -adrenergic agonists such as epinephrine or phenylephrine should be attempted first. This approach utilizes the smooth muscle contractile properties of the α -agonist that acts on the penile arteries of the corpus cavernosum, causing blood to flow out of the area. (Some urologists have instead advocated the use of β -agonists, e.g. terbutaline. Beta-agonists cause vasodilation by blocking β -receptors. This leads to smooth muscle relaxation of the vasculature which allows oxygenated arterial blood to enter the cavernosa and wash out sickle cells. However, theoretically there is the possibility that with an increase of arterial blood flow back into the corpus cavernosum, the condition could be worsened. There have been no controlled, randomized trials examining the superiority of one type of drug over the other.) Use of phenylephrine is associated with fewer cardiovascular side effects than epinephrine and is actually preferred by the American Urological Association.^{104, 112} A solution of phenylephrine diluted with normal saline to a concentration of 100-500 mcg/ml should be instilled in a volume of 1 ml every 3-5 minutes for one hour. **Aspiration and irrigation should only be performed by a urologist and after conscious sedation and local anesthetic.**

Transfusion. There is no set or established role for transfusion of packed red blood cells in the treatment of priapism.^{113, 114} However, if all else fails, transfusion may be considered. Both simple and exchange transfusions have been employed in the treatment of priapism and response can be seen within 6-8 hours.¹¹⁵ However, detumescence may not occur for 24-48 hours, if it occurs at all. In those who have not achieved detumescence over a period of 12 hours, red cell exchange can be considered but should not delay surgery for priapism that has lasted >24 hours. Exchange transfusion, however, has been associated with the development of neurologic sequelae such as headaches, seizures, and obtundation (Association of Sickle cell disease, Priapism, Exchange transfusion, Neurologic events; ASPEN syndrome.^{116, 117} This is not felt by some to be a strong association and no comparable neurologic symptoms were seen after erythrocytapheresis or partial exchange transfusion.) At any rate, it should be remembered that ischemic stroke can occur 1-10 days after the onset of priapism, especially after transfusion therapy.

Surgery. If detumescence has not occurred within 12 to 24 hours after corporal irrigation, transfusion, or both, then surgery should be performed to shunt blood away from the corpus cavernosum to the corpus spongiosum to relieve vascular occlusion. Such surgery would usually involve distal glans-cavernosal shunting, while proximal shunting generally involved spongiosal-cavernosal or cavernosal-saphenous shunting and is reserved for those individuals in whom the distal shunting procedure did not work. Unfortunately, distal shunting often requires reoperation and may result in erectile dysfunction. Both shunting procedures have a significant impotency rate.^{118, 119} However, it should be remembered that priapism with or without surgical shunting procedures is by itself associated with a high rate of erectile dysfunction; such dysfunction may be an outcome of the prolonged ischemia associated with priapism and not always due to the shunt itself.^{120, 121}

Recurrent or stuttering priapism

The term stuttering priapism refers to repetitive episodes of priapism having shorter duration. There is no standard treatment. However, the following measures have been taken by us:

- Oral alpha- and beta-agonists.¹²² The use of these agents primarily involves the use of pseudoephedrine which is taken at bedtime at a starting dose of 30 to 60 mg/day. An additional dose of 30 mg can be given when the episode of priapism occurs.
- Home intracavernosal injections.¹²³ Patients who have frequent priapic episodes can be taught, usually by a urologist, to inject themselves via the cavernosum with phenylephrine, an alpha-1 selective adrenergic agonist or with epinephrine, a mixed alpha- and beta-adrenergic agent.
- Chronic blood transfusions. There is no data supporting this practice but monthly, chronic blood transfusions have been used to prevent priapism and to treat stuttering priapism.
- Hydroxyurea. Since hydroxyurea has been used to reduce vasoocclusive events in sickle cell disease, it has been employed also in the prevention of priapism. The series demonstrating efficacy in preventing this complication of sickle cell disease have been small, and the evidence predominantly anecdotal.¹²⁴ However, if patients present with a history of recurrent priapism, a starting dose of 10 mg/kg/ per day can be given and the dose increased up to 30 mg/kg/day as tolerated.
- Hormonal therapy. In the event when nothing else has worked, hormonal therapy can be considered.^{125, 126} This includes diethylstilbestrol and leuprolide (DepoLeupron), a gonadotropin-releasing hormone agonist. These agents have had variable success in preventing episodes of recurrent priapism but there is little published data on their use in priapism.

Proposed timing of treatment sequence

Time Interval (Hours)	Treatment
0-<2	Home therapy: empty bladder, increase fluid intake, exercise, or take warm or sitz bath, or application of warm pack, and take oral analgesics
2-<4	Go to ER: IVFs and parenteral analgesics; O ₂ or anxiolytics as needed
4-<12	Intracavernosal aspiration of blood and injection of phenylephrine (or epinephrine); local anesthetic should be given along with conscious sedation. IVFs, analgesics, anxiolytics, and O ₂ . If refractory to instillation and aspiration, then may consider rbc exchange via erythrocytapheresis
>12 (sooner if medically indicated)	Surgery, if instillation and aspiration, and rbc exchange unsuccessful. Shunt placement should be performed by urologist.

Therapies available for treatment of stuttering priapism

Therapy	Treatment
1 st line	Oral adrenergic agonist (e.g. pseudoephedrine) at bedtime or divided BID@
2 nd line	Oral β -agonist (e.g. terbutaline)
3 rd line	Gonadotropin-releasing hormone analogue (leuprolide) (or diethylstilbestrol)*
4 th line	Hydroxyurea
	@patients and parents can be taught how to aspirate the cavernosa and inject intracavernosal epinephrine or phenylephrine if there are prolonged episodes of priapism or stuttering priapism *patients may not like side-effects of diethylstilbestrol which include feminizing effects

Hydroxyurea Use

Hydroxyurea is known to induce the production of hemoglobin F which in turn reduces hemoglobin S polymerization and subsequent sickling. It has been shown to bring about a reduction in the number of vasoocclusive pain, acute chest syndrome episodes, number of hospitalizations, and decrease in the number of transfusions required by patients. It has been used in children ages ≥ 2 years but may now be considered for those as young as 9 months of age.

Recommendations regarding those that should be considered for placement on hydroxyurea include the following: ^{127, 128}

- Those who have ≥ 3 moderate to severe pain episodes in a 12-month period
- Those children with SSD who have a history of ACS or symptomatic anemia
- **Infants and children age 9 months or older with SSD who are asymptomatic or have infrequent pain episodes**
- Patients with SSD who have a history of stroke and a contraindication to chronic transfusions, as an alternative to receiving no transfusion

Dosing starts at 15 mg/kg/day daily and doses can be escalated by 5 mg/kg every 8-12 weeks. Since the most common side-effects of the drug are hematologic (myelosuppression resulting in thrombocytopenia, neutropenia, or anemia), close monitoring of counts is extremely important. Presence of cytopenia should lead to discontinuation of the drug, usually temporarily; once recovery of normal counts is attained, the drug can be resumed at a lower dose. Again, close monitoring of blood counts is warranted. The dose should be given at bedtime to avoid complaints of nausea and rarely, vomiting. Patients should be seen more frequently than

they would otherwise be seen; a recommended frequency of visits is every month to every 3 months with counts being performed monthly; once assured of stable counts, the physician can then obtain counts on a monthly basis. After initiation of the medication, counts should be obtained weekly (x4-6). Side-effects include not only cytopenias but also GI disturbance, skin and nail changes, leg ulcers, and a report of azoospermia. The drop in sperm count was not always seen to be reversible with discontinuation of the drug but subsequent decrease in fertility or pregnancy did not materialize.¹²⁹⁻¹³¹ Parents may sometimes voice concerns regarding carcinogenic potential of hydroxyurea i.e., the later development of malignancy. The reported incidence of malignancy after hydroxyurea use was 0.5% compared to 0.06% in those who were not on the drug.¹²⁸ However, the benefits of this medication greatly outweigh any concerns regarding malignancy and the likelihood of development of this complication has been considered to be minimal. Hydroxyurea is supplied in capsule form and daily dosing should be calculated on the basis of proposed weekly total dosing (e.g., a 19 kg patient might receive dosing for 4 days of the week to achieve an intended dose of 15 mg/kg/day, etc.). The drug can be compounded to have a concentration of liquid suspension of 100 mg/ml for those who are too young to swallow the capsule.

Leg Ulcers

Leg ulcers can be a particularly vexing problem for the patient with sickle cell disease as well as for the practitioner, since they can be intractable and frequently recurring. This complication is seen with a widely varying prevalence as cited in the literature of patients with the hemoglobinopathy and is probably the result of arteriovenous shunting which subsequently deprives skin, over areas of thinner skin with little subcutaneous fat, of oxygen; activated endothelial cells may also interact with sickle cells, with subsequent increased expression of endothelial cell adhesion molecules, with the initiation of thrombotic vasoocclusion.¹³²⁻¹³⁵ The ulcers usually occur over the medial and lateral malleoli, although they can also be seen over the anterior tibia, dorsum of the foot, and Achilles tendon. Although infection does not necessarily have to be present, trauma, infection, and inflammation may play a causal role in the evolution of this problem. Leg ulcers can be very painful but also indolent, healing over a relatively long period of time. They are seen in those with greater severity of disease and with those having significant hemolysis. Accordingly, this is a problem seen more often with homozygous disease, rather than in those with SC disease or $S\beta^0$ -thalassemia. Controlled clinical trials in management of leg ulcers have not been conducted and treatment of leg ulcers is variable and usually based upon experiential data or anecdote.

Management.

When the patient presents to the physician with a leg ulcer, he/she should be carefully assessed.

Risk factors for the development of leg ulcers include:¹³⁶⁻¹³⁸

- Older age. While patients 10 years and younger can develop leg ulcers, this complication is usually seen in the older adolescent and adult.
- Hemoglobin levels <6 gm%
- Thrombocytosis
- Having concomitant antithrombin deficiency
- Having low level of HbF
- Central African Republic (CAR)-polymorphism
- Homozygous SS disease and SS-alpha-thalassemia

Assessments suggested:

On history, we want to know:

- Duration of ulceration
- Whether recurrent or first episode
- Extent of pain
- Sensory loss
- Evidence of antecedent trauma
- If problems with mobility

On Physical Exam, we need to

- Check pulses and look for evidence of edema or venous stasis.
- Check for evidence of DVT
- Check for signs of infection, especially evidence of septicemia
- Check range of motion of joints
- Exclude the possibility of osteomyelitis. If necessary, order bone scan, MRI, and consult orthopedics for bone biopsy if there is sufficient evidence of bone infection.

The ulcer should be staged based upon its depth:¹³⁹

Stage 1: nonblanchable erythema of intact skin, discoloration of skin, warmth, edema, induration, or hardness

Stage 2: partial-thickness skin loss involving epidermis, dermis, or both. Ulcer is superficial and presents clinically as abrasion, blister, or shallow crater

Stage 3: full-thickness skin loss involving damage to or necrosis of subcutaneous tissue that may extend down to, but not through, underlying fascia. Ulcer is deep crater with or without undermining of adjacent tissue

Stage 4: Full thickness skin loss with extensive destruction, tissue necrosis, or damage to muscle, bone, or supporting structures (e.g., tendon, joint capsule). Undermining and sinus tract may be present.

Labs to Order:

- CBC, diff, with platelets and reticulocyte count
- CMP
- UA
- Hb electrophoresis (if not previously known)

- Cultures from bases of ulcer
- X-ray of underlying bone

Treatment¹³⁵

General recommendations for care of leg ulcers are available from a number of articles.^{135, 139-141} Physical therapy (and possibly surgeons) should be consulted for advisement re. wound care. The wound should be carefully cleaned (mild soap or diluted solution of liquid household bleach (1 tbsp in 1 gallon of water.) Repeated wet to dry dressing change should be performed. If there is extensive necrosis or if the wound is sufficiently deep, debridement by surgeons, with the patient under conscious sedation and with local anesthetic, may be necessary.

Additional measures that can be considered may include:

- Parenteral antibiotics such as clindamycin or cephalosporin, if there is evidence of infection. Choice of antibiotic should be directed by results of wound culture obtained at the first visit of the patient to the clinic or emergency room, if they are available.
- Ointments can include zinc oxide or zinc sulfate, topical herbal applications, or topical application of platelet-derived growth factor (Procuren or Regranex) or granulocyte-macrophage colony-stimulating factor (GM-CSF).^{139, 142} Alternatively, RGD peptide matrix (argidene gel) can be used.¹⁴³ This is a topical viscous gel that is said to provide a macromolecular scaffold to facilitate migration of fibroblasts, endothelial cells, and keratinocytes to the wound site. The gel is applied once a week prior to application of the Unna boot. This process should be repeated until healing is seen.
- Use semi-permeable polymeric membrane dressings.
- Manuka honey (from New Zealand) has been used to heal diabetic foot ulcers¹⁴⁴ and may have efficacy here.
- Analgesic therapy, including opioids as needed.
- Patients may need to keep the leg elevated as much as possible. Complete bedrest may be necessary for 7-10 days. During the day, wet saline dressings can be frequently applied. However, at night, dry nonstick adhesive dressings should be considered and the leg should be wrapped with Kerlix dressing.
- Unna (zinc-oxide-impregnated) or sheepskin boots can be used. It is recommended that these boots be applied for at least 2-3 weeks. It should be left in place for 1 week and then removed. It should be applied 3-4 times before healing may become evident. Once healing is observed, application of saline dressings should be continued. Antibiotics or other ointments should not be applied under the Unna boot bandage since they could react with the zinc and lead to allergic reaction.
- If the patient fails to respond to these modalities, then one can consider the use of the hyperbaric chamber to facilitate healing.¹⁴⁵
- Chronic transfusion of prbc can also be considered for slowly healing or non-healing ulcers. Again, the targeted level of hemoglobin and HbS should be respectively 10 gm% and <30%. If there is no healing in 6 months, the transfusions should be discontinued. However, if there is healing, then the transfusions should be slowly withdrawn over 3-6 months.
- If leg ulcers become chronic, then one can refer the patient for skin-grafting.
- If the patient has a habit of smoking, he/she should be encouraged to stop smoking.

Prevention of leg ulcers

About 97% of leg ulcers will recur in less than one year.¹⁴⁶ Patients should be reminded that close attention be given to the state of their skin. Proper cleaning and use of moisturizing lotion should be emphasized. Properly fitting shoes and the use of support stockings should be considered. Additional measures that may need to be taken may include use of insect repellent. Picking at insect bites or untended minor abrasions or wounds may predispose one to the subsequent development of leg ulcers. Any lesion(s) that appear, especially in an individual with a prior history of leg ulcer, should be reported immediately.

Pulmonary Hypertension

Cardiovascular disease has become a major cause of mortality and morbidity in hemoglobinopathies and other chronic hemolytic anemias. Pulmonary hypertension is the predominant form of cardiovascular disease that should be monitored for. It has been described in a variety of hemolytic anemias, including congenital hereditary spherocytosis, microangiopathic hemolytic anemia, pyruvate kinase deficiency, hereditary stomatocytosis, and alloimmune-mediated hemolytic anemia, as well as paroxysmal nocturnal hemoglobinuria and unstable hemoglobin variants. Apropos to our current discussion, however, it has been seen with increasing frequency in β -thalassemia and sickle cell disease. Among adult patients, pulmonary hypertension is described as a silent killer and has been diagnosed in between 30-50% of individuals with sickle cell disease.¹⁴⁷⁻¹⁵¹ (Prevalence may be even higher in those with thalassemia). There has been less certainty as to its prevalence among children, in whom it has been reported that anywhere from 10% to as high as 50% of them have incurred this problem.¹⁵²⁻¹⁵⁴

Although the pathophysiology of this complication is not entirely known, it has become increasingly apparent that pulmonary hypertension is likely a consequence of nitric oxide depletion resulting from increased nitric oxide scavenging, arginine catabolism, and endogenous nitric oxide synthesis inhibition. Thus, there appears to be a correlation between severity of hemolysis, as indicated by LDH and reticulocyte count, and risk of development of pulmonary hypertension. This correlative relationship is not, however, firm. Other considerations that must be factored into the pathophysiology include the hypercoagulability seen in sickle cell anemia; vasculopathic tendencies; prior lung injury as in acute chest syndrome, pulmonary embolism, and in-situ thrombosis; other vasoocclusion, even if not lung-related; iron overload; and recurrent respiratory tract infections.

While right-sided heart catheterization is considered the gold-standard of diagnosis, this procedure is usually not performed on pediatric patients unless the index of suspicion is very high. Doppler ECHOCardiography has been employed to make the diagnosis, using a modification of the Bernoulli equation to approximate right atrial pressure. Tricuspid valve regurgitant velocity (TRV) is then measured; a velocity of ≥ 2.5 m/sec has generally been equated to a right ventricular systolic pressure of >35 mm Hg, which would be defined as indicative of pulmonary hypertension.¹⁵⁵⁻¹⁵⁷ (A higher cutoff of 2.9 m/sec has been proposed in order to select patients for performance of the confirmatory catheterization.¹⁵⁸ However, a higher threshold was felt to likely lead to higher false negative rates.)

We have proposed a modification of this commonly used diagnostic process in the following way:

	No PHTN	Borderline results	Mild PHTN	Moderate PHTN
Mean PAP*	<25 mm Hg	<25 mm Hg	>25 mm Hg	>25 mm Hg
Syst. PAP**	<30 mm Hg	31-36 mm Hg	37-51 mm Hg	>51 mm Hg
TRV	<2.5 m/sec	2.5-2.7 m/sec	2.8-3.4 m/sec	>3.4 m/sec
IVS (Eccentricity Index) ratio	<1.10 (not flattened)	<1.10 (not flattened)	1.15-1.40 (slightly flat)	>1.40 (flat)
RVP ratio***	<0.5	<0.5	0.5-1.0	>1.0

*Calculated using the Chemla formula, mean PAP=0.61 (syst PAP)+2 mm Hg

** Calculated using the modified Bernoulli Equation, syst PAP=4(TRV)²±5 mm Hg

*** RVP Ratio=syst PAP/systolic BP

PAP, pulmonary arterial pressure; TRV, tricuspid valve regurgitant velocity; IVS, intraventricular septum ratio; RVP, right ventricular pressure

We feel that utilizing these stricter criteria has resulted in greater accuracy in the diagnosis of pulmonary hypertension and has allowed avoidance of unnecessary use of invasive procedures such as catheterization. We have also found that there is considerable fluidity with regards to recorded data. Some patients with abnormal values have had subsequent measurements that were clearly within normal limits. However, other patients have had fluctuating values that have not achieved stability nor have they been clearly abnormal with each reading. We suspect that children who would otherwise have been diagnosed as having pulmonary hypertension utilizing the widely used criteria of TRV alone may be at risk but have not yet manifested permanent changes of pulmonary hypertension that would warrant initiation of treatment. **It is for that reason that we have continued to follow patients with annual ECHOCardiograms, enlisting the diagnostic skills of the cardiologists in our Pediatric Department.**

Recommendations for follow-up are therefore:

- Annual performance of ECHOCardiograms for patients with all forms of sickle cell disease. Those having sickle beta-thalassemia or SC Disease, while having much lower prevalence of pulmonary hypertension, may still be at risk and should also have this examination. The age at which this assessment should be performed is not universally agreed on. It has been suggested that children as young as 2 years should be examined. However, we have performed the test in all individuals, regardless of phenotype, who are 6 years and older.
- Patients having an abnormal result should then be scheduled to have a 6' walk or stress test.
- Cardiac catheterization may be considered for those individuals for whom both tests are abnormal

It should be remembered that all testing for pulmonary hypertension should be performed during steady state, i.e., patients should not have been in a state of acute crisis, infection, fever, or other complications of sickle cell disease. Patients in whom the testing was performed in anything other than steady state should have ECHOCardiography repeated after a suitable time has passed to allow them to return to their usual state of health.

Treatment

Treatment of pulmonary hypertension, whether in patients with sickle cell disease or idiopathic disease, is controversial. There have been no randomized, controlled trials establishing the benefit of currently available treatments for pulmonary hypertension in sickle cell disease. Therapeutic trials examining efficacy of treatment with sildenafil and bosentan have had to be suspended, due to poor enrollment, lack of demonstrable efficacy, and also as in the case of sildenafil, for adverse side-effects.¹⁵⁹⁻¹⁶¹ Nevertheless, therapeutic options that have been proposed for use in pulmonary hypertension in sicklers include the following:

- Phosphodiesterase-5 inhibitors. Sildenafil is the primary drug in this class that has been used for the treatment of pulmonary hypertension.
- Endothelin receptor antagonists. Bosentan is the main drug used in this class of agents used for pulmonary hypertension.
- Prostacyclin analogues. Flolan, Tyvaso, Remodulin, and Ventavis are all approved with the indication for use in individuals with pulmonary hypertension having limited exercise capacity.

Sildenafil has been associated with an increase in vasoocclusive episodes during its use. Bosentan has not had a similar association with adverse side-effects but studies investigating its use have not shown conclusive benefits. Accordingly, we have left the decision of whom to treat, and how to treat pulmonary hypertension to the discretion of the cardiologists who have conjoint care responsibilities for these patients.

Stronger recommendations concerning treatment of patients with pulmonary hypertension and sickle cell disease have been that they be “treated with therapies known to improve outcomes in sickle cell disease patients”. These have included:

Use of hydroxyurea. It should be understood that there is no definitive proof that treatment with hydroxyurea is preventive for this complication although there have been small retrospective and nonrandomized trials that suggest benefit. It can, however, improve the overall outcome in these individuals and should be considered in those having the diagnosis of pulmonary hypertension.

Aggressive iron chelation. It is hoped that iron accumulation can be prevented or treated and lead to less oxidative tissue damage, as well as prevention of cardiac hemosiderosis and lung injury.

Chronic Transfusion. Again, transfusion is not preventive but should be considered in those with the diagnosis of pulmonary hypertension as it may ameliorate symptoms experienced by the patient, such as dyspnea and fatigue, by restoring proper tissue oxygen delivery and suppress hemolysis, hypercoagulability, tissue hypoxia, and volume overload; and perhaps mitigate progression of the disorder.

Pulmonary Complications

Patients with sickle cell disease may frequently complain of diminished exercise tolerance and dyspnea.¹⁶² For this reason, when the physician discusses athletic participation in physical education and organized

sports, they may refer to the need for self-limitation of activities by patients. Dyspnea can then be just a complaint manifested only during exertion, but it can increase as the patient ages and can become more overt in adulthood---a complaint that is seen regardless of phenotype. Dyspnea can be a result of anemia but can also have other etiologies, as well. Causes can include asthma, pulmonary hypertension, pulmonary fibrosis after recurrent acute chest syndrome episodes, pulmonary hypertension, and myocardial dysfunction.

Many of these conditions may first be discovered on performance of pulmonary function tests. The majority of patients with sickle cell disease may have no symptoms indicating abnormal lung function. Over ¾ of patients with sickle cell disease have evidence of restrictive lung disease; this was first thought to be a problem seen only in adults.¹⁶³ However, it is now evident that children also have indications of restrictive function.^{164, 168} A small percentage of individuals may have signs of both restrictive and obstructive disease while an even smaller number of patients have solely obstructive disease. Function may decline with passage of time.¹⁶⁶ In addition, the pulse oximetry saturation is usually lower in patients with sickle cell disease, especially in adults.¹⁶⁷

We find asthma to be particularly common among children with sickle cell disease (as it is among African-American children in general).¹⁶⁷ In one study of children with sickle cell disease, obstructive airway disease was seen in just over 1/3 of children with the disorder.¹⁶⁸ Many of these children had family or personal history of asthma or wheezing.

There is also evidence that patients with sickle cell disease can have a higher than usual incidence of venous thromboembolism and pulmonary arterial thrombosis. This complication was seen in up to ~20-25% of patients with sickle cell disease.¹⁶⁹ Pulmonary embolism was seen with a frequency that was 3 times higher among patients with sickle cell disease than in those who did not carry the diagnosis. Among patients who had experienced acute chest syndrome, 17% had evidence of pulmonary artery thrombosis on CT scan.¹⁷⁰

Pulmonary fibrosis is sometimes seen after repeated episodes of acute chest syndrome.¹⁷¹ Patients having this complication may present with dyspnea. High resolution CT scan of the chest may demonstrate honeycombing of the lungs.

Obstructive sleep apnea can also occur in individuals with sickle cell disease.¹⁷² Individuals with this problem may “fly under the radar.” That is, they may not realize that symptoms of daytime fatigue, dyspnea, disrupted sleep are the result of obstructive sleep apnea or sleep disordered breathing. (Obstructive sleep apnea has been associated with an increase in vasoocclusive episodes, and there is some evidence that it may also predispose one to pulmonary hypertension later in life.)¹⁷³ Parents may complain of the child’s very noisy breathing or report obvious apneic episodes when the child is asleep. In this event, attention should be paid to the child’s tonsillar size or to the presence of mouth-breathing or nasal intonation. Individuals with sickle cell disease, however, are more likely to have nocturnal hypoxemia or desaturation, whether obstructive sleep apnea is present or not; this finding is present in 40=50% of children and adolescents.¹⁷⁴ Additionally, sickle cell patients are also more likely to have longer durations of oxygen desaturation when it is present. End-tidal carbon dioxide levels may be >50 mmHg.

Oxygen desaturations at night can be associated with daytime hypoxemia in patients with sickle cell disease, as well.

Assessments to be considered

Pulmonary function testing should be performed annually for those patients with sickle cell disease who are 6 years and older. Of course, performance of the test will depend upon the ability of the child to understand instructions for the testing to proceed. The test should, if possible, be performed with a trial of bronchodilator to determine whether the patient has evidence of obstructive disease and need for future treatment with bronchodilator.

A patient demonstrating potential need for bronchodilator use should be evaluated by the pulmonologist. Subsequent treatment of asthma or wheezing can be then managed jointly by the pediatrician and the specialist.

Pulse oximetry reading should be done annually at least to obtain a baseline.

If there is evidence of obstructive sleep apnea, the patient should have a sleep study. Polysomnography will be performed and attention will be given to bouts of snoring, nocturnal gasping, choking, and apnea during sleep. It is recommended that all individuals in whom TRV elevation is observed or there is other evidence of pulmonary hypertension should also have sleep study to rule out the possibility of sleep apnea. Lateral neck films can be obtained to demonstrate the present of probable airway obstruction. Referral should then be made to the ENT specialist so that the patient can be further evaluated. A decision may then be made, at times without the results of the sleep study, to perform tonsillectomy and adenoidectomy, which can be curative.

Treatment

Asthma. There have been no controlled trials of asthma treatment methods in patients with sickle cell disease. However, we have proceeded with standard asthma treatment (oxygen administration, bronchodilator therapy with a short-acting β_2 -agonist, e.g., albuterol or xopenex, and use of corticosteroids) in those individuals admitted to the hospital with acute asthma exacerbation. Concern has been voiced about the use of corticosteroids since they have been associated with worsening (rebound) of vasoocclusive episodes.^{175, 176} However, most physicians would not withhold steroids, feeling that the good they may do will greatly outweigh any considerations of adverse effect.¹⁷⁷ It is also generally accepted in the non-sickle cell population that systemic steroids decrease rates of admission and prevent relapse.

Pulmonary fibrosis. There is no known treatment for pulmonary fibrosis except prevention of acute chest episodes (e.g. transfusion of prbc and hydroxyurea).

Obstructive sleep apnea. As noted, many of those individuals reporting disordered sleep may be eventually diagnosed as having sleep apnea. Once a sleep study has been performed and the diagnosis of sleep apnea substantiated, the patient should be referred to ENT and if tonsillar and/or adenoidal hypertrophy is documented, then tonsillectomy/adenoidectomy should be considered. The patient

should be transfused preoperatively, as discussed above, and a suitable screening for coagulopathy should be performed prior to surgery.

All patients having abnormal pulmonary function testing should be evaluated by the pulmonologist, with follow-up arranged by him/her as deemed necessary.

Retinopathy¹⁷⁴⁻¹⁷⁶

Patients may experience retinal arteriolar infarction or arteriolar occlusions, anastomoses, neovascularization or hemorrhage and retinal detachment. Retinal arteriolar infarctions are associated with nonproliferative retinopathy that usually does not affect vision and requires no therapy.

Proliferative retinopathy can present in childhood, although it is generally seen in the second and third decade of life in the sickle cell patient. Notably, perhaps because of the higher hemoglobin and higher blood viscosity, the patient with SC disease has a higher prevalence of retinal neovascularization. Once present, proliferative retinopathy can progress rapidly, with the end result being blindness. For that reason, the patient with sickle cell disease should undergo annual ophthalmologic examinations. Parents will often confuse specialists in optometry with those specializing in ophthalmology and the hematologist should instruct them on the examinations performed by each and the need for them to be seen by an *ophthalmologist* who can perform a thorough examination of the eyegrounds. Patients and their parents should also be apprised of the fact that visual changes that could imperil vision are often painless or subtle. They should be aware that our preference is that a preventive approach be taken, rather than one that aims to treat disease that has already developed.

Laser photocoagulation can be effective in treating proliferative retinopathy by occluding feeder vessels in the advanced proliferative lesions. Photocoagulation may, however, carry a risk of neovascularization of the choroid and cause retinal breaks. If retinopathic changes are present, a retinal specialist should be consulted, in addition to the general ophthalmologist. It is true that some of these lesions may spontaneously regress. Yet the risk of visual loss dictates a greater sense of urgency; in most cases, the rate of complications attendant upon photocoagulation is low.

Retinal detachment can occur as a result of vitreous degeneration and fibrosis; it can also be associated with vitreous hemorrhage. These complications are the major cause of blindness in individuals with sickle cell disease. Vitrectomy may be necessary in those individuals in whom resolution of the hemorrhage does not take place within 3-6 months. In some individuals, tractional retinal detachment is seen. In both of these instances, vitrectomy may be necessary; patients may also require an operation to repair retinal detachment (called scleral buckling). Transfusion, in particular partial exchange transfusion or actual erythrocytapheresis should be performed preoperatively. Exchange transfusion has been suggested for bilateral retinopathy, in an effort to preserve vision.

In the event of traumatic injury involving the anterior chamber, it should be remembered that conditions in the anterior chamber generally favor sickling. For that reason, hyperosmotic or diuretic agents or carbonic anhydrase inhibitors should be avoided since they can promote sickling. Agents such as topical β -adrenergic antagonists or α_2 -adrenergic agonists may be effective, if there is blunt-force trauma to the

eye. However, surgical evacuation of anterior chamber blood should be performed as soon as possible for those who present with trauma to the eye since buildup of intraocular pressure, even to a moderate degree, can produce permanent reduction in vision.

Renal Functional Impairment

Renal consequences of sickling can be seen early in the life of a child with sickle cell disease.¹⁸¹ These changes occur as a result of sickling that is facilitated by the hypertonicity of the renal medulla and patterns of blood flow in the kidney, that lead to hypoxia, hypertonicity and acidosis in the renal medulla. One of the first manifestations of these renal changes is hyposthenuria, failure of the kidneys to concentrate urine. This is seen in most individuals with sickle cell disease by the age of 3-5 years. It is because of this complication that parents will frequently complain about the frequent urination of the patient (in essence, a form of nephrogenic diabetes insipidus) and the “excessive”, compensatory thirst experienced by him/her. These symptoms are often a source of misunderstanding by the lay-person, in particular teachers and others in the education system, who may see the child’s frequent requests for bathroom breaks, even daytime wetting, and thirst as attempts at attention-seeking or malingering. The child may be forbidden to seek extra bathroom privileges or to drink extra fluid. However, we have created a letter detailing the reasons for the child’s requests and urging educators and others in the school to allow extra bathroom breaks and slaking of thirst as needed by the child. The physicians are readily available to discuss this with school employees and to insure that the child is able to avoid dehydration. Similarly, patients should be informed that they should take frequent breaks from activities in hot weather. During those breaks, they should be allowed to drink water or other liquid liberally to prevent dehydration. Consideration of the patient’s hyposthenuria should be made when/if he/she is to be given furosemide or mannitol since they may actually be hyporesponsive to loop or osmotic diuretics.

Hyposthenuria is also a reason for another annoying feature in the life of a sickle cell patient, enuresis.¹⁸²
¹⁸³ Enuresis is bedtime or nocturnal wetting. Early on, it can be reversed by transfusion. However, transfusion would not be chosen as means of retarding the onset of this problem. While there occasionally may be a familial history of similar bedwetting habits in other older family members, this problem is a manifestation of the inability to concentrate urine. Nevertheless, just as one would with other children with enuresis, there should be an attempt to exclude other renal abnormalities first, such as infection. A urinalysis and urine culture should be obtained in these children, especially since they are more prone to renal infection than other children. Parents should be instructed on behavioral modification techniques that are commonly used for children with this problem. They include: voiding just before bedtime, prohibition of drinking liquids 1-2 hours before bedtime, and getting the child up to void several times during the night. Discussion should be made of aids such as the bed-wetting alarm, which has been shown to be most efficacious in treating enuresis. The alarm, however, can be expensive and cost may prevent its consideration by parents.

Additionally, patients may respond to desmopressin acetate (DDAVP) which can be given in either a dose of 0.2 mg or 0.4 mg at bedtime. Parents should be instructed to be aware of potential complications associated with DDAVP such as excessive urinary retention, somnolence, or seizures. Once the patient

has been placed on this medication, they should be carefully monitored for the possible development of electrolyte abnormalities.

As the patient with sickle cell disease ages, impairment of renal tubular function can become apparent.^{184, 185} This can be seen as an inability to acidify urine, in the face of an acid load, leading at times to systemic acidosis. If this complication is present, then patients should be evaluated for renal hydrogen ion excretion, which if observed can be corrected with sodium bicarbonate either via oral or intravenous route.

Hyperkalemia can also be seen; this problem may not be amenable to administration of lasix. If the potassium is ≥ 5.5 meq/L, then other causes, e.g. hemolysis should be sought. Patients with sickle cell disease may also occasionally have elevated serum uric acid levels. This finding results from the increased cellular turnover associated with hemolysis and increased erythropoiesis. Treatment is not usually required. However, if the uric acid is very high (≥ 5 mg/dL, then the patient may require placement on allopurinol. Flank pain may signal the formation of kidney stones, including those due to urate deposition. Urinary alkalization should be initiated, using sodium bicarbonate, and the patient should be started on IV fluids (one to one and a half times maintenance) with close attention being paid to intake and output volumes.

Gross hematuria may be seen in both sickle cell disease and sickle trait.¹⁸⁵⁻¹⁸⁷ The bleeding is usually mild and asymptomatic. However, bleeding can be severe enough to cause blood loss. Clots within the renal pelvis or ureter can cause significant pain. Unfortunately, this complication can recur. One must exclude the possibility of other entities including infection, glomerulonephritis, tuberculosis, tumor, or stones. A CT and renal ultrasound should be obtained to look for calyceal clots and for evidence of renal tumor, in particular renal medullary carcinoma. Patients should be queried about possible bleeding disorder and coagulation studies (PT, PTT, CBC with platelets, and possibly platelet function assay (PFA)) should be considered. Urine culture should be obtained along with urinalysis. Hydration should be instituted as soon as possible, with a rate of about 2 times maintenance or higher, depending upon the patient's tolerance. The CBC should be monitored closely and at the first sign of a drop in the hemoglobin/hematocrit, transfusion should begin. Patients should be on bedrest. Urine output should be at least >3 ml/kg/hr.

In cases of intractable bleeding, the use of epsilon aminocaproic acid (EACA or Amicar) can be considered. A dose of 2 to 8 gm/day can be given. However, EACA use has a significant drawback, in that it may cause the formation of clots in the renal pelvis and ureter. This medication should never be given as outpatient therapy but requires close monitoring. It may also become necessary to replace iron in those who have lost significant amounts of blood. Exchange transfusion may also be considered in an effort to dilute the concentration of sickle hemoglobin and inhibit sickling. In those with a history of recurrent or refractory bleeding, consideration may be given to starting a regimen of erythrocytapheresis.

Renal papillary necrosis is commonly seen in patients with sickle cell anemia, as an asymptomatic renal complication or with accompanying bleeding as noted above or proteinuria.^{188, 189} We have screened patients for this form of renal complication by performing urinary analysis for microalbuminuria. This is

diagnosed when the ratio of albumin to creatinine is >20 . In those with significant urinary protein excretion, referral is made to the nephrologist who may decide to place the patient on an ACE-inhibitor such as enalapril to reduce further urinary protein loss. Patients should be made aware of a possible contributory relationship to nonsteroidal analgesics such as ibuprofen or naproxen.

Sickle cell disease patients may experience an increased frequency of urinary tract infections, in particular pyelonephritis. Frequent urinalysis and urinary culture, when indicated, should be performed. Appropriate antibiotic therapy, led by the sensitivity profile, is necessary. As indicated above, patients with febrile illness should always have a urine culture ordered. For the initial urinary tract infection, it is suggested that a renal ultrasound be performed. Voiding cystourethrogram may also be ordered. Patients with recurrent urinary tract infections should be placed on prophylactic antibiotic coverage. If reflux is observed, the patient should be followed by a urologist as well.

Patients may, at times, develop nephrotic syndrome, exhibiting chronic severe proteinuria. This may be associated with membranoproliferative glomerulonephritis. Patients should be evaluated with a 24 hour creatinine clearance and a 24 hour protein quantitation. The patient should be referred to a nephrologist and biopsy should be performed. IGGAME should be obtained, as should proteins C, S, and Antithrombin III. If the latter levels are depressed, it may be necessary to place the patient on suitable anticoagulant therapy, as they may exhibit hypercoagulability.

Patients with sickle cell disease are not usually hypertensive. Most of the time, hypertension is seen only as a manifestation of pain during pain crisis. In fact, hypertension is seen in about 5% of children with the disorder.¹⁹⁰ Although blood pressure readings may increase in adults, the presence of hypertension in children with sickle cell disease may signal the presence of renal disease and should be investigated accordingly. Renin and aldosterone levels should be obtained. Treatment should consist of commonly used antihypertensives. Diuretics, although used in non-sickle cell patients for treatment of hypertension, should be used with caution since dehydration could occur with their use. Angiotensin-converting enzyme (ACE) inhibitors, e.g., enalapril have been used and are able to bring about hypertensive control and reduce urinary excretion of protein. Unfortunately, this agent has not been successful in preventing progression of glomerular disease. Hydroxyurea has been suggested as a way to improve renal function.

Chronic renal failure can be seen with end-stage renal disease. This is a problem that can be seen as the patient ages. Patients should be followed by Nephrology and if renal failure progresses, then patient may require dialysis or renal transplantation. Patients, however, should be made aware of the fact that the sickle nephropathy that was responsible for the development of kidney failure in the first place can recur. Chronic transfusion may be necessary since the patient may have anemia due to chronic renal disease. While recombinant erythropoietin can ameliorate the anemia of renal failure in patients who do not have sickle cell disease, the use of erythropoietin in those with sickle nephropathy may not be as successful, since the patient usually will need larger doses of erythropoietin to achieve any significant rise in hemoglobin.

Hepatobiliary

Cholecystitis is seen in up to 40% of patients with sickle cell disease and can be present in children as young as 2-4 years of age.¹⁹¹⁻¹⁹³ Abdominal ultrasounds are repeated every year. Sludge is often reported but it is not always a precursor to stones. If stones are present, the gallbladder should be evaluated for the presence of thickening of its wall or evidence of common bile duct obstruction. If possible, the pancreas should also be visualized for evidence of pancreatitis. Abnormalities of the liver can also be seen through the use of ultrasound. If there are concerns about cystic duct occlusion, then the performance of a technetium-99m iminodiacetic acid (HIDA) scan can be ordered.

Patients may present with

Colicky right upper quadrant pain	} both seen after meals that are fatty
Nausea and/or vomiting	

Patients should upon being diagnosed with gallstones be immediately referred to Surgery for cholecystectomy. Until surgery can be performed, the patients should follow a low-fat diet (Examples of such diets can be found on the internet and should be shared with the patient/parents.) If the patient becomes symptom-free, parents may be reluctant to consider surgery but they should be strongly encouraged to have the child go for elective cholecystectomy since the goal is to prevent the development of acute cholecystitis ---a potential complication of untreated cholelithiasis.¹⁹¹⁻¹⁹³ Morbidity with emergent cholecystectomy is relatively great, while performance of elective surgery has been accomplished with few complications. In fact, every attempt should be made to avoid emergent surgery in the face of cholecystitis, which if present should be treated with antibiotics, hydration, and supportive measures. However, if there is evidence of common bile duct obstruction, emergency surgery may be necessary. If obstruction is present, then endoscopic retrograde cholangiography (ERCP) may be required as well. (At Children's Hospital of New Orleans, we do not have the capacity to perform this examination. Arrangements are then necessary to have the patient transferred to neighboring facilities to have this procedure performed.) Surgery is usually performed laparoscopically.

Surgical preparation should entail preoperative transfusion, as discussed above. Patients should be monitored postoperatively for evidence of hypoxemia, atelectasis, pneumonia or vasoocclusive episodes. They usually will require observation for at least 24 hours after surgery.

Hepatic complications can include cholestasis and intrahepatic sickling.^{194, 195} Pain with this complication can mimic that of cholelithiasis. Liver enzymes can be quite elevated. While transaminemia can be a manifestation of cholestasis or intrahepatic sickling, care should be taken to rule out the possibility of viral illness. Such illness would include either hepatitis A, B, or C, cytomegalovirus or Epstein-Barr virus. Gastroenterology should be consulted and liver biopsy should be performed if the abnormalities are persistent. The pathologist should be asked to look for evidence of hemochromatosis, although the prevalence of hemochromatosis is usually lower than would be seen in thalassemia. In the case of both severe cholestasis and significant intrahepatic sickling, chronic simple transfusion or erythrocytapheresis should be initiated.¹⁹⁶

Hearing

A substantial number of sickle cell patients have sensorineural hearing loss.^{197, 198} This is an association that is not related to previous episodes of otitis media or meningitis. It is a result of sickling within the cochlear vasculature with subsequent destruction of hair cells. We have not performed hearing assessments routinely but do ask parents to report any suspected hearing loss in the child. When hearing deficit is suspected, audiometry is then requested.

Osteonecrosis

While patients with sickle cell disease are known to have bony changes as a result of repeated bony infarction and marrow expansion, the most problematic of skeletal complications is avascular necrosis (AVN).^{199, 200} Its development is insidious and patients initially may be asymptomatic. In fact, most of the time an effort to make the diagnosis is not made unless the patient complains of pain and/or limitation of range of motion. It is most frequently seen in the femoral head, but can also present in the humerus--- and other joints. On plain film, it is characterized by the presence of subepiphyseal lucency and widened joint space or fragmentation and scarring of the epiphysis. The most effective imaging method that allows diagnosis of AVN, however, is magnetic resonance imaging (MRI). Some individuals will be asymptomatic but many are plagued by chronic pain and limitation of range of mobility of the joint. Placement of the patient on bedrest is usually not practical. The patient should be referred to an orthopedist for consideration of further treatment. Symptomatically, NSAIDS have been used for symptomatic relief and narcotic analgesics are reserved for the most severe pain.

However, several surgical approaches can be taken for relief of pain. They include hip core decompression, femoral revascularization, and total hip replacement arthroplasty.^{201, 202} Shoulder arthroplasty has also been performed for the treatment of humeral AVN. Unfortunately, none of these procedures has been completely successful in alleviating pain from this bony complication. With hip replacement, 50% of patients subsequently needed to return for surgical revision within 10 years.^{203, 204} With all forms of remediation of AVN, there can be significant complications, seen with reported rates as high as 50%. These include osteomyelitis, development of acute chest syndrome, deep venous thrombosis, and development of orthopedic complications during and after surgery.

We have then customarily performed erythrocytapheresis in those patients who will undergo corrective surgery for AVN. The rationale for this practice has been that by reducing the hemoglobin S level significantly below 30%, we should be able to avoid precipitation of sickling complications such as acute chest syndrome, especially when most of the surgical approaches outlined above entail lengthy operations. Other precautions that can be taken to improve postoperative complication rates have included systemic antibiotic use concurrently with antibiotic-infused cement for local application. We have not routinely advocated the use of prophylactic anticoagulation for DVT prevention but would evaluate patients on a case-by-case basis based upon risk factors such as obesity, family history of PE or DVT,

Patients may also develop vertebral changes that result in the "codfish vertebrae" appearance of the spine. This appearance is usually of flattened vertebrae. Patients may often complain of chronic,

especially lower, back pain. This complication can be difficult to treat. Patients should be taught to differentiate between this chronic pain and the more acute pain associated with pain crisis. Although the patient may be accustomed to taking narcotic analgesia for this pain, he/she should be taught to resort to other means of pain control, when possible.

Growth and Metabolic Disturbances

Growth

It is generally acknowledged that children with homozygous sickle cell disease may experience growth and sexual maturational delays.²⁰⁵⁻²⁰⁸ While the birthweight of those with sickle cell disease is normal, growth rates in those with SS disease and S-beta⁰-thalassemia are slower than those of children with SC disease and S-beta⁺-thalassemia, as well as normal children. This growth deficit may be seen as early as two years of age but may have greater divergence in adolescence. It may also be more evident in males with the disease than females. The reasons for this difference are not clearly understood. It is known that growth hormone levels are usually normal, although rarely levels of the hormone can be deficient. Investigators have, however, noted that there are deficits in the growth hormone-insulin growth factor-I-IGF-binding protein 3 axis that have been linked to the defective growth pattern seen in sickle cell disease.^{209, 210} Patients also may have inadequate nutritional intake, something which again is only incompletely understood.²¹¹ This includes intake of macro- and micronutrients, such as vitamins D and E, folate, calcium, and fiber.

However, there are conflicting results to studies investigating the role of nutritional intake and energy expenditure in growth delay. In one study, children with the disorder who received chronic transfusions and maintained a hematocrit of >30% had significant improvement of growth parameters after at least 2 years of transfusion.²¹² This may indicate that elevated total energy expenditure and overall hematologic status were also important factors in determining growth in these children. Yet in another study, there was no effect of transfusion therapy on changes in growth status over time.²¹³ It is for this reason that serial measurements of height, weight, and in infants head circumference should be carefully and regularly monitored. This should be a job that is left not just to the general pediatrician but to the hematologist/oncologist also. We would posit that a child's falling "off the growth curve" is a key indicator of a child who is in need of nutritional counseling. It may also be that weight and height of <5th percentile or BMI <5th percentile should warrant an assessment of the child's nutritional status and calls for a nutritional consultation to see if oral nutritional supplementation is necessitated, but in a child with chronic illness, this may not be the most reliable indicator of growth deficiency. Unfortunately, as of yet, there is no consensus as to nutritional measures or programs that would be optimal for this population of children. Each child's needs must be assessed and programs individualized.

Vitamin D Deficiency²¹⁴⁻²¹⁶

Ninety percent of vitamin D3 (cholecalciferol) is manufactured in the skin through ultraviolet radiation. Blacks and other ethnicities with high skin pigment content may be deficient in this vitamin which is necessary for the promotion of normal bone mineralization and normal calcium homeostasis. Consequences of deficiency include osteopenia/osteoporosis, myopathy, chronic bone pain, and poor

immune function, as well as increased risk of asthma. In one study, a 2011 study by Osunkwo and others, just under 30% of patients had severe vitamin D deficiency with levels ≤ 10 ng/ml.²¹⁷ The number of patients with sickle cell and vitamin D insufficiency, however, may vary according to study. In a study published in 2014, 91% of children with sickle cell disease had vitamin D levels < 20 ng/ml.²¹⁸ Vitamin D deficiency was associated with chronic pain in a significant number of patients with deficiency.^{214, 219} Bone fragility was also inversely correlated with vitamin D levels. There was also similar correlation with avascular necrosis and vertebral compression prevalence. Patients with sickle cell disease should therefore be reminded of the risk factors for vitamin D insufficiency. These include: lack of sun exposure, hepatic and renal abnormalities, and lack of dietary inclusion of fish, eggs, and meats (vitamin D3) and vegetables (vitamin D2). Placement of patients on oral cholecalciferol at high doses (e.g. 4000 to 100,000IU per week for 6 weeks followed by continued low-dose supplementation has been shown to result in normalized vitamin D levels and significantly, fewer days of pain, better resolution of chronic pain symptoms, and improvement in bone density.²²⁰

Zinc Deficiency^{221, 222}

Zinc deficiency has been identified in patients with sickle cell disease and has been associated with many concurrent problems, including sexual maturational delay, hyperammonemia and encephalopathy, poor wound healing (as in the leg ulcers experienced by this population), abnormal growth, and immune dysfunction. Excess excretion of the mineral in the urine may be one of the causes of the deficiency. Inadequate dietary intake, increased demand for zinc because of hemolysis, decrease in intake, or poor absorption from the gut, and high protein turnover are also felt to play a role. Zinc has also been reported to decrease oxidative stress and inflammatory cytokines, as well as increase the levels of anti-inflammatory proteins. Dietary Zinc deprivation has also been shown in animal studies to increase osmotic fragility of red cells.

Magnesium, selenium, and folate^{221, 223}

Variable results have been published with regards to magnesium levels. However, there may be a subset of patients with sickle cell disease who have low Mg^{2+} levels. Low levels of Mg^{2+} have been reported to be associated with more sickling and also with red cell dehydration. Magnesium, along with copper, iron, and selenium has been shown to relieve the oxidative stress of sickle cell disease. Selenium plays an important role as a cofactor for the reduction of antioxidant enzymes such as glutathione peroxidase. There is currently no standardized protocol or regimen for the replacement of these minerals.

Folic acid is, however, given routinely as a safeguard against development of deficiency of this nutrient in the face of increased folate need resulting from increase marrow turnover in sickle cell disease. There has, however, been only one controlled trial that examined the role of folate deficiency in sickle cell disease and, as a result, there is considerable controversy regarding its use in sickle cell disease and other chronic hemolytic disorders.²²⁴ Trials looking at this issue have been heterogeneous and have included “n’s” that were small, making any statistical comparison of use vs. non-use difficult. Various cited is evidence of megaloblastic anemia and red cell and serum folate deficiency in the disease. On the other side of the coin is the fact that megaloblastic changes are uncommon and that there are no signs of

improvement to either parameter with supplementation. Still others feel that dietary folate intake can be borderline in individuals with chronic disease, whether it is due to sickle cell or not. Although the usage of folic acid is not evidence-based, we would suggest continuation of the medication at the current recommended dosage of 1 mg daily.

Sexual maturation²⁰⁵⁻²⁰⁸

Sexual maturational delay is also seen in sickle cell disease and has been a significant cause for consternation among adolescents with the disease. In both sexes, there is delay in onset of puberty. This includes a delay in spontaneous menarchal onset and breast development in girls, and smaller testicular volume and lower testosterone concentrations in boys. This delay's etiology is unclear although it has been hypothesized that it is the result of primary testicular failure, hypothalamic and/or pituitary dysfunction, zinc deficiency or it is thought by some to be constitutional. Patients with sickle cell disease may also have decreases in sperm count and other indices of sperm quality. Infertility has been said to be a preferentially occurring problem among males with the disorder, while women may have higher fetal wastage, higher incidence of premature births, and higher risk pregnancies and deliveries overall. The estimated median age for attainment of Tanner Stage is shown in the following Table (age in years; approximate ages):^{25, 226, 227}

	Tanner Stage	SS	S beta ⁰	Normal
Females	2	12	10-11	11
	3	14	13	12
	4	15	14-15	13
	5	19	21	16
Males	2	12-13	12-13	12
	3	14-15	12-13	12-14
	4	16	13-14	13-14
	5	18	18-19	17

Practitioners are encouraged to discuss the issue of growth and pubertal delay with the patients and their parents. Psychological counseling has rarely been needed, once patients are reassured that growth or sexual development, while delayed, will eventually "catch up." However, every effort should be made to have the patient seen by social worker or psychologist if concern persists. Also, if the patient appears to be significantly delayed beyond the stage or time expected for age, hormonal levels (e.g., LH, FSH and testosterone for males, estradiol for females, as well as IGF and thyroid levels should be obtained. If significant hormonal deficiency is suspected, then patients should be referred to Endocrinology for a more thorough workup and hormonal replacement, if necessary.

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