

Policies, Procedures, Management Guidelines

Pediatric Sickle Cell Disease Program
University of Florida
Department of Pediatrics
Division of Pediatric Hematology/Oncology

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Special thanks to Amos Kedar, MD who originally wrote the above guidelines

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Note: These guidelines do not indicate an exclusive course of treatment or serve as a standard of care. Variations based on a physician's best medical judgment may be appropriate in individual cases.

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Pediatric Sickle Cell Program

The information on the following pages has been designed to acquaint health care providers, viz., physicians, physician assistants, nurses, fellows, residents, or students; with the functions and activities of the Pediatric Sickle Cell Program at the University of Florida in Gainesville, FL.

Purpose

The Sickle Cell program is a component of the division of Pediatric Hematology/Oncology and is designed to provide consultation, comprehensive specialty medical care, psychosocial/financial support, and education/information to patients with sickle cell disease and their families.

Location

The Sickle Cell clinic is located at the Shands Medical Plaza on the second floor.

Address

Pediatric Specialty Clinic
2000 SW Archer Road
Gainesville, Florida 32610-0383

Clinic Days

Patients with sickle cell disease are seen in the clinic on any scheduled clinic day but are mainly seen on Mondays and Wednesdays.

Primary Care

The sickle cell program does not provide primary care. All patients are encouraged to have a primary care physician or neighborhood clinic to provide routine immunizations, offer anticipatory guidance, and be available to assist with the acute care of sickle cell related problems.

Program Personnel

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Hematology-Oncology Attendings

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Hematology-Oncology Fellows

Angela Rivers, MD

Paul LoDuca, MD

Clinic Nurses

Donna McAffe, RN
Christie Glenn, RN

Dax Balch, RN

Social Workers

Sandra Powers, MSW

Child Life Specialist

Jenna Priest

Other faculty physicians, fellows, and nurses as well as residents, medical students, nursing assistants, phlebotomist, and other consultants also participate in the management of sickle cell patients as needed.

Satellite Clinics

We participate in several satellite clinics in the State of Florida that are sponsored by the Children's Medical Services (CMS). These clinics are held four times a year in Daytona Beach, and 10 times a year in Tallahassee. Staffs participating in these outpatient clinics are Dr. Vishwas Sakhalkar, Dr. Levette Dunbar and Ms. Lynn Davidson, physician assistants as well as CMS nurses. The staffs will usually service 20-25 patients (with non-acute issues) a clinic. If complex treatment is recommended, the patients are referred to Gainesville. Phone follow-up consultations on these patients continue throughout the year. While most of these are patients covered by CMS, a limited number of consultations of non-CMS patients take place by prior arrangements.

Special thanks to Dr. Amos Kedar who originally wrote the above guidelines

Policies and Procedures

I. Frequency of Outpatient Visits

1. **Initial Visit:** Infants diagnosed by the Newborn Screening Program of Florida should be seen by the Pediatric Sickle Cell Program before 3 months of age. The purpose of the initial clinic visit is to perform hematological studies, confirm the exact diagnosis, perform family studies, if desired, and to provide initial education and counseling to the parents. For newly diagnosed patients, a follow-up visit occurs one month later to discuss the results of the confirmatory studies with the family, and to review issues regarding prophylactic penicillin, spleen palpation, genetics, and routine health maintenance. Older patients with an established diagnosis of sickle cell disease are seen at 3 to 12 month intervals as appropriate for age.

Follow-up Outpatient Visits At each routine visit a CBC and reticulocyte count should be done to document steady state values (which may change during the first several years of life). A comprehensive metabolic panel may be done yearly on patients over 5 years of age. Oxygen saturation is measured at every visit in patients over 2 years of age, if possible. Routine visits usually occur at the following minimum intervals. Children are seen more often if clinically indicated. For children with a private pediatrician knowledgeable about sickle cell disease, the interval between follow up visits can be doubled.

Sickle Cell Anemia and Sickle Beta Zero-Thalassemia

- ◆ Less than 2 years of age: every 3 months
- ◆ 2 years to 5 years of age: every 4 months
- ◆ Over 5 years of age: every 6 months.

Hemoglobin SC Disease and Sickle Beta-Plus Thalassemia, and Hemoglobin E Disease

- ◆ Less than 2 years of age: every 3 months
- ◆ 2 years to 5 years of age: every 4 months
- ◆ Over 5 years of age: Document in the medical record, inform and educate the parents and referring physician. They should be seen every 6 to 12 months.

S-Hereditary Persistence of Fetal Hemoglobin

These patients have hemoglobin F of 15% or more and the hemoglobin is homogeneously distributed (i.e. each red blood cell has some hemoglobin F on Kliehauer-Betke stain). Please note: This diagnosis can only be made at 3-4 years of age, since this is when permanent hemoglobin distribution settles in. Once a diagnosis is made, they usually need annual visits. Some children carrying this diagnosis may actually have a mild form of sickle cell anemia and may need closer follow-up.

II Clinic Follow up After Hospital Discharge at University of Florida

1. **Vaso-Occlusive (painful) Event:** Keep next regularly scheduled clinic appointment.
2. **Fever, Rule out Sepsis (with negative blood cultures) with or without pain:** Keep previously scheduled appointment.
3. **Acute Chest Syndrome:** Follow up within 7 days after discharge for physical examination, hemogram, reticulocyte count, pulse oximetry and an X-ray, if needed, to document clearance of infiltrate. Pulmonary function testing should be arranged 2 months after discharge.
4. **Aplastic Crisis:** Follow up from 2 to 7 days later (depending upon patient's discharge hemoglobin and reticulocyte count). Upon return to clinic, children should wear masks and be isolated from other patients until their reticulocyte count has risen over 1-2%. Siblings with sickle cell anemia who have not had an aplastic crisis should have a hemogram and reticulocyte count performed at once and again 7-14 days later due to the contagiousness of parvovirus B19.
5. **Acute Splenic Sequestration Crisis (ASSC):** Follow up 1 to 3 days later for a hemogram, check spleen size, and a general clinical status, until spleen size and hemogram are stable.
6. **Following elective surgery:** Keep regularly scheduled clinic appointment.

III. **Use of Penicillin to Prevent Pneumococcal Infection**

1. **Penicillin Prophylaxis in Sickle Cell Anemia and S-Beta-Zero Thalassemia Disease.** Prophylaxis penicillin is initiated in all babies suspected of having sickle cell anemia or sickle beta-zero thalassemia at 1 to 3 months of age. Prophylaxis consists of penicillin VK 125 mg BID until 36 months of age and 250 mg BID thereafter. Tablets (crushed if necessary, for infants and small children) are preferred to suspension because of the short 14 day shelf life and requirements for refrigeration of the suspension. Once prophylactic penicillin is begun, it is continued until 5 years of age (exception noted below). The same protocol is followed for infants suspected of having S-C disease and S-Beta-Plus thalassemia.
2. Based on the results of the PROPS II study, we recommend that routine prophylactic penicillin be discontinued in all patients at five years of age (one month after the second dose of pneumococcal polysaccharide vaccine is administered) with the exception of the following. Parents may choose to continue prophylactic penicillin, and any patient who has had a splenectomy should be placed on prophylactic penicillin for life. Patients who have had a documented pneumococcal bacteremia should also receive penicillin prophylaxis indefinitely. Except for the above patients, penicillin prophylaxis is

discontinued one month after the second dose of pneumococcal polysaccharide vaccine is administered at 5 years of age.

3. Other Issues Regarding Penicillin

- a. Routine prescription refills are given only during clinic visits and/or by telephone during working hours. At night or during the weekends sufficient medication is prescribed to cover the patient until the next regular working day. The family is instructed to call the clinic for further refills.
- b. Prophylactic penicillin is generally not taken when the child is receiving therapeutic antibiotics for another reason. The parent should be reminded to resume the penicillin following completion of the other antibiotic. Children who are allergic to cephalosporin should remain on penicillin even while taking another antibiotic to prevent sensitization.
- c. Children with a proven allergy to penicillin should receive prophylaxis with erythromycin. Children up to age 3 years of age should receive 125 mg bid and children over 3 years of age should receive 250 mg bid.

IV Immunizations

1. Pneumococcal Vaccine:

Children with sickle cell disease are at high risk of invasive pneumococcal infection. Heptavalent pneumococcal conjugate vaccine (Prevnar) is recommended for universal use in children 23 months and younger; to be given concurrently with other recommended childhood vaccines at 2, 4, 6 and 12 to 15 months of age. For children 7 to 23 months old who have not received previous doses of Prevnar, administration of a reduced number of doses is recommended. Two doses of Prevnar are recommended for children 24 to 59 months old at high risk of invasive pneumococcal infection-including children with functional, anatomic, or congenital asplenia; infection with human immunodeficiency virus; and other predisposing conditions-who have not been immunized previously with Prevnar. Recommendations have been made for use of 23-valent pneumococcal polysaccharide (23PS) vaccine in high-risk children at 2 years, 5 years of age and later, to expand serotype coverage. High-risk children should be given vaccines at the earliest possible opportunity. Use of antibiotic prophylaxis in children younger than 5 years with functional or anatomic asplenia, including children with sickle cell disease, continues to be recommended. Children who have not experienced invasive pneumococcal infection and have received recommended pneumococcal immunizations may discontinue prophylaxis after 5 years of age.

Recommended Immunization Schedule for Persons Aged 0 Through 6 Years—United States • 2009

For those who fall behind or start late, see the catch-up schedule

Vaccine ▼	Age ►	Birth	1 month	2 months	4 months	6 months	12 months	15 months	18 months	19–23 months	2–3 years	4–6 years
Hepatitis B ¹	HepB	HepB	HepB		^{see footnote 1}	HepB						
Rotavirus ²				RV	RV	RV ²						
Diphtheria, Tetanus, Pertussis ³				DTaP	DTaP	DTaP	^{see footnote 3}	DTaP				DTaP
<i>Haemophilus influenzae</i> type b ⁴				Hib	Hib	Hib ⁴		Hib				
Pneumococcal ⁵				PCV	PCV	PCV		PCV			PPSV	
Inactivated Poliovirus				IPV	IPV			IPV				IPV
Influenza ⁶								Influenza (Yearly)				
Measles, Mumps, Rubella ⁷								MMR		^{see footnote 7}		MMR
Varicella ⁸								Varicella		^{see footnote 8}		Varicella
Hepatitis A ⁹								HepA (2 doses)			HepA Series	
Meningococcal ¹⁰											MCV	

Range of recommended ages

Certain high-risk groups

This schedule indicates the recommended ages for routine administration of currently licensed vaccines, as of December 1, 2008, for children aged 0 through 6 years. Any dose not administered at the recommended age should be administered at a subsequent visit, when indicated and feasible. Licensed combination vaccines may be used whenever any component of the combination is indicated and other components are not contraindicated and if approved by the Food and Drug Administration for that dose of

the series. Providers should consult the relevant Advisory Committee on Immunization Practices statement for detailed recommendations, including high-risk conditions: <http://www.cdc.gov/vaccines/pubs/acip-list.htm>. Clinically significant adverse events that follow immunization should be reported to the Vaccine Adverse Event Reporting System (VAERS). Guidance about how to obtain and complete a VAERS form is available at <http://www.vaers.hhs.gov> or by telephone, 800-822-7967.

1. Hepatitis B vaccine (HepB). (Minimum age: birth)

At birth:

- Administer monovalent HepB to all newborns before hospital discharge.
- If mother is hepatitis B surface antigen (HBsAg)-positive, administer HepB and 0.5 mL of hepatitis B immune globulin (HBIG) within 12 hours of birth.
- If mother's HBsAg status is unknown, administer HepB within 12 hours of birth. Determine mother's HBsAg status as soon as possible and, if HBsAg-positive, administer HBIG (no later than age 1 week).

After the birth dose:

- The HepB series should be completed with either monovalent HepB or a combination vaccine containing HepB. The second dose should be administered at age 1 or 2 months. The final dose should be administered no earlier than age 24 weeks.
- Infants born to HBsAg-positive mothers should be tested for HBsAg and antibody to HBsAg (anti-HBs) after completion of at least 3 doses of the HepB series, at age 9 through 18 months (generally at the next well-child visit).

4-month dose:

- Administration of 4 doses of HepB to infants is permissible when combination vaccines containing HepB are administered after the birth dose.

2. Rotavirus vaccine (RV). (Minimum age: 6 weeks)

- Administer the first dose at age 6 through 14 weeks (maximum age: 14 weeks 6 days). Vaccination should not be initiated for infants aged 15 weeks or older (i.e., 15 weeks 0 days or older).
- Administer the final dose in the series by age 8 months 0 days.
- If Rotarix[®] is administered at ages 2 and 4 months, a dose at 6 months is not indicated.

3. Diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP). (Minimum age: 6 weeks)

- The fourth dose may be administered as early as age 12 months, provided at least 6 months have elapsed since the third dose.
- Administer the final dose in the series at age 4 through 6 years.

4. *Haemophilus influenzae* type b conjugate vaccine (Hib). (Minimum age: 6 weeks)

- If PRP-OMP (PedvaxHIB[®] or Comvax[®] [HepB-Hib]) is administered at ages 2 and 4 months, a dose at age 6 months is not indicated.
- TriHiBit[®] (DTaP/Hib) should not be used for doses at ages 2, 4, or 6 months but can be used as the final dose in children aged 12 months or older.

5. Pneumococcal vaccine. (Minimum age: 6 weeks for pneumococcal conjugate vaccine [PCV]; 2 years for pneumococcal polysaccharide vaccine [PPSV])

- PCV is recommended for all children aged younger than 5 years. Administer 1 dose of PCV to all healthy children aged 24 through 59 months who are not completely vaccinated for their age.

- Administer PPSV to children aged 2 years or older with certain underlying medical conditions (see *MMWR* 2000;49[No. RR-9]), including a cochlear implant.

6. Influenza vaccine. (Minimum age: 6 months for trivalent inactivated influenza vaccine [TIV]; 2 years for live, attenuated influenza vaccine [LAIV])

- Administer annually to children aged 6 months through 18 years.
- For healthy nonpregnant persons (i.e., those who do not have underlying medical conditions that predispose them to influenza complications) aged 2 through 49 years, either LAIV or TIV may be used.
- Children receiving TIV should receive 0.25 mL if aged 6 through 35 months or 0.5 mL if aged 3 years or older.
- Administer 2 doses (separated by at least 4 weeks) to children aged younger than 9 years who are receiving influenza vaccine for the first time or who were vaccinated for the first time during the previous influenza season but only received 1 dose.

7. Measles, mumps, and rubella vaccine (MMR). (Minimum age: 12 months)

- Administer the second dose at age 4 through 6 years. However, the second dose may be administered before age 4, provided at least 28 days have elapsed since the first dose.

8. Varicella vaccine. (Minimum age: 12 months)

- Administer the second dose at age 4 through 6 years. However, the second dose may be administered before age 4, provided at least 3 months have elapsed since the first dose.
- For children aged 12 months through 12 years the minimum interval between doses is 3 months. However, if the second dose was administered at least 28 days after the first dose, it can be accepted as valid.

9. Hepatitis A vaccine (HepA). (Minimum age: 12 months)

- Administer to all children aged 1 year (i.e., aged 12 through 23 months). Administer 2 doses at least 6 months apart.
- Children not fully vaccinated by age 2 years can be vaccinated at subsequent visits.
- HepA also is recommended for children older than 1 year who live in areas where vaccination programs target older children or who are at increased risk of infection. See *MMWR* 2006;55[No. RR-7].

10. Meningococcal vaccine. (Minimum age: 2 years for meningococcal conjugate vaccine [MCV] and for meningococcal polysaccharide vaccine [MPSV])

- Administer MCV to children aged 2 through 10 years with terminal complement component deficiency, anatomic or functional asplenia, and certain other high-risk groups. See *MMWR* 2005;54[No. RR-7].
- Persons who received MPSV 3 or more years previously and who remain at increased risk for meningococcal disease should be revaccinated with MCV.

Recommended Immunization Schedule for Persons Aged 7 Through 18 Years—United States • 2009

For those who fall behind or start late, see the schedule below and the catch-up schedule

Vaccine ▼	Age ►	7–10 years	11–12 years	13–18 years
Tetanus, Diphtheria, Pertussis ¹		see footnote 1	Tdap	Tdap
Human Papillomavirus ²		see footnote 2	HPV (3 doses)	HPV Series
Meningococcal ³		MCV	MCV	MCV
Influenza ⁴		Influenza (Yearly)		
Pneumococcal ⁵		PPSV		
Hepatitis A ⁶		HepA Series		
Hepatitis B ⁷		HepB Series		
Inactivated Poliovirus ⁸		IPV Series		
Measles, Mumps, Rubella ⁹		MMR Series		
Varicella ¹⁰		Varicella Series		

Range of recommended ages

Catch-up immunization

Certain high-risk groups

This schedule indicates the recommended ages for routine administration of currently licensed vaccines, as of December 1, 2008, for children aged 7 through 18 years. Any dose not administered at the recommended age should be administered at a subsequent visit, when indicated and feasible. Licensed combination vaccines may be used whenever any component of the combination is indicated and other components are not contraindicated and if approved by the Food and Drug Administration for that dose of

the series. Providers should consult the relevant Advisory Committee on Immunization Practices statement for detailed recommendations, including high-risk conditions: <http://www.cdc.gov/vaccines/pubs/acip-list.htm>. Clinically significant adverse events that follow immunization should be reported to the Vaccine Adverse Event Reporting System (VAERS). Guidance about how to obtain and complete a VAERS form is available at <http://www.vaers.hhs.gov> or by telephone, 800-822-7967.

1. Tetanus and diphtheria toxoids and acellular pertussis vaccine (Tdap). (Minimum age: 10 years for BOOSTRIX® and 11 years for ADACEL®)

- Administer at age 11 or 12 years for those who have completed the recommended childhood DTP/DTaP vaccination series and have not received a tetanus and diphtheria toxoid (Td) booster dose.
- Persons aged 13 through 18 years who have not received Tdap should receive a dose.
- A 5-year interval from the last Td dose is encouraged when Tdap is used as a booster dose; however, a shorter interval may be used if pertussis immunity is needed.

2. Human papillomavirus vaccine (HPV). (Minimum age: 9 years)

- Administer the first dose to females at age 11 or 12 years.
- Administer the second dose 2 months after the first dose and the third dose 6 months after the first dose (at least 24 weeks after the first dose).
- Administer the series to females at age 13 through 18 years if not previously vaccinated.

3. Meningococcal conjugate vaccine (MCV).

- Administer at age 11 or 12 years, or at age 13 through 18 years if not previously vaccinated.
- Administer to previously unvaccinated college freshmen living in a dormitory.
- MCV is recommended for children aged 2 through 10 years with terminal complement component deficiency, anatomic or functional asplenia, and certain other groups at high risk. See *MMWR* 2005;54(No. RR-7).
- Persons who received MPSV 5 or more years previously and remain at increased risk for meningococcal disease should be revaccinated with MCV.

4. Influenza vaccine.

- Administer annually to children aged 6 months through 18 years.
- For healthy nonpregnant persons (i.e., those who do not have underlying medical conditions that predispose them to influenza complications) aged 2 through 49 years, either LAIV or TIV may be used.
- Administer 2 doses (separated by at least 4 weeks) to children aged younger than 9 years who are receiving influenza vaccine for the first time or who were vaccinated for the first time during the previous influenza season but only received 1 dose.

5. Pneumococcal polysaccharide vaccine (PPSV).

- Administer to children with certain underlying medical conditions (see *MMWR* 1997;46[No. RR-8]), including a cochlear implant. A single revaccination should be administered to children with functional or anatomic asplenia or other immunocompromising condition after 5 years.

6. Hepatitis A vaccine (HepA).

- Administer 2 doses at least 6 months apart.
- HepA is recommended for children older than 1 year who live in areas where vaccination programs target older children or who are at increased risk of infection. See *MMWR* 2006;55(No. RR-7).

7. Hepatitis B vaccine (HepB).

- Administer the 3-dose series to those not previously vaccinated.
- A 2-dose series (separated by at least 4 months) of adult formulation Recombivax HB® is licensed for children aged 11 through 15 years.

8. Inactivated poliovirus vaccine (IPV).

- For children who received an all-IPV or all-oral poliovirus (OPV) series, a fourth dose is not necessary if the third dose was administered at age 4 years or older.
- If both OPV and IPV were administered as part of a series, a total of 4 doses should be administered, regardless of the child's current age.

9. Measles, mumps, and rubella vaccine (MMR).

- If not previously vaccinated, administer 2 doses or the second dose for those who have received only 1 dose, with at least 28 days between doses.

10. Varicella vaccine.

- For persons aged 7 through 18 years without evidence of immunity (see *MMWR* 2007;56[No. RR-4]), administer 2 doses if not previously vaccinated or the second dose if they have received only 1 dose.
- For persons aged 7 through 12 years, the minimum interval between doses is 3 months. However, if the second dose was administered at least 28 days after the first dose, it can be accepted as valid.
- For persons aged 13 years and older, the minimum interval between doses is 28 days.

The Recommended Immunization Schedules for Persons Aged 0 Through 18 Years are approved by the Advisory Committee on Immunization Practices (www.cdc.gov/vaccines/recs/acip), the American Academy of Pediatrics (<http://www.aap.org>), and the American Academy of Family Physicians (<http://www.aafp.org>).

DEPARTMENT OF HEALTH AND HUMAN SERVICES • CENTERS FOR DISEASE CONTROL AND PREVENTION

Catch-up Immunization Schedule for Persons Aged 4 Months Through 18 Years Who Start Late or Who Are More Than 1 Month Behind—United States • 2009

The table below provides catch-up schedules and minimum intervals between doses for children whose vaccinations have been delayed. A vaccine series does not need to be restarted, regardless of the time that has elapsed between doses. Use the section appropriate for the child's age.

CATCH-UP SCHEDULE FOR PERSONS AGED 4 MONTHS THROUGH 6 YEARS					
Vaccine	Minimum Age for Dose 1	Minimum Interval Between Doses			
		Dose 1 to Dose 2	Dose 2 to Dose 3	Dose 3 to Dose 4	Dose 4 to Dose 5
Hepatitis B ¹	Birth	4 weeks	8 weeks (and at least 16 weeks after first dose)		
Rotavirus ²	6 wks	4 weeks	4 weeks ²		
Diphtheria, Tetanus, Pertussis ³	6 wks	4 weeks	4 weeks	6 months	6 months ³
<i>Haemophilus influenzae</i> type b ⁴	6 wks	4 weeks if first dose administered at younger than age 12 months 8 weeks (as final dose) if first dose administered at age 12-14 months No further doses needed if first dose administered at age 15 months or older	4 weeks ⁴ if current age is younger than 12 months 8 weeks (as final dose) ⁴ if current age is 12 months or older and second dose administered at younger than age 15 months No further doses needed if previous dose administered at age 15 months or older	8 weeks (as final dose) This dose only necessary for children aged 12 months through 59 months who received 3 doses before age 12 months	
Pneumococcal ⁵	6 wks	4 weeks if first dose administered at younger than age 12 months 8 weeks (as final dose for healthy children) if first dose administered at age 12 months or older or current age 24 through 59 months No further doses needed for healthy children if first dose administered at age 24 months or older	4 weeks if current age is younger than 12 months 8 weeks (as final dose for healthy children) if current age is 12 months or older No further doses needed for healthy children if previous dose administered at age 24 months or older	8 weeks (as final dose) This dose only necessary for children aged 12 months through 59 months who received 3 doses before age 12 months or for high-risk children who received 3 doses at any age	
Inactivated Poliovirus ⁶	6 wks	4 weeks	4 weeks	4 weeks ⁶	
Measles, Mumps, Rubella ⁷	12 mos	4 weeks			
Varicella ⁸	12 mos	3 months			
Hepatitis A ⁹	12 mos	6 months			
CATCH-UP SCHEDULE FOR PERSONS AGED 7 THROUGH 18 YEARS					
Tetanus, Diphtheria/ Tetanus, Diphtheria, Pertussis ¹⁰	7 yrs ¹⁰	4 weeks	4 weeks if first dose administered at younger than age 12 months 6 months if first dose administered at age 12 months or older	6 months if first dose administered at younger than age 12 months	
Human Papillomavirus ¹¹	9 yrs	Routine dosing intervals are recommended ¹¹			
Hepatitis A ⁹	12 mos	6 months			
Hepatitis B ¹	Birth	4 weeks	8 weeks (and at least 16 weeks after first dose)		
Inactivated Poliovirus ⁶	6 wks	4 weeks	4 weeks	4 weeks ⁶	
Measles, Mumps, Rubella ⁷	12 mos	4 weeks			
Varicella ⁸	12 mos	3 months if the person is younger than age 13 years 4 weeks if the person is aged 13 years or older			

1. Hepatitis B vaccine (HepB).

- Administer the 3-dose series to those not previously vaccinated.
- A 2-dose series (separated by at least 4 months) of adult formulation Recombivax HB[®] is licensed for children aged 11 through 15 years.

2. Rotavirus vaccine (RV).

- The maximum age for the first dose is 14 weeks 6 days. Vaccination should not be initiated for infants aged 15 weeks or older (i.e., 15 weeks 0 days or older).
- Administer the final dose in the series by age 8 months 0 days.
- If Rotarix[®] was administered for the first and second doses, a third dose is not indicated.

3. Diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP).

- The fifth dose is not necessary if the fourth dose was administered at age 4 years or older.

4. *Haemophilus influenzae* type b conjugate vaccine (Hib).

- Hib vaccine is not generally recommended for persons aged 5 years or older. No efficacy data are available on which to base a recommendation concerning use of Hib vaccine for older children and adults. However, studies suggest good immunogenicity in persons who have sickle cell disease, leukemia, or HIV infection, or who have had a splenectomy; administering 1 dose of Hib vaccine to these persons is not contraindicated.
- If the first 2 doses were PRP-OMP (PedvaxHib[®] or Comvax[®]), and administered at age 11 months or younger, the third (and final) dose should be administered at age 12 through 15 months and at least 8 weeks after the second dose.
- If the first dose was administered at age 7 through 11 months, administer 2 doses separated by 4 weeks and a final dose at age 12 through 15 months.

5. Pneumococcal vaccine.

- Administer 1 dose of pneumococcal conjugate vaccine (PCV) to all healthy children aged 24 through 59 months who have not received at least 1 dose of PCV on or after age 12 months.
- For children aged 24 through 59 months with underlying medical conditions, administer 1 dose of PCV if 3 doses were received previously or administer 2 doses of PCV at least 8 weeks apart if fewer than 3 doses were received previously.
- Administer pneumococcal polysaccharide vaccine (PPSV) to children aged 2 years or older with certain underlying medical conditions (see *MMWR* 2000;49[No. RR-9]), including a cochlear implant, at least 8 weeks after the last dose of PCV.

6. Inactivated poliovirus vaccine (IPV).

- For children who received an all-IPV or all-oral poliovirus (OPV) series, a fourth dose is not necessary if the third dose was administered at age 4 years or older.
- If both OPV and IPV were administered as part of a series, a total of 4 doses should be administered, regardless of the child's current age.

7. Measles, mumps, and rubella vaccine (MMR).

- Administer the second dose at age 4 through 6 years. However, the second dose may be administered before age 4, provided at least 28 days have elapsed since the first dose.
- If not previously vaccinated, administer 2 doses with at least 28 days between doses.

8. Varicella vaccine.

- Administer the second dose at age 4 through 6 years. However, the second dose may be administered before age 4, provided at least 3 months have elapsed since the first dose.
- For persons aged 12 months through 12 years, the minimum interval between doses is 3 months. However, if the second dose was administered at least 28 days after the first dose, it can be accepted as valid.
- For persons aged 13 years and older, the minimum interval between doses is 28 days.

9. Hepatitis A vaccine (HepA).

- HepA is recommended for children older than 1 year who live in areas where vaccination programs target older children or who are at increased risk of infection. See *MMWR* 2006;55(No. RR-7).

10. Tetanus and diphtheria toxoids vaccine (Td) and tetanus and diphtheria toxoids and acellular pertussis vaccine (Tdap).

- Doses of DTaP are counted as part of the Td/Tdap series
- Tdap should be substituted for a single dose of Td in the catch-up series or as a booster for children aged 10 through 18 years; use Td for other doses.

11. Human papillomavirus vaccine (HPV).

- Administer the series to females at age 13 through 18 years if not previously vaccinated.
- Use recommended routine dosing intervals for series catch-up (i.e., the second and third doses should be administered at 2 and 6 months after the first dose). However, the minimum interval between the first and second doses is 4 weeks. The minimum interval between the second and third doses is 12 weeks, and the third dose should be given at least 24 weeks after the first dose.

TABLE 1

IMMUNIZATIONS AND PROPHYLATIC MEDICATIONS

Age	Pneumococcal conjugate Vaccine (Pneumovax)	Pneumococcal Polysaccharide Vaccine (Pneumovax)	Meningococcal Vaccine	Influenza Vaccine	Penicillin	Folic Acid
2 mo	X				8	
4 mo	X				8	
6 mo	X(1)			7	8	9
12-15 mo	X(2)			7	8	9
2 yrs	3	X (3)	6	7	8	9
5 yrs	4	X(4)	6	7	8	9
>10 yrs	4	5		7		9

1. For children 7-11 months of age not previously immunized with Prevnar, 2 doses 2 months apart followed by a third dose at 12-18 months.
2. For children 12-23 months of age not previously immunized with Prevnar, 2 doses 2 months apart.
3. For children 24-59 months of age previously immunized with Pneumovax, but not Prevnar, 2 doses of Prevnar 2 months apart > 2 months after Pneumovax. Second Pneumovax 3 years after first Pneumovax and > 2 months after second Prevnar. For children 24-59 months of age not previously immunized with Pneumovax or Prevnar, 2 doses of Prevnar 2 months apart, followed by 1 dose of Pneumovax > 2 months later and second dose of Pneumovax 3-5 years after the first Pneumovax.
4. For children >5 years of age previously immunized with Pneumovax but not Prevnar, 1 dose of Prevnar > 2 months after last dose of Pneumovax. If not previously given, second dose of Pneumovax > 2 months after Prevnar and 3-5 years (<10 yrs of age) or >5 years (>10 yrs of age) after first dose of Pneumovax. For children >5 yrs of age not previously immunized with Pneumovax or Prevnar, 1 dose of Prevnar followed by first dose of Pneumovax > 2 months later and second dose Pneumovax 3-5 yrs (< 10 yrs of age) or >5 yrs (> 10 yrs of age) after first Pneumovax.
5. As it is recommended by some experts, we shall administer a third dose of Pneumovax >5 years after its second dose.
6. Recommended for anatomically and functionally asplenic patients by AAP Red Book, We shall administer the vaccine to all our sickle cell patients.
7. Yearly for children >6 months of age.
8. Penicillin prophylaxis (125 mg PEN VK P.O. bid < 3 yr; 250 mg P.O. bid > 3 yr) from 2 months to 5 years of age in all infants with Hb SS, SC and S B⁰thalassemia. Prophylaxis considered on case by case basis for older children and for those with Hb SB⁺ thalassemia. Note: tablets have a longer shelf-life than suspension, which must be reconstituted with water, kept refrigerated, and expire in 14 days. Erythromycin may be used as a substitute for children with proven or suspected penicillin allergy.
9. Controversial. Folic acid 400mcg or 1 mg P.O. q.d. may be considered for children with significant hemolysis (Hb SS, SC, SB⁰-thalassemia)

Management Guidelines for the Infant and Young Child with Sickle Cell Anemia

1. INTRODUCTION

Since August of 1988, Florida HRS has performed hemoglobinopathy screening on all newborn infants. When a clinically significant hemoglobinopathy is detected, the primary physician or health care provider is notified so that appropriate follow up care can be arranged. Consultation with a pediatric hematologist is also advised. The purpose of this brochure is to provide recommendations from the Pediatric Sickle Cell Disease Program at the University of Florida for health care during the first years of life for patients with sickle cell anemia (SCD-SS), sickle Beta-zero Thalassemia (SCD-S β^0 thal), sickle C (SCD-SC) and sickle Beta-Plus Thalassemia (SCD-S β^+ thal). It is imperative that the primary care provider and the patient's parents be educated about the major risks of the disease and standard management principles.

2. GENERAL MANAGEMENT

Infants and young children with sickle cell anemia should, in general, be treated as normal children. They should receive all routine immunizations, good nutrition, and other preventative health care measures. It is important that each child have a primary health care provider with whom there is a mechanism for prompt emergency care when the need arises.

A. Infection: By 3 to 4 months of age (when the fetal hemoglobin declines to below 50% of the total), children with sickle cell anemia and sickle Beta-Zero Thalassemia develop clinically significant hemolytic anemia and impairment of the splenic function. Even though the spleen may be enlarged during the first years of life, its phagocytic function is markedly reduced. Therefore, children with sickle cell anemia are at risk of overwhelming septicemia, often without a primary focus due to the encapsulated organisms *Streptococcus pneumoniae* and *Haemophilus Influenza* type b. If special measures are not taken, 15-20% of infants and young children with sickle cell anemia die before 5 years of age, usually of septicemia and/or meningitis. In order to reduce this high mortality, we strongly recommend the following measures:

1. Early diagnosis of sickle cell anemia with intensive education by knowledgeable providers (both verbally and by explanatory brochures) provided to the parents detailing the risk of serious infection. A source of medical care, at all hours of the day and night, must be available in event of high fever and other emergencies.
2. Prophylactic Penicillin should be prescribed as soon as the diagnosis is suspected and continued until 5 years of age. We suggest Pen VK 125 mg BID prior to 3 years of age and 250 mg BID from 3 years of age. We suggest Pen VK 125 tablets which can be crushed and given in a small amount of formula or food since the suspension necessitates a prescription refill every 2 weeks and refrigeration. It should be impressed upon the parents that the penicillin **must be**

taken twice a day. Missing just a few doses or using liquid penicillin that is out of date can result in entry of the pneumococcus into the bloodstream, with possible fatal sequelae. Despite these measures, septicemia may still occur. Therefore, whenever a child with sickle cell anemia has a temperature > 101^vF he/she should be seen by a physician at once. Following a rapid history and physical examination, a blood culture should be performed and an immediate intravenous injection of ceftriaxone (Rocephin 75mg/kg, maximum 2 grams) or another antibiotic effective against *S. pneumoniae* and *H influenzae* type b should be given. A decision can then be made whether or not the child should be admitted to the hospital. Many such febrile patients can be treated as outpatients as long as they appear clinically well and close outpatient follow up can be assured. A fever management protocol is available.

- B. Splenomegaly and Acute Splenic Sequestration: By four or five months of age, splenomegaly develops in some infants with sickle cell anemia, and by 12 months of age a palpable spleen is noted in nearly half of the patients. Although enlarged, the spleen does not properly perform its filtration function. However, its reservoir function is overactive, and sequestration of large quantities of blood (often half or more of the child's blood volume) may occur rapidly. This complication, termed the acute splenic sequestration (ASSC), is characterized by sudden marked enlargement of the spleen associated with a precipitous decline in hemoglobin. Parents should be instructed on how to palpate the infant's spleen and asked to do it on a daily basis. When the spleen is larger than usual, the child should be seen at once by a physician and a blood count performed. Mild episodes of ASSC (e.g. hemoglobin <2 gm/dl below the baseline steady state value and spleen only slightly larger than usual) can be followed closely in the outpatient setting. More severe episodes (hemoglobin below 5.5 gm/dl, hemoglobin >2gm/dl (or >25% whichever is less) below the baseline or massive rapid splenic enlargement which can lead to hypovolemic shock) should be managed by hospitalization and packed red blood cell transfusion. Episodes of ASSC are self-limited (often lasting just a few days) but can be recurrent. Splenectomy may be necessary for those patients with severe or repetitive events. The enlarged spleen characteristic of infants with sickle cell undergoes fibrosis ("autoinfarction") and usually is no longer palpable by five years of age. Patients with hemoglobin SC disease or sickle Beta-Thalassemia may have ASSC at any age.
- C. Pneumonia (Acute Chest syndrome): A common cause for hospitalization of sickle cell patients is an acute febrile event associated with cough, dyspnea, chest pain, and pulmonary infiltrates. This has been termed acute chest syndrome rather than pneumonia, since an infection etiology usually cannot be confirmed. The syndrome probably results from intrapulmonary sickling superimposed upon inflammation from a viral infection and/or from fat embolism derived from infarcted marrow. Children with clinical compromise (hypoxemia, respiratory distress) from this complication should be hospitalized and managed with parenteral antibiotics such as cefuroxime or ceftriaxone (covering *S pneumoniae* and *H. influenzae* type b), azithromycin (or similar to cover *mycoplasma pneumoniae*) maintenance fluids, and oxygen. There is often a decline in hemoglobin and reticulocyte value during these episodes, so daily hemoglobin and

reticulocyte determinations should be performed. Blood transfusions are often necessary. Clinical deterioration may occur suddenly. Occasionally the outcome is fatal. A special Acute Chest Syndrome Management Protocol is available.

- D. Other infections: There is no evidence that children with sickle cell anemia have increased incidence (compared to normal healthy children) of upper respiratory infections, otitis media, or other common infectious illnesses.
- E. Vaso-Occlusive “Pain Crisis”: Children with sickle cell disease may have painful vaso-occlusive episodes characterized by bone and/or bone marrow infarction. Severe pain occurs without prominent swelling, tenderness, or other symptoms, commonly in the arms, back, or leg. Pain in the abdomen or chest wall may suggest the possibility of chest syndrome (see above). Management of the pain crisis consists of administration of fluids (oral or intravenous) at 1 ½ maintenance rates (unless contraindicated) initially for 2-3 days and analgesics (oral acetaminophen, ibuprofen or ketorolac codeine, or IV morphine). A special Pain Management Protocol is available.
- F. Dactylitis (Hand and Foot Syndrome): One of the most common clinical manifestations of sickle cell anemia during the first two years of life is the hand and foot syndrome, characterized by painful tender swelling of one or more bones in the hands/and or feet. These episodes, which usually last a number of days, may be recurrent. Management is the same as for other vaso-occlusive episodes and consists of fluids and analgesics.
- G. Bone infarcts: Occasionally, localized infarction of an area of bone can occur resulting in swelling, warmth, and severe tenderness. Sometimes, this is accompanied by fever. These events must be distinguished from osteomyelitis which is usually slower in onset and may be accompanied by a positive blood culture. Bone infarcts may take weeks to resolve. They should be managed like any other severe painful event.
- H. Aplastic Crisis: This results from infection with Parvovirus B19, a common viral pathogen that is the cause of erythema infectiosum or Fifth’s disease. In aplastic crisis the bone marrow stops producing red cells, and the hemoglobin value drops far below the steady state value. The reticulocyte count characteristically is zero. Signs and symptoms are due to severe anemia (pallor, weakness, and syncope). Packed red blood cell transfusion is usually necessary. We recommend slow transfusion to a hemoglobin of 8.5 to 10 gm/dl then close follow up until reticulocyte count rises. The episodes rapidly resolve and do not recur. The infection is very contagious and poses a risk to non-immune health care providers, immunocompromized or pregnant exposures or those suffering from hemolytic anemia, and siblings with sickle cell anemia. A sibling with sickle cell anemia who has not had documented aplastic crisis should have a hemoglobin and reticulocyte count checked immediately and again in 10 to 14 days. When in the hospital or clinic, the patient must wear a mask and be under contact isolation.
- I. Other Medications: Iron supplementation should be avoided unless concomitant iron deficiency is documented. Folic acid (1 mg/ day) is given to all SCD patients.

- J. Newer Therapies: Treatment of sickle cell disease has generally been supportive in nature, including fluids, analgesics, penicillin, transfusion, antibiotics, and good general quality of life and reduction in mortality. Hydroxyurea, an oral anti-cancer drug, appears to be effective in decreasing the frequency of hospitalization for pain and episodes of acute chests syndrome in adults and some children with sickle cell disease. It is also now possible to cure sickle cell anemia by means of bone marrow or cord blood transplant from an HLA matched donor (who does not have sickle cell anemia). These interventions however, should be restricted to protocol studies due to their potential toxicity. Most of these new therapies are available in our center. Further research in the development of anti-sickling drugs, bone marrow transplantation, and gene therapy will certainly be “in the headlines” during the next decade.

3. Comprehensive Care

We believe that much of the special care necessary for children with a sickle hemoglobinopathy can and should be given by the primary care physician or health care provider. The personnel of the Pediatric Sickle Cell Disease Program at the University of Florida are available to provide telephone or in person consultation and periodic follow up of affected patients. This involvement will allow us a greater understanding of the natural history of sickle cell disease during childhood. In return, our staff of physicians, pediatric nurses, and social workers can offer their resources to assist the patient, their family, and you with the management of the disorder. For these reasons, we are interested in seeing all children with sickle cell disease in our outpatient unit on at least a semi-annual or annual basis. Regular follow up recommendations will be provided to referring physicians after each visit.

MANAGEMENT PROTOCOL FOR FEBRILE INFANTS AND CHILDREN WITH SICKLE CELL DISEASE

Septicemia due to *Streptococcus pneumoniae* and *Haemophilus influenzae* type b is the most common cause of death in young children with sickle cell anemia. Fever is usually the initial manifestation of sepsis. Prompt antibiotic therapy can be life saving. All children with all types of sickle cell disease syndromes with temperature greater than 101^v F should be promptly evaluated as follows:

1. Brief history and physical including pulse oximetry.
2. Obtain a CBC, differential, reticulocyte count, and blood culture. Immediately give an intravenous dose of ceftriaxone (Rocephin) 75 mg/kg (maximum 2 gm). If ceftriaxone is unavailable, cefuroxime 50 mg/kg, or ampicillin 75 mg/kg may be given. For cephalosporin allergic patients, clindamycin may be used.
3. Chest X-ray should be considered when the child has a cough, tachypnea, chest pain, or physical findings suggesting pneumonia (acute chest syndrome) and in all patients with fever greater than or equal to 102^v F or under 2 years of age (even without the above mentioned physical findings). (Morris C, Vichinsky E, Styles L: Clinician assessment for acute chest syndrome in febrile patients with sickle cell disease: Is it accurate enough? *Ann Emerg Med.* July 1999;34: 64-69).
4. Other laboratory tests may be indicated (e.g. type and cross match for possible red blood cell transfusion, CSF analysis and culture, urine culture, etc), depending on the clinical findings. Prompt and careful physical assessment and administration of IV antibiotics should have high priority. Do not wait until after the chest X-ray or blood count results return to start antibiotics.

IF THE CHILD IS “TOXIC” OR HAS AN ALTERED MENTAL STATE, HE/SHE SHOULD BE PROMPTLY ADMITTED (SEE BELOW FOR INPATIENT MANAGEMENT GUIDELINES) FOR OBSERVATION AND ADDITIONAL PARENTERAL ANTIBIOTIC THERAPY. IF IN DOUBT, ADMIT THE PATIENT TO THE HOSPITAL FOR AT LEAST 23 HOURS OF OBSERVATION.

If any of the following factors exist, then hospitalization should be strongly considered:

1. Temperature is greater than or equal to 104^v F.
2. Child is under 12 months of age.
3. Child has respiratory distress or other unstable vital signs.
4. There is a segmental or lobar infiltrate on chest X-ray or abnormal oxygen saturation.
5. WBC is over 30,000 or under 5,000 per mm³ and shifted to the left, and/or other hematologic parameters are below baseline values (e.g. hemoglobin < 5 gm/dl, platelet < 100,000 per mm³)

6. Previous history of pneumococcal sepsis.
7. Follow up (telephone contact, return visit, etc) is uncertain or unlikely because of distance, inconvenience, or poor compliance.
8. History of splenectomy.
9. Recent doses of prophylactic penicillin have been missed.

Outpatient Management

If the evaluation suggests that outpatient management is possible, a short period (about three hours) of observation is advised, followed by re-evaluation prior to discharging the patient. Re-evaluation should include assessment of vital signs, level of consciousness, and ability to take oral fluids or medications. Give Ceftriaxone 75 mg/kg intravenously daily for three days for selected patient. Azithromycin (Zithromax) can be given orally for five days following the initial Ceftriaxone. Other choices are Clarithromycin (Biaxin), Clindamycin or Loracarbef (Lorabid). Follow up by telephone or repeat outpatient visit should be arranged within 24-36 hours. Blood culture results must be checked daily and patient recalled at once if positive. If referred to sickle cell clinic for follow up, ask the family to call first for an appointment not just walk in.

Inpatient Management:

Administer Ceftriaxone 75 mg/kg QD or Cefepime 50 mg/kg Q 8 hours until cultures are sterile and clinical status improves. Penicillin allergic patients can be treated with Clindamycin 10 mg/kg/dose Q6 hours maximum 600 mg/dose.

Observe closely for deterioration in clinical status, which may indicate septicemia or development of acute chest syndrome. Repeat blood cultures every 24 hours for persistent fever. Obtain sensitivities on all positive blood cultures and repeat culture to document clearance of pathogen.

On rare occasions, when the cultures are negative, and the patient continues to spike very high fever despite adequate antibiotic treatment (cephalosporin and zithromax) or in patient in septic shock, consider increasing the dose of ceftriaxone to 100 mg/kg and later consider an empiric trial of vancomycin 10 mg/kg/dose every 6 hours to cover for possible penicillin resistant pneumococci infection.

References: Rogers Z., Morrison R., Vedro D., Buchanan G: Outpatient Management of Febrile Illnesses in Infants and Young Children with Sickle Cell Anemia. J. Pediatr 117:736-739.1990

Wilimas JA, Flynn PM, Harris S, Day SW, Smith R, Chesney PJ, Rodman JH, Eguiguren JM, Faircloth DL, Wang: A Randomized Study of Outpatient Treatment with Ceftriaxone for Selected Febrile Children With Sickle Cell Disease. N. Eng J. Med 329:472-6, 1993.

ALTERNATIVE THERAPIES FOR FEBRILE ILLNESS IN ASPLENIC PATIENTS WITH KNOWN ALLERGIES TO PENICILLIN AND OR CEPHALOSPORINS

1. Children with allergies to these medications will have their databases and shadow charts so labeled. Specific recommendations for management of that child will be generated, sent to the family, and attached to every copy of the database.
2. Please notify the sickle cell nurse if penicillin or cephalosporin allergy is suspected in any patient with sickle cell disease or who is asplenic with a hematologic diagnosis.

Our general recommendation for an asplenic child (due to sickle cell anemia or following a surgical splenectomy) whose chart has been marked as allergic to cephalosporins who presents with fever (single temperature of 101[°]F or above or persistent low grade temperatures for greater than 24 hours) are:

- A. DO NOT GIVE ANY CEPHALOSPORIN even if the patient “did okay” in the past.
- B. Give Clindamycin 10-15 mg/kg IV (to maximum of 600 mg).
- C. Admit the child for 48-72 hours of IV antibiotics.
- D. If a cephalosporin allergic patient is on chronic prophylactic penicillin, **DO NOT STOP ORAL PENICILLIN** regardless of alternative antibiotic therapy.
- E. Please contact the hematologist on call with questions for further advice.

Patient-Parent Handout

WHAT TO DO WHEN YOUR CHILD HAS FEVER

Fever usually means that there is an infection somewhere in the body. People with sickle cell disease are at increased risk of infection and may die if the infection involves the blood (blood poisoning or septicemia). Fever may be a sign of infection in the blood. Some young children with sickle cell anemia take penicillin twice a day, all the time, to lower the possibility of death from these serious infections. For our patients, including your child, we recommend a different approach.

IN CLINIC YOU WILL BE GIVEN A PRESCRIPTION FOR PENICILLIN PILLS. YOU SHOULD BUY THIS MEDICATION AND KEEP THE PILLS AT HOME (OR TAKE WITH YOU WHEN YOU ARE TRAVELING) IN CASE YOUR CHILD HAS A FEVER.

VERY IMPORTANT POINTS TO REMEMBER:

1. If your child has a fever or feels warm or seems sick, he/she should be immediately checked with a thermometer to measure the temperature.
2. If your child gets a high fever (over 101^vF), shaking chills, or feels very sick, you should take him/her to the doctor or the Emergency Room if the doctor's office is closed.
3. If your child has a fever and sees a doctor, be sure to tell the doctor that your child has sickle cell disease and is/or is not taking penicillin.
4. Never let your penicillin supply run low. When the supply gets low, please call your primary care physician, or the sickle cell clinic between 9:00 a.m. and 4:00 p.m. so that the prescription can be refilled.
5. Please do not give child Tylenol or another fever medicine such as ibuprofen or Advil or Motrin if the child has temperature above 99 and below 101. Keep checking the fever about every half hour until it goes down below 99. When checking the fever, if the fever goes to 101 or above you may give Tylenol, but bring the child to emergency IMMEDIATELY.

If you have any questions about the risk of blood poisoning (septicemia) or other infections in children with sickle cell disease, please ask any member of the sickle cell team at **352-265-0680 ext 88239 (during day)** or 1-888-4UF-SHANDS or 352-265-0111.

MANAGEMENT OF ACUTE CHEST SYNDROME(ACS) (OR PNEUMONIA) IN SICKLE CELL DISEASE

DEFINITION: Sickle cell acute chest syndrome is an acute respiratory illness characterized by cough, **fever**, chest pain, respiratory distress and lobar or segmental pulmonary **infiltrate** on chest X-ray. Its exact cause is uncertain, but in most cases it probably represents infection and/or intrapulmonary sickling. It is a common and serious clinical problem in patients with sickle cell hemoglobinopathy.

CRITERIA FOR HOSPITAL ADMISSION:

ACS is usually treated as an inpatient. Respiratory distress (tachypnea, dyspnea, retractions, flaring, and prominent cough), or any of the following signs are also present are especially important:

- ◆ Moderate or severe chest pain.
- ◆ Fever greater than 38.3^v C or 101^v F
- ◆ A new documentation of oxygen saturation > 3% below baseline or <92 % in room air

INPATIENT MANAGEMENT:

1. Blood culture initially; repeat after 48- 72 hours for persistent temperature over 38.5^v C.
2. Total fluid (intravenous plus oral) at maintenance rate; watch for volume overload.
3. Daily weight, strict I & O, frequent vital signs.
4. Supplemental oxygen by mask (not nasal canula) to maintain O₂ saturation > 91% or within 3% of baseline (if known); oxygen should be continuously monitored by pulse oximetry. Consider NOT administering oxygen for 'comfort' but consider administering oxygen for respiratory distress or hypoxemia.
5. Chest X-ray initially and then as clinically indicated.
6. CBC with differential and reticulocyte count initially, then daily. The hemoglobin often falls by 2-3 gm/dl during severe acute chest syndrome.
7. Antibiotic coverage for S pneumoniae and H. influenzae type b. Our current recommendations: Ceftriaxone 75 mg/kg q 24 hr or Cefuroxime 50 mg/kg q8h IV, AND Zithromax 10 mg/kg/day x 5 days (zithromax for children above 1 years of age).
8. Analgesic management (the use of parenteral opioids is discouraged due to the risk of hypoventilation):

- a) If analgesia is required ibuprofen (10 mg/kg to a maximum single dose of 600 mg) should be started every 6 hours around the clock. Daily maximum adult doses 2.4 to 4.8 grams.
 - b) Alternatively, give Ketorolac 0.5-1 mg/kg (maximum 30 mg/dose) IM or IV every six hours **for no more than 5 days.**
 - c) Add acetaminophen with codeine (0.5-1 mg/kg/dose) every 4 hours prn. Alternate ibuprofen with the codeine so that some medication is given every 3 hours.
 - d) If parenteral medication is needed for severe pain, give morphine sulfate 0.1 mg/kg/dose every 2 hours prn or preferably consider a low dose morphine PCA (always write for incentive spirometry and pulse oximetry with opioid PCA).
9. If patient is able, incentive spirometry should be taught to patient and family by respiratory therapist and then used at least 10 times every 2 hours while awake. CPT should be considered for severe consolidation.
10. Airway hyper-reactivity should be assumed to be present, even if the patient is not wheezing, and treatment with bronchodilator should be considered.
11. Blood transfusion support-post transfusion hemoglobin should be between 10 and 11 gm/dl to prevent hyperviscosity which may exacerbate ACS or contribute to a stroke.
- A. Simple transfusion of 10-15 ml/kg of packed red blood cells [round off to nearest whole unit blood (250ml) or pediatric split pack volume (80 ml)] (or a small volume partial exchange transfusion [10 ml/kg removal followed by 10 ml/kg pRBC transfusion] considered if patient's hemoglobin is ≥ 9.0) should be administered for:
 1. A decline in hemoglobin by 2.0 gm/dl or more below patients usual steady state level
 2. Worsening of oxygenation or respiratory distress.
 - B. Exchange transfusion should be performed if patient cannot maintain O₂ saturation > 90% or arterial PO₂ > 60 mm/Hg with maximal supplemental oxygen and simple packed red blood cell transfusion.

The therapeutic goal of exchange transfusion is hemoglobin between 10 and 11 gm/dl and a percent hemoglobin S level less than 30%.

Vichinsky EP et al: Causes and outcome of the acute chest syndrome in sickle cell disease. N Eng J Med 2000; 342:1855-65.

OUTPATIENT ASSESSMENT AND MANAGEMENT OF SICKLE CELL-RELATED VASO-OCCLUSIVE EPISODES

- A. MILD PAINFUL EVENTS: The child with MILD pain may not appear uncomfortable but complains of pain (5-6/10 on 1-10 pain scale).

TREATMENT: Acetaminophen (15 mg/kg/dose) and/or ibuprofen (10 mg/kg/dose) every 6 hours and plenty of fluids. Send home with prescription for at least 20 doses of acetaminophen with codeine (but preferably not more than 40 doses). For more severe pain, ibuprofen may be alternated with the acetaminophen or acetaminophen with codeine so that some medication is given every 3 hours.

- B. MODERATE PAINFUL EVENTS: The child with MODERATE episodes evidences discomfort by facial grimacing, unhappiness, irritability, a poor appetite, and has not responded to home treatment (7-8/10 on 1-10 pain scale).

TREATMENT: If child has not received codeine, give appropriate dose of acetaminophen with codeine (0.5-1 mg/kg/dose) in addition to ibuprofen. If child has received an appropriate dose at home or pain does not improve within 1-2 hours, treat as severe painful event. (see below).

- C. SEVERE PAINFUL EVENTS: The child with severe pain is uncomfortable, complains of pain and may be agitated, crying, screaming, and may not be able to be consoled (9-10/10 on 1-10 pain scale).

TREATMENT:

1. If the patient has been taking codeine and ibuprofen at home in appropriate doses: immediately start IV fluids at 1½ times the maintenance rate for up to 6 hours and give an IV bolus injection of morphine.
2. Reassess patient 20 – 60 minutes later. If pain remains, or has returned, repeat morphine sulfate 0.025 – 0.05 mg/kg and repeat assessment in an additional 20-60 minutes. Repeat a third time if needed. Closely monitor respiratory status (continuous pulse oximetry is strongly advised).
3. If pain decreases, discuss with patient if they can manage their pain at home. If so, give an appropriate oral dose of acetaminophen with codeine or hydrocodone and observe for three to four hours after the last dose of morphine. If patient still wants to go home, discharge with instructions to alternate (Tylenol with) codeine with ibuprofen every 3 hours as above (i.e. each medicine q 6 hrs), around the clock for at least 24-48 hours.

4. If child does not feel that they can go home after a minimum of 3-4 hours in ED and at least 3 doses of parenteral morphine, consider inpatient 23 hour observation or admission. See Inpatient Management Protocol.
5. In a child with poor venous access consider SC or IM injection application. When sending a child home with a prescription for acetaminophen with codeine, give only 20-30 doses. Remind the parents to call the sickle cell nurse the next day. Reassure family that pain is not dangerous and will resolve in a few days.

DRUG DOSE PREPARATIONS

Codeine: 0.5 - 1 mg/kg every 4-6 hours PO

Morphine: 0.1 mg/kg IV (preferred) or SQ repeat every 1-3 hours. Maximum 8 mg per dose. The very first dose administered in a patient's life should be 0.05 mg/kg).

Ibuprofen: 10 mg/kg every 6 hours PO

Meperidine (Demerol): In the past, Meperidine was often used instead of morphine. It should **NOT** be used for patients with sickle cell disease, because of the long plasma half-life of its toxic metabolite normeperidine (which is responsible for extreme excitability and even seizures).

ACETAMINOPHEN WITH CODEINE:

All tablets contain 300 mg acetaminophen. The dose of codeine is:

- #1 7.5 mg
- #2 15 mg
- #3 30 mg
- #4 60 mg

Elixir: 12 mg codeine and 120 mg acetaminophen per 5cc.

INPATIENT MANAGEMENT OF SEVERE SICKLE CELL-RELATED VASO-OCCLUSIVE EPISODES

Rationale: Patients with sickle hemoglobinopathies at times experience severe unrelenting pain for several days. In such cases intravenous opioid analgesia, ideally by patient adjusted continuous infusion, is the preferred management approach until the vaso-occlusive episode resolves. Oral analgesics alone (non-steroidal anti-inflammatory agents and acetaminophen with codeine) are sometimes ineffective. In severe pain, intramuscular injections are inappropriate when the patient already has an intravenous line for hydration. The goal of treatment is to control the patient's pain, even if minor side effects of opioids (i.e. itching, constipation, lethargy, etc) occur. The decision to use bolus doses or a continuous infusion of morphine depends on the severity of the child's pain and logistics of administration.

GENERAL MANAGEMENT

1. Total fluids (IV plus PO including volumes for medications) at one and a half maintenance rate unless the patient is dehydrated or fluid requirements are increased. CBC, reticulocyte count for patients who are clinically unstable or previous hemoglobin indicates potential for transfusion therapy (i.e. hemoglobin < 6 ml/dl or 25% below baseline especially with low reticulocyte count). **Please note: Urine specific gravity is not a reliable indicator of hydration status in older patients with sickle cell disease.**

BOLUS THERAPY

1. Morphine sulfate 0.1 mg/kg/dose (maximum dose 8 mg) IV every 2-3 hours PRN for severe pain.
2. If 3 or more bolus doses are needed in any 24 hour period, the patient should be placed on a continuous infusion with additional boluses via PCA as outlined below.
3. In addition, give Ketorolac 0.5 mg/kg/dose q 6 hours for children older than 2 years old (maximum 30 mg/dose).
DO NOT GIVE FOR MORE THAN 5 DAYS (may administer ibuprofen instead)

Forrest JB, Heitlinger EL, Revell S. Ketorolac for postoperative pain management in children. Drug Saf. 1997 May;16(5):309-29.

CONTINUOUS INFUSION

1. Administer narcotic separately from hydration fluids. Use Y connector to give through same IV site, but an infusion pump is necessary to assure precise rate of narcotic. A PCA (patient controlled analgesia) pump is the MOST satisfactory method to administer continuous infusion.
2. Give bolus of 0.1 mg/kg morphine sulfate within 1 hour of beginning infusion.

3. If patient controlled analgesia (PCA) pump is available;
 - a. Mix morphine as 1.0 mg morphine sulfate per 1 ml of fluid.
 - b. Start basal rate of continuous infusion at 0.02-0.05 mg/kg of morphine sulfate per hour (maximum 2.5 mg). Consider starting at half of patient's usual maximum dose required at earlier visits.
 - c. PCA bolus in addition to basal rate at 0.01 mg/kg/dose with a 10-15 minute lockout. (maximum 0.5 mg).
4. In addition, give ketorolac 0.5 mg/kg/dose q 6 hours for children > 2 years old (maximum 30 mg/dose). Give for a maximum of 5 days. Give H₂ blockers while on ketorolac.
5. If the patient remains in pain after 3 to 4 hours or is requiring 1 or 2 more additional PCA bolus doses every hour, give an additional bolus of 0.05 mg/kg and increase the continuous infusion rate by 0.01 to 0.04 mg/kg/hour.
6. If PCA pump is not available, consider use of continuous infusion only:
 - a. Mix morphine as 0.01 mg of morphine sulfate per 1 ml of fluid.
 - b. Start at rate of 0.02-0.05 mg/kg/hour.
7. If infusion infiltrates and is restarted, a bolus should be given when IV resumes. Dose of bolus would depend on the duration of stoppage of PCA.

MANAGING SIDE-EFFECTS:

1. **ITCHING:** Naloxone (0.4 mg/ml)

Adult: 40 mcg (0.1 ml) IV then place remainder of vial in 500 cc maintenance fluids, and run at maintenance rate (10-20 ml/hour).

Child: 1-2 mcg/kg bolus, then 0.5-1.0 mcg/kg/hr prn.

Naloxone drip is preferred for better control with lesser side-effects.

You can also try:

Atarax:

Adult: 25-100 mg PO q 6-8 hours prn

Child: 1mg/kg/day (max 25 mg) PO q6-8 hours

Benadryl:

Adult: 25-50 mg PO q 6-8 hours prn (max. 400mg/day)

Child: ½ mg/kg/dose (max 25 mg) PO q6-8 hours (side-effect – sedation).

2. **NAUSEA:**

Adult: Metoclopramide 10 mg IV, repeat PRN every six hours.

Child: Metoclopramide 0.1 mg/kg IV once, maximum dose = 10 mg.

Adult: Phenergan 12.5-25 (maximum 50 mg PO/PR/IM/IV

Child: Phenergan 0.25-1 mg/kg (maximum 25 mg) PO/PR/IM/IV every 4-6 hours

Ondansetron 0.1 – 0.15 mg/kg/dose every 8 hr prn (max dose 8 mg).

Notify MD if:

1. Urinary retention for more than 8 hours
2. Respiratory rate < 12/minute in adult
3. Respiratory rate < 16/minute in school age child
4. Respiratory rate < 20/minute in preschool child
5. Sp O₂ < 90

8. **DO NOT TAPER THE DOSE AS SOON AS THE PATIENT BECOMES COMFORTABLE. THIS OFTEN RESULTS IN A RETURN OF PAIN AND INCREASED ANXIETY.** The infusion should be maintained for at least 24 to 36 hours or until return of a normal affect suggests that pain is less and can be managed with oral analgesics. The duration of prior painful events experienced by a patient may also guide the management plan. When indicated, the infusion can be **ABRUPTLY STOPPED WITHOUT TAPERING.** About 1 hour before discontinuing the infusion, give a dose of oral analgesic (acetaminophen with codeine or equivalent, MS Contin is preferred when morphine is used for PCA). Continue oral analgesic on a schedule (every 4 hours) for 12 to 24 hours after stopping infusion, then prn. Some patients may choose to go home at this point, even if they are still in some pain. Often, full doses of acetaminophen with codeine can be alternated with ibuprofen so that some medication is given every 3 hours. Maintain intravenous access until it is clear that oral analgesia is adequate. Resume the infusion immediately if moderate to severe pain returns.
9. If patient is able, incentive spirometry should be taught to patient and family by respiratory therapist then used 10 times every 2 hours while awake.

PATIENT ASSESSMENT AND MONITORING

1. Daily weight, strict intake and output monitoring, oxygen saturation monitor on all patients.
2. Frequent vital signs and clinical monitoring especially for respiratory depression and fluid balance.

3. CBC (no differential) with reticulocyte count on admission and every other day. CMP on admission for all patients over age 5 years.
4. If patient is not receiving Ketorolac (Toradol), give ibuprofen in standard doses (10 mg/kg po to a maximum dose of 600 mg every 6 hours) can be used with morphine and is of particular value in musculoskeletal pain.
5. Ask the patient and parent about the level of pain and degree of pain relief. The level of pain may vary immensely hour to hour. The aim is to “titrate” the infusion to control pain without causing dangerous side effects.
6. Pericolace or other stool softener should be ordered on admission to prevent opioid induced constipation.
7. Incentive spirometry should be prescribed to all patients using PCA (used 10 times every 2 hours while awake).

PRACTICAL POINTS

1. **PLACEBO SHOULD NEVER BE GIVEN.** Children and adolescents with sickle cell disease rarely make false complaints of pain.
2. Short-term opioid use for management of vaso-occlusive pain does not result in addiction.
3. Low grade fever may accompany a crisis. However, a temperature of 38.3 °C suggests an infection and/or chest syndrome. Blood culture and chest X-ray (if clinically indicated) should be performed.
4. Parenteral morphine can lead to itching which can be managed with hydroxyzine (Atarax) or diphenhydramine (Benadryl) in usual doses either by mouth or parenterally.

MANAGEMENT GUIDELINES FOR APLASTIC CRISIS IN SICKLE CELL DISEASE

DEFINITION AND PATHOPHYSIOLOGY

Aplastic crisis is an acute complication of sickle cell disease and other hemolytic anemias. It is characterized by rapid decline in hemoglobin concentration resulting from a direct effect of parvovirus B19 on erythroid progenitors in the bone marrow. (In rare occasions, other viruses may cause a transient marrow RBC hypoplasia). In individuals with sickle cell anemia, erythroid precursors disappear from the bone marrow for about 10 days during Parvovirus infection, resulting in a reticulocyte count usually less than 0.1% and a reduction in hemoglobin values, often to 3-5 gm/dl. Patients with hemoglobin S-C disease and sickle Beta-Plus Thalassemia are less severely affected.

Parvovirus is a DNA virus easily spread by respiratory secretion. Patients with aplastic crisis do not usually exhibit the “slapped cheek” rash of erythema infectiosum (Fifth Disease) or arthralgia/arthritis. Patients develop an antibody response which results in viral neutralization and allows resumption of marrow erythroid activity. This results in a rapid rise in the reticulocyte count and hemoglobin that is often heralded by a large number of nucleated red blood cells on the peripheral blood smear within 1 to 2 weeks.

CLINICAL MANIFESTATIONS

Patients usually present with fever, malaise, lethargy, and possible syncope due to anemia. Physical examination shows pallor, tachycardia and possibly congestive heart failure. The spleen is not larger than usual. Laboratory abnormalities include severe anemia (hemoglobin usually 2-6 gm/dl) and reticulocyte count < 1.0%. The WBC and platelet count are usually normal, but mild and transient leukopenia and thrombocytopenia have been described.

MANAGEMENT AND OUTCOME:

1. Transfusion is often required if the patient has symptomatic anemia and no signs of bone marrow recovery (no nucleated RBC on peripheral smear and/or retic count < 1%). Transfuse the patient to hemoglobin of 7 to 8 gm/dl. Dividing PRBC into aliquot of 5 to 7 ml/kg and serially transfusing each over 4 hours can usually do this. Watch carefully for fluid overload. Following transfusion the patient may be promptly discharged.
2. Hemodynamically stable patients with less severe anemia (i.e. over 5.0 gm/dl or less than 25% lower than patient's usual Hgb) may be managed in the outpatient setting but with very close follow up.
3. Hemoglobin levels and reticulocyte count should be followed every 2-3 days as an outpatient until reticulocyte count rises and hemoglobin increases, regardless if transfusion is given.

4. Patients must be placed in contact isolation since Parvovirus B19 is highly contagious. As it can cause miscarriage, patient should not have contact with pregnant personnel. Patient must wear a mask when in the hospital or clinic until reticulocyte count rises.
5. While parvovirus diagnostics are not required, they may be very helpful in identifying patients that need isolation. They can also help for future patient management as an immuno-competent patient should only get parvovirus infection once.
6. Serum parvovirus antibodies and antigen studies are available. Parvovirus PCR has the advantage of not being confounded by transfusions.
7. Siblings with sickle cell disease (or other patients with hemolytic anemia with whom the patient has come in close contact with) who do not have a documented history of aplastic crisis should have a hemoglobin and reticulocyte count immediately and again in 10 to 14 days to be sure that they are not simultaneously or sequentially infected.
8. Fever during an aplastic crisis is most likely due to Parvovirus infection. BUT patients should still receive a blood culture and parenteral antibiotics as per our fever management protocol.

ACUTE SPLENIC SEQUESTRATION CRISIS (ASSC) IN SICKLE CELL DISEASE

DEFINITION AND PATHOPHYSIOLOGY

Acute splenic sequestration (ASSC) is characterized by sudden enlargement of the spleen and decline in the hemoglobin concentration. Episodes of ASSC are characterized by pooling of large quantities of sickled erythrocytes in the splenic red pulp, resulting in a precipitous decline in hemoglobin concentration and sometimes platelet numbers. At one time, ASSC was one of the most common causes of death in infants with sickle cell anemia.

CLINICAL FEATURES

ASSC occurs most commonly in infants and young children with sickle cell anemia between 6 months and 5 years of age. It may also occur in older patients with SC disease or SS patients with chronic splenomegaly. There is usually no obvious triggering event. Signs and symptoms are non-specific, including lethargy or irritability, pallor, tachycardia, and sometimes pain in the left upper quadrant (especially in older patients). Patients with severe ASSC may present in frank cardiovascular collapse. On physical examination, patients show signs of anemia, hypovolemia and the spleen is larger than the baseline, sometimes massively so. Mild cases of ASSC are often asymptomatic.

LABORATORY FEATURES

The hemoglobin is at least 2 gm/dl below the baseline steady state value. In severe cases, the hemoglobin may decline to life threatening levels. Reticulocyte counts are often elevated and nucleated RBC's may be present on the blood smear. The WBC count usually remains normal or slightly elevated, but the platelet count often declines to 50,000 to 150,000/mm³.

MANAGEMENT AND OUTCOMES

1. If the spleen is palpable, verify with the patient or database that it is larger than normal. Obtain a CBC to document hemoglobin and platelet count.
2. In mild cases of ASSC (i.e. spleen only slightly larger than usual, hemoglobin <2-3 gm/dl below baseline, patient hemodynamically stable) and parents reliable, the child may be followed as an outpatient with daily or every other day physical examinations and blood counts. Reinforce with parents how to palpate their child's spleen and when to return.
3. Patients with more severe ASSC should be hospitalized for:
 - a) Careful repeated physical assessment (every 4-6 hours) for spleen size (measure with tape and record) and hemoglobin (every 8-12 hours).
 - b) Type and cross match for 10-15 ml/kg PRBC.

4. If hemoglobin declines to below 4.5 – 5.5 gm/dl or >2 gm% below patients baseline, transfuse with 10 ml/kg RBC (repeated if necessary) to raise the hemoglobin and maintain cardiovascular stability.
5. An acute sequestration episode usually resolves within 2-5 days. When the hospitalized patient shows stable or rising hemoglobin value and smaller spleen size, he or she should be discharged, with close outpatient follow-up.
6. Following an episode of ASSC, some patients have persistent splenomegaly and hypersplenism, with lower than usual hemoglobin and platelet values lasting weeks or months. All children who experience an episode of ASSC are at risk of repeat events.
7. Recurrent episodes requiring transfusion should be treated with complete or partial splenectomy. Splenectomy should be postponed until the age of 2 years by instituting chronic blood transfusions until the child is 2 years old and has received the polysaccharide 23 valent pneumococcal vaccine and meningococcal vaccine. Some patients may not require splenectomy, however, and will exhibit gradual diminution in spleen size, with eventual autoinfarction.

If there are any questions regarding these management guidelines, please call the Sickle Cell Program at 352-265-0680 ext 88239.

MANAGEMENT GUIDELINES FOR PRIAPISM IN SICKLE CELL DISEASE

DEFINITION AND PATHOPHYSIOLOGY

Priapism is a painful prolonged erection of the penis that has been documented to occur at least once in 75% of boys with sickle cell anemia before age 21. It commonly occurs during the early morning hours. Priapism occurs in two forms; 1) stuttering episodes which last less than 2 hours but may be recurrent and 2) severe events which last more than 2 hours and may result in impotence. Stuttering spells may herald a severe episode.

MANAGEMENT

1. Severe or prolonged events (lasting more than 2 hours). An event lasting more than 2 hours is to be considered an emergency that requires prompt medical intervention, requiring admission to the hospital.

Initial history taking of event should include the following information:

- a) Onset of symptoms
- b) Frequency of present episode
- c) Duration of present episode
- d) Previous similar attacks
- e) Pain, dysuria, frequency, discharge
- f) Association with dreams
- g) Association with sexual activity
- h) Association with masturbation

Initial physical examination of the patient should include:

- a) Temperature
- b) Blood Pressure
- c) Size and turgor of penis (penile length and circumference at base, mid-shaft and glans)
- d) Discharge

Initial laboratory data should include the following:

- a) CBC, differential, reticulocyte
- b) Urinalysis
- c) Urine culture (if urinalysis positive)
- d) GC smear and culture (if urethral discharge)

TREATMENT

1. Acute episode

In the Emergency Room

- a) Start IV D5 ½ NS at 1 ½ maintenance
- b) Institute morphine PCA (preferred) or administer adequate pain medications
- c) Consider adding ketorolac
- d) Consider giving anxiolytics (e.g. lorazepam, midazolam or hydroxyzine)
- e) If the patient does not improve within 2 hours of onset of priapism, ask for an emergency Urology consult for intracavitary aspiration of blood and instillation of an alpha agonist (phenylephrine or epinephrine) to be performed preferably within 3-4 hours of the duration of priapism. Repeat as needed.

On the inpatient floor

- a) Continue with hydration, pain medication (consider PCA).
- b) Transfuse PRBC to hemoglobin of 10, hematocrit of 30.
- c) If there is no response 2 hours after the onset of priapism, Urology should be re-consulted for aspiration (preferably within 3-4 hours of the onset of priapism). Consider exchange transfusion if multiple attempts at penile aspiration have failed (to commence exchange within 8-12 hours of onset of priapism) to decrease Hgb S to below 30%. Later consider penile shunt placement if exchange transfusion fails.

2. Stuttering Priapism

No specific intervention is recommended for a single episode of transient priapism. Simple maneuvers such as pushing oral fluids, use of pain medications, warm water bottle, warm shower, frequent urination or moderate exercise may help to end an episode. However, patients who have more than 2 episodes within one month or more than 4 episodes within one year should be evaluated for and treated.

- a) First line: Oral adrenergic agonist Pseudoephedrine (30 mg PO [maximum 120mg/day] every 6 hours for children 6-12 years old; 60 mg PO [maximum 240 mg/day] every 6 hours for patients 12 years or older).
- b) Second line: Oral beta agonist Terbutaline (2.5 mg/dose every 6 hours PO for children 12-15 years of age, and 5 mg/dose every 6 hours PO for patients 15 years or older).
- c) Third line: Consider Gonadotropin-releasing hormone analogue (leuprolide preferred) plus flutamide.
- d) Hydroxyurea: In patients with other indications for hydroxyurea this may be started earlier and in addition to other treatments. See chapter on hydroxyurea).

Maples Bl et al: Treatment of priapism in pediatric patients with sickle cell disease. Am J Health-Syst Pharm 2004; 61:355-63.

CHRONIC RBC TRANSFUSION MANAGEMENT PROTOCOL

- A. All newly diagnosed patients with sickle cell disease should have a complete red blood cell phenotype. This will be done along with the confirmatory hemoglobin electrophoresis or shortly thereafter. (Preferably before they have been transfused. For patients that have been transfused wait at least 90 days after the transfusion before drawing blood for RBC phenotype).
- B. For transfusion, send 5 ml in blood bank tube to Shand's Blood Bank with a request for required units of leuko-filtered, sickledex negative, red blood cells (as fresh as possible). When possible the blood should be matched for blood groups C, c, E, e, Kell (K), and Kidd (JkA, JkB). Two 7 ml purple tops may be needed to be drawn if there is a history of prior difficulty with cross matching. Type and cross may be obtained up to 72 hours prior to the transfusion.
- C. Obtain the following laboratory studies before transfusion at intervals indicated:
1. Before each transfusion : CBC with reticulocyte count, hemoglobin electrophoresis
 2. Every six months: LFT's, ferritin level.
 3. Annually: HIV, hepatitis panel, audiology, ophthalmology – retinal exam.
 4. After a year (100 ml/kg) of transfusion, MRI of the liver for volumetric assessment of iron stores should be done and repeated every year.
- D. Transfuse in order to maintain hemoglobin between 10-12 gm/dl, and reticulocyte less than 5% and hemoglobin S 30% or less (pre-transfusion). They should be done every 4-6 weeks. Whenever possible, exchange transfusion should be done with phlebotomy along with the transfusion. For patient who have been on a hyper-transfusion program for three years or more and are stable clinically and radiographically, the level of pre-transfusion hemoglobin S can be increased to 50% or less.
- E. Transfuse the following volumes of packed red blood cells over no longer than 4 hours in patients on chronic transfusion protocol at their steady state:
1. If pre-transfusion hemoglobin 10.5-11 gm/dl, have child return in one week.
 2. However, if the patient has a variant of sickle cell disease with base-line high hemoglobin, do a partial exchange transfusion. (10 ml/kg in, 10ml/kg out. See protocol).
 3. If pre-transfusion hemoglobin 10-10.4 gm/dl give 5ml/kg,
 4. If pre-transfusion hemoglobin < 10 gm/dl, give 12 ml/kg.
- F. Patients with Sickle Cell Disease who have been receiving transfusions for over three years and have had no new clinical problems may receive a less intensive transfusion program. The goals would be pre-transfusion hemoglobin of 8.5 – 9 gm/dl, percent of

hemoglobin S less than 50% and patient symptom free. If a child is transfused, regardless of amount, have them return to clinic in 4 – 6 weeks.

- G. Blood should be of leukofiltered, sickledex negative, freshest available unit. Do not start next unit if less than 75 ml will be used from it.
- H. Hepatitis B vaccine is administered to all patients receiving chronic transfusion therapy (if they have not received it in the past). Obtain hepatitis B serology before beginning vaccination series.
- I. Sickle cell patients should continue to take prophylactic penicillin while on chronic transfusion therapy. Patients with implanted venous access devices or who have had a surgical splenectomy should have a low threshold for having a blood culture to obtain in the event of a fever.

IRON OVERLOAD SYNDROME IN SCD – CHELATION PROTOCOL

Definition of Iron overload: After a cumulative amount of blood transfusion of 100ml/kg (about 10 transfusions) or persistent serum ferritin over 1000mg/ml, we should perform a MRI of the liver for volumetric assessment of iron stores. (Gandon, Y et al. Non-invasive assessment of iron stores by MRI. Lancet 2004; 363:357-62. Commentary page 341). Normal values are <36 micromole/g. Iron overload is defined as greater than 60 micromoles/g, which is the level that chelation should start.

A liver biopsy may alternatively be performed (less strongly recommended) for iron content. Iron content of > 6mg/g dry liver weight is the standard definition of iron overload. Chelation is begun when iron content is > 7mg/g dry liver weight.

Evaluation before starting chelation: Baseline laboratory evaluation before beginning chelation therapy: Ferritin level, MRI of liver for iron overload (per iron overload protocol), possible liver biopsy (not required). Audiometry test, ophthalmologic evaluation (including field and color vision) before starting chelation and at yearly intervals. Consider performing 2D Echocardiogram in patients with significant iron overload.

Exjade: Exjade (**Deferasirox**) is preferred first line of therapy. Begin oral Exjade at a dose of 20 mg/kg/day once daily and increase by 5 mg/kg/day every 4 weeks upto a maximum of 30 mg/kg/day.

Desferal: Begin Desferal (Deferoxamine) at a dose of 20 mg/kg/day sc once daily over 8-12 hours 5 nights a week and increase by 5 mg/kg/day every 4 weeks upto a maximum of 40 mg/kg/day. Hydrocortisone 11 mg is added to each gram of Desferal to decrease skin irritation. The goal is to achieve a net negative iron balance which usually correlates with a serum ferritin below 1,000 mg/dl. Consider vitamin C 100 mg p.o. q day for children 10 years or older and 50 mg p.o. q day for children under 10 years given when administering the infusion for improved iron chelation.

Monitoring on chelation: Perform CBC, reticulocyte count and CMP every two weeks, until a steady dose is achieved, later monthly x three months then continue with CBC and reticulocyte count monthly with CMP once every two months. Ferritin level, yearly MRI of liver for iron overload (per iron overload protocol/T2 star), possible liver biopsy (not required). Audiometry test, ophthalmologic evaluation (including field and color vision) before starting chelation and at yearly intervals. Growth should be closely monitored. Patient deviating from his/her growth curve he/she should be considered for referral to endocrinology. Lung hypersensitivity is a rare complication.

Liver biopsy (or MRI of the liver) will be repeated every year to monitor success (or failure) of chelation.

Alternative chelating methods:

Give the total daily desferal dose in two divided doses administered 12 hours apart. The desferal is diluted in 10 ml distilled water and administered through a 25 gauge scalp needle subcutaneously at the rate of 2 ml/minute or more rapidly as tolerated. (Borgna-Pignatti C and Cohen A. evaluation of a New Method of Administration of the Iron Chelating Agent Deferoxamine. J. Pediatr 130:86-8, 1997). Also give Vitamin C 100 mg p.o. q day for children 10 years or older and 50 mg p.o. q day for children under 10 years. Hydrocortisone 11 mg is added to every gram of Desferal to decrease skin irritation. This method should be considered only in exception conditions of failure of Exjade and slow continuous desferal administration.

In non-compliant patients or when the ferritin level is very high (above 4000) or liver iron content is rising, desferal can be given as a continuous infusion over 48 hours at a maximum rate of 15 mg/kg/hour (with a maximum total daily dose of 6 grams). (See infusion orders). Whatever the total dose, it should be given over no less than 48 hours. This can be given as often as every two weeks. This method should be considered only in exception conditions of failure of Exjade and slow continuous desferal administration.

Patients with iron overload as also those patients actively getting iron chelation therapy are at greater risk of developing serious infections due to *Yersinia enterocolitica* and *vibrio vulnificus* (oysters) (ferrophilic organisms).

Korones DN et al: Intermittent high-dose deferoxamine for patients with iron overload and sickle cell anemia. Intern J Pediatr Hematol Oncol 1996; 3:53-56.

Cohen A et al: Vision and hearing during deferoxamine therapy. J Pediatr 1990; 117:326-30.

Exchange Transfusion for Patients with Sickle Cell Disease

Goal: Rapid reduction of hemoglobin S to less than 30 percentage while maintaining total hemoglobin of 10-11 gm%.

Indications:

Acute neurological event

Severe pneumonia or pulmonary infarct (acute chest syndrome)

Acute arterial hypoxia

Ophthalmologic surgery

Priapism

High dose high osmolar intravascular contrast studies

Emergency surgery with general anesthesia

High risk surgery with general anesthesia

Automated Red Cell Exchange

Pheresis is the preferred method. A 2-red cell volume exchange by erythrocytapheresis will decrease the hemoglobin S percentage to less than 25%. The calculation is done to end the pheresis with hemoglobin 10gm% (HCT of 30%). This is followed, when needed, by simple transfusion to adjust hemoglobin to 10gm%-11gm% (**never above 12gm %**) or Hct to 30%-33% (**never above 35%**).

Type of Blood to be used:

PRBC, filtered, freshest available units, sickledex negative. Ideally it should be a partial phenotypical match.

Estimation of Exchange Transfusion Volume:

Assumption:

The Hct of PRBC is 70% (use 0.7 for calculations)

Total Blood volume is 75ml/kg

PRBC needed for single volume exchange = $[75\text{cc} \times \text{weight in kg} \times \text{HCT}] / 0.7$

We usually do double volume exchange.

Rapid Manual Partial Exchange Transfusion

Goal: Rapid decrease the percentage of hemoglobin S without increasing the hemoglobin level.

Indication: For patients with baseline hemoglobin of 10 gm% and above (HCT of 30% and above) who are scheduled for surgery or have experience a neurological event and all patients on hyper-transfusion (to decrease iron overload).

Technique:

Infuse 6 ml/kg of normal saline

Phlebotomize 6-7 ml/kg

Transfuse 10-15 ml/kg of PRBC

Alternate Technique:

1. Use “Mr. Liver” set-up (see schema)
2. Order 10 ml/kg of PRBC
3. Ask the blood bank to adjust the hematocrit to 35% using saline
4. Simultaneously remove the same amount as the reconstituted blood and transfuse the ordered blood.
5. If needed, add a simple transfusion to reach hemoglobin of 10-11 gr%

References:

1. Ohene-Frmpong, K: Indications for red cell transfusion in sickle cell disease. *Semin Hematol* 38(suppl 1):5-13, 2001
2. Eckman JR: Techniques for blood administration in sickle cell patients. *Semin Hematol* 38(suppl 1):23-29, 2001
3. Schmalzer EA et al: Viscosity of mixtures of sickle and normal red cells at varying hematocrit levels. Implications for transfusion. *Transfusion* 27:228-233, 1987
4. Jan K et al: Effects of transfusion on rheological properties of blood in sickle cell anemia. *Transfusion* 22:17-20, 1982

DEFEROXAMINE (DESFERAL) INFUSION ORDERS PEDIATRIC HEMATOLOGY/ONCOLOGY

1. Admit Peds Hem/Onc patients
2. Diagnosis
3. Condition
4. VS:TPR BP Q 4 hours
5. Activity: up ad lib
6. Diet:
7. Ht: _____ cm; Wt: _____ kg
8. Allergies
9. Lab pre admission

CBC with reticulocyte count, Type and Cross match _____ cc PRBC filtered, sickledex negative and freshest available.
10. Central line catheter care per protocol
11. Remove _____ ml/kg = _____ cc PRBC IV over _____ hrs
12. Administer _____ ml/kg = _____ cc PRBC IV over _____ hrs
13. Volume transfused may vary 20% above or below the volume ordered; if amount ordered is within 10% of a total unit, may give total unit. Total volume to be transfused in a 4 hour period is not to exceed 20 ml/kg.
14. Administer IV Desferoxamine (Desferal) 15 mg/kg/hr (**maximum 6gram/24 hours**) = _____ mg/24 hr. Place _____ grams Desferoxamine in 250 ml NS to infuse at _____ ml/hr x 24 hours, for two days.
15. Notify HO: Temp > 38; pulse > 140; BP systolic > 160 or < 60 diastolic > 100 or < 30.
16. Medications:
Vitamin C 100 mg po with start of each 24 hour IV Desferal
Vitamin E with start of each 24 hour IV Desferal:
< 1 year old give 100 IU
1 – 6 years give 200 IU
> 6 years give 400 IU

PERI-OPERATIVE MANAGEMENT OF CHILDREN WITH SICKLE CELL DISEASE

Patients are divided into very high risk, high risk and low risk.

Surgeries may be divided into very high risk, high risk and low risk.

Very high risk patients are those defined with the criteria below:

1. History of stroke or at high risk of stroke (abnormal TCD, silent infarcts on MRI).

High risk patients are defined as those with one of the criteria below:

1. Other (than above) pre-existing cardiovascular, neurological, or pulmonary dysfunction.
2. History of multiple hospitalizations in previous one year before surgery.
3. History of multiple ACS.

Low risk patients are defined as those having none of the above risk factors.

Very high risk surgeries consist of cardiopulmonary bypass, ECMO, hypothermia, prolonged CNS surgeries associated with hypothermia, procedures involving high osmolar IV contrast or other hyperosmotic agents.

High risk surgeries

1. Major body cavity surgery (other cranial, thoracic, abdominal, or pelvic).
2. Tonsillectomy, adenoidectomy and other surgeries involving the airway.
3. Surgery requiring over 25-30 minutes of general anesthesia.
4. Oxygen desaturation is anticipated.

Low risk surgeries

1. Minor surgery in which oxygen desaturation is unlikely especially surgery requiring under 25 minutes of general anesthesia.
2. Surgery in which no general anesthesia is used (no NPO).

Pre-Operative Management

Ideally, preparation should start a month before surgery date. Transfusion will be given weekly, or bi-weekly with enough time to reach the goal of hemoglobin/hematocrit and hemoglobin S, about a week before surgery. Whenever possible a partial manual exchange should be done with 5-7 ml/kg of blood phlebotomized and 10-15 ml/kg transfused.

All patients undergoing high risk surgeries will be transfused pre-operatively to hemoglobin level of 10-11 gm/dl (but no higher than 12 gm/dl to avoid hyperviscosity and risk of a stroke).

All patients of high risk groups will be considered for transfusion pre-operatively to hemoglobin level of 10-11 gm/dl (but no higher than 12 gm/dl to avoid hyperviscosity and risk of a stroke).

In very high risk patients and very high risk surgeries the goal is to have presurgery Hgb at 10-11 gm% and hemoglobin S level should be reduced to below 30-40% (30 % for those SCD patients with high risk of stroke or history of stroke within the last 3 years and 40% for the rest of patients, i.e. patients with history of stroke more than 3 years prior to the surgery).

All groups will receive pre-operative hydration. In high risk patients, this will be done with 8 hours of IV hydration. Low risk patients or those requiring low risk surgeries will receive either IV hydration as above or oral hydration with NPO clear liquids until 3-4 hours pre-op. (If case is delayed the patient will be given IV hydration). All patients should receive IV hydration at 1½ maintenance when NPO.

Intra-Operative Management in all procedures in all SCD patients

1. At least 50% FiO₂ during surgery and 100% FiO₂ for few minutes before intubation and after extubation.
2. Awareness to the fact that hypoxia, acidosis, hypothermia, and hypovolemia may promote crisis.
3. Controlled ventilation is preferable to avoid hypercapnia and hypocapnia.
4. Heat preservation techniques (warm OR and RR environment – 80-85⁰F).
5. Hydration at 1.5 maintenance.
6. Cell saver should not be used.

Post-Operative Management especially in high risk procedures and high risk patients

1. Consider supplemental oxygen for at least 12 hours post-op, especially in very high risk patients and after very high risk surgeries.
2. IV hydration for at least 12 hours post-op.
3. Post-op overnight pulse oximetry

Patients with hemoglobin SC disease or sickle beta-Thalassemia whose hemoglobin is between 10 and 12 gm/dl usually need no pre-operative transfusion for low risk procedures. For high risk patients and high risk procedures either a transfusion (if their hemoglobin is close to 10) or partial exchange consisting of transfusion of 10-15 ml/kg of pRBCs following, if required, phlebotomy. In very high risk patients and very high risk procedures it is recommended to reduce hemoglobin S to 30-40%(30 % for those SCD patients with high risk of stroke or history of stroke within the last 3 years and 40% for the rest of patients). In all SCD patients the final goal of Hgb is 10-11 g% (not to exceed 12 g%).

THE DENTAL MANAGEMENT OF CHILDREN WITH SICKLE CELL DISEASE

1. Children with sickle cell disease must be managed in close liaison with a pediatric hematologist. Therefore, their dental care may best be provided by a hospital based dentist.
2. Every effort should be made to arrange the dental care so as to minimize the disruption from school attendance and social life.
3. Children with sickle cell disease should be seen at least yearly by a dentist, starting after the eruption of the first tooth (6 – 12 months of age). A rigorous prevention regiment must be implemented, including oral hygiene instruction, diet counseling, appropriate use of topical and fissure sealant. Some children (based on the dentist's evaluation) may need to be seen more often (3-6 month intervals).
4. All dental infections should be treated aggressively with an appropriate antibiotic agent.
5. Although many texts recommend the use of a local anesthetic without vasoconstrictor, there is no evidence to support this practice.
6. In apprehensive or uncooperative children the use of a good behavior management strategy, supplemented by inhalation sedation, wherever required, is preferable to the use of general anesthesia.
7. When using nitrous oxide for inhalation sedation, care should be taken to avoid diffusion hypoxia at the termination of the nitrous oxide administration by giving 100% oxygen for at least five minutes at the end of the procedure. These children should be well hydrated before sedation is started.
8. Anti microbial prophylaxis similar to that used for children with heart defect is recommended prior to all invasive procedures. Amoxicillin 50 mg/kg maximum 2.0 g p.o. or Ampicillin 50 mg/kg maximum 2 g IM or IV one hour before the procedure. For patients allergic to penicillin use clindamycin 20 mg/kg maximum 600 mg p.o. or IV or Azithromycin or Clarythromycin 15 mg/kg p.o. one hour before the procedure. Other drugs that can be used are: Cephalexin 50 mg/kg (maximum 2.0 g) p.o. and Cefazolin 25 mg/kg (maximum 1.0 g) IM or IV. **Prophylactic antibiotics are especially important for patients who have an indwelling infusaport or broviac.**
9. Restoration of teeth is preferable to extraction. If extractions are needed, local anesthesia is preferable. General anesthesia should be selected only if sedation is unsuccessful or too risky, or if the required treatment is very extensive.

10. Due consideration should be given to the use of stainless steel crowns for the restoration of primary molars, in preference to other restorative materials such as amalgams, composites, or glass-ionomers. (They seldom need to be replaced).
11. General anesthesia must be carried out in a hospital with full anesthesia facilities and in close cooperation with a pediatric hematologist. For most patients (those who do not have pre-existing cardiovascular, neurological or pulmonary dysfunction) a simple transfusion to raise the hemoglobin to 10-11 gm/dl (but no higher than 12 gm/dl) is adequate. The child should be well hydrated pre-operatively.

Intra-operatively, the patient should; a) receive at least 50% FiO₂ b) heat preservation techniques should be utilized c) controlled ventilation is preferable to avoid hypercapnia, d) hydration should be maintained at 1.5 x maintenance.

Post-operatively, the patient should; a) receive supplemental oxygen for at least 12 hours, b) maintenance IV hydration, and c) post-op pulse oximetry.
12. Patients who have pre-existing cardiovascular, neurological, or pulmonary dysfunction or those, in whom oxygen desaturation can be anticipated, are defined as high risk. In those patients, in addition to adjusting their hemoglobin level to 10-11 gm/dl (but no more than 12 gm/dl to avoid hyperviscosity and the risk of stroke) the hemoglobin S level should be reduced to below 60%. In these patients, there should be at least 8 hours of pre-operative hydration. The intra and post operative precautions are the same for the low risk patient.
13. If general anesthesia is required, it is advisable to carry out comprehensive dental treatment, including any extraction or restoration that may be required, so as to avoid a second procedure.
14. Pain medications for patients with sickle cell disease include Tylenol, Tylenol with Codeine, NSAID's and narcotics especially morphine. **However, the use of Meperidine (Demerol) should be avoided as much as possible since one of its toxic metabolites (normeperidine) has a long plasma half-life and can cause seizures.**

PEDIATRIC DENTISTRY AND THE SICKLE CELL PROGRAM STAFF MEMBERS
ENDORSE THIS MANAGEMENT PROTOCOL.

LEG ULCERS IN SICKLE CELL DISEASE

Leg ulcers are one of the complications of sickle cell disease. They start in adolescence and eventually appear in 75% of adults. Low steady state hemoglobin values are associated with a higher incidence of ulcer formation. A high fetal hemoglobin production correlates with a lower incidence of leg ulcers.

The ulcers usually present over the medial surface of the lower tibia or just posterior to the medial malleolus.

Treatment is in many instances temporary and recovery may take a long time. Below are current recommendations:

Acute Ulcer

1. Surgical debridement if there is unhealthy tissue, especially if the ulcer is chronic and there is slow or minimal healing.
2. Scrupulous hygiene
3. Topical antibiotics
4. Moist-wound dressing – one to four times a day (with wet to dry gauze - saline dressings) it helps in gentle debridement and healing.
5. Rest
6. Elevation of leg

Chronic Ulcer

1. Consider chronic transfusion program (every 4 weeks for 6 – 12 months)
2. Consider oral zinc sulfate to promote healing
3. Consider split thickness skin grafts
4. Consider treatment with hydroxyurea, with or without erythropoietin, depending on response to hydroxyurea

To prevent ulceration pay close attention to improved venous circulation by using above-the-knee elastic stocking.

References:

Cackocic M et al: Leg ulceration in the sickle cell patient. *J Am Coll Surg* 187:307-309, 1998

Peachey R: Leg ulceration and haemolytic anemia: an hypothesis. *Br J Dermatol* 98:245, 1978

Wolfort FC et al: Skin ulceration in sickle cell anemia. *Plast Reconstr Surg* 43:71, 1969

Koshy M et al: Leg ulcers in patients with sickle cell disease. *Blood* 74:1403, 1989

Alleye S et al: Social effect of leg ulceration in sickle cell anemia. *South Med J* 702:213, 1977

Role Of Hydroxyurea In Sickle Cell Disease

Initial dose: 15 mg/kg as a single daily dose rounded to increments of 250 mg. The dose will be increased by 5mg/kg or a rounded equivalent every 8-12 weeks as tolerated. For patients who are a size that rounding will bring them to a capsule size that is not a multiple of 250, they will be instructed to take the medication on an alternating day basis such that the overall total approximates a 5 mg/kg increment.

Day of beginning HU therapy: Baseline CBC, differential, reticulocyte count, creatinine and ALT/GGT (i.e. CMP), and a history and physical examination should be obtained. Written informed should be obtained. Hemoglobin electrophoresis may be obtained.

Therapeutic Monitoring on starting HU therapy and until a steady dose or maximum tolerated dose (MTD) is reached:

- ◆ CBC and differential and reticulocyte count will be obtained every 2 weeks while escalating HU dosage.
- ◆ At the end of first 2 weeks and then at every 4 week interval, a CBC, differential, reticulocyte count, creatinine and ALT/GGT (i.e. CMP), and a history and physical examination will be obtained (with special emphasis on checking for side-effects of HU).
- ◆ At **every visit for blood counts** patients will be asked about possible medication side-effects such as rash, hair thinning, renal, liver, general (malaise, weakness) and GI disturbance.

Four weeks after the steady dose or MTD is reached, CBC and reticulocyte count shall be obtained every 4 weeks and a history, physical examination and CMP shall be performed every two months. Hemoglobin electrophoresis may be obtained every 2-3 months.

Dose escalation may be continued every 8-12 weeks until toxicity is encountered or 35 mg/kg daily dose is reached.

Once the patient is stabilized on their monthly tolerated daily dose a CBC, differential, and reticulocyte count will be checked monthly. Every 2 months they will have a physical exam, assessment of toxicity and ALT/GGT, creatinine (CMP) and hemoglobin electrophoresis will also be obtained.

Toxicities: Any one of the following is sufficient to stop the drug immediately. If the drug is stopped it will be held for one week, the value rechecked and, if back within normal limits, the medication will be continued at the same level. If the same toxicity occurs a second time when the medication is resumed after toxicity has cleared, the dose is decreased by 5mg/kg (the last tolerated dose).

Toxicities

- ◆ Absolute neutrophil count [total white blood count x (segments + bands)] <1500/mm³
- ◆ Platelet count <100,000/mm³
- ◆ A 20% decrease in hemoglobin concentration from patient's baseline
- ◆ An increase in the creatinine 0.5mg/dl over patient's baseline

- ◆ A 200 % increase in the ALT or GGT from patient's baseline (or a level that is three times the upper range of normal)

Compliance: Compliance to HU may be monitored by eliciting patient history, checking pharmacy records, MCV, hemoglobin electrophoresis, counting pills, etc.

Note: A refill of HU must not be given beyond the date of anticipated FU. If the patient cannot FU at the last minute, a one time refill for HU up to seven days may be given at the physician's discretion (based on history and laboratory tests, etc). Compliance, side-effects, prolonged duration of therapy should be stressed before HU therapy is instituted.

Gallstones

Patients with sickle cell disease have an increased risk for developing gallstones. Age and the degree of hemolysis correlate with the incidence of cholelithiasis. The onset of cholelithiasis occurs as early as 2 to 4 years of age (12% in some studies) and progress to 30% to 50% by age 20. In addition to pigment stones, some xenobiotics like third generation cephalosporins may crystallize in the gallbladder and possibly increase the incidence of gall stones.

Biliary sludge is a viscous material detected by ultrasound. Sludge may be promoted by some antibiotics like ceftriaxone. Sludge is often found with stones. Sludge by itself may or may not progress to stone formation.

By adulthood over 50% of SCD patients develop cholelithiasis, some are symptomatic. Symptoms associated with gallstones include: Fat intolerance, postprandial cramping, nausea, vomiting, acute cholecystitis and ascending cholangitis. In addition, the gallbladder may act as a reservoir for Salmonella that may precede Salmonella bacteremia.

Because of these, the current recommended treatment in some centers is elective cholecystectomy (preferably laparoscopic) in above patients with significant symptoms affecting their day to day activities. Morbidity is much lower in asymptomatic patients (i.e. not having acute cholecystitis).

Patients with symptomatic cholelithiasis but no active cholecystitis should be prepared for surgery with blood transfusions to increase the hemoglobin to between 10 and 11 gr/dl and the hematocrit to between 30% and 33%. The patients should be admitted the night before for maintenance hydration. During surgery patients should be kept warm, and adequately oxygenated before, during and at recovery. Patients with active cholecystitis should be treated conservatively with hospitalization ,IV antibiotics and IV fluids without oral feeds. An interval cholecystectomy should be performed after 4-8 weeks once the inflammation is controlled.

Sarnaik S et al: Incidence of cholelithiasis in sickle cell anemia using the ultrasonic gray-scale technique. J Pediatr 1980; 96:1005-1008.

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Ware RE et al: Laparoscopic cholecystectomy in young patients with sickle hemoglobinopathy. J Pediatr 1992; 120:58-61.