Comprehensive Care for Children and Adolescents with Sickle Cell Diseases

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New England Pediatric Sickle Cell Consortium

Objectives

- To review the system for newborn screening of infants for sickling diseases
- To provide the framework for a comprehensive medical home for sickle cell disease patients by both primary care and hematology providers
- To present recommendations for routine health maintenance in children and adolescents with sickle cell diseases

Sickle Cell Diseases

- Group of genetic red cell disorders characterized by vaso-occlusion and hemolysis
- Varying severity from mild to life-threatening
- Complications involve multiple organ systems

Background

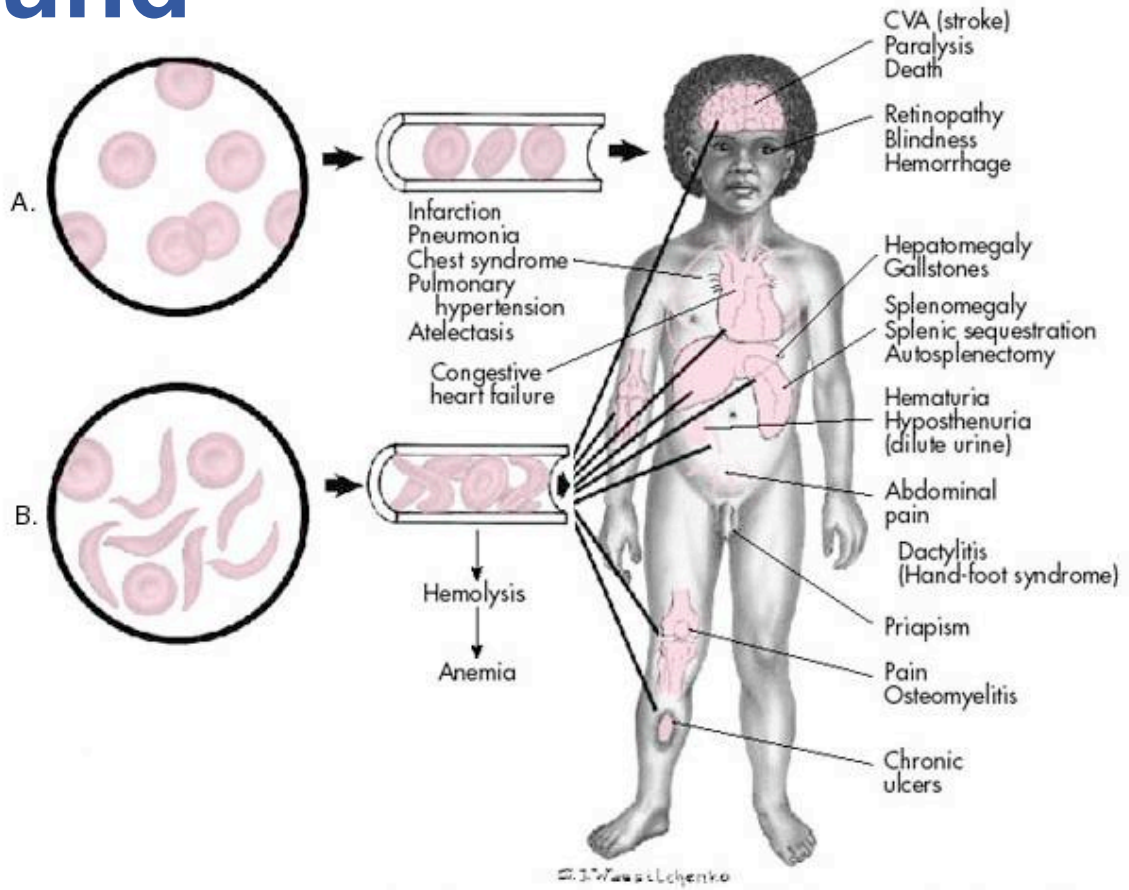
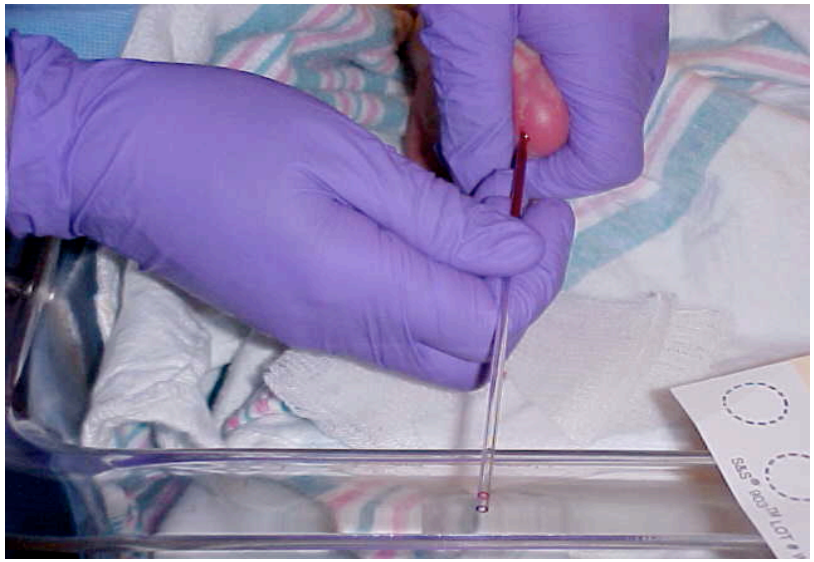


Fig. 35-4, A & B Differences between effects of, **A,** normal and, **B,** sickled RBCs on circulation with selected consequences in a child.

Diagnosis

Newborn Screening for Hemoglobin Diseases

- Primary aim of NBS for sickling diseases is to identify affected infants to start penicillin prophylaxes in infancy



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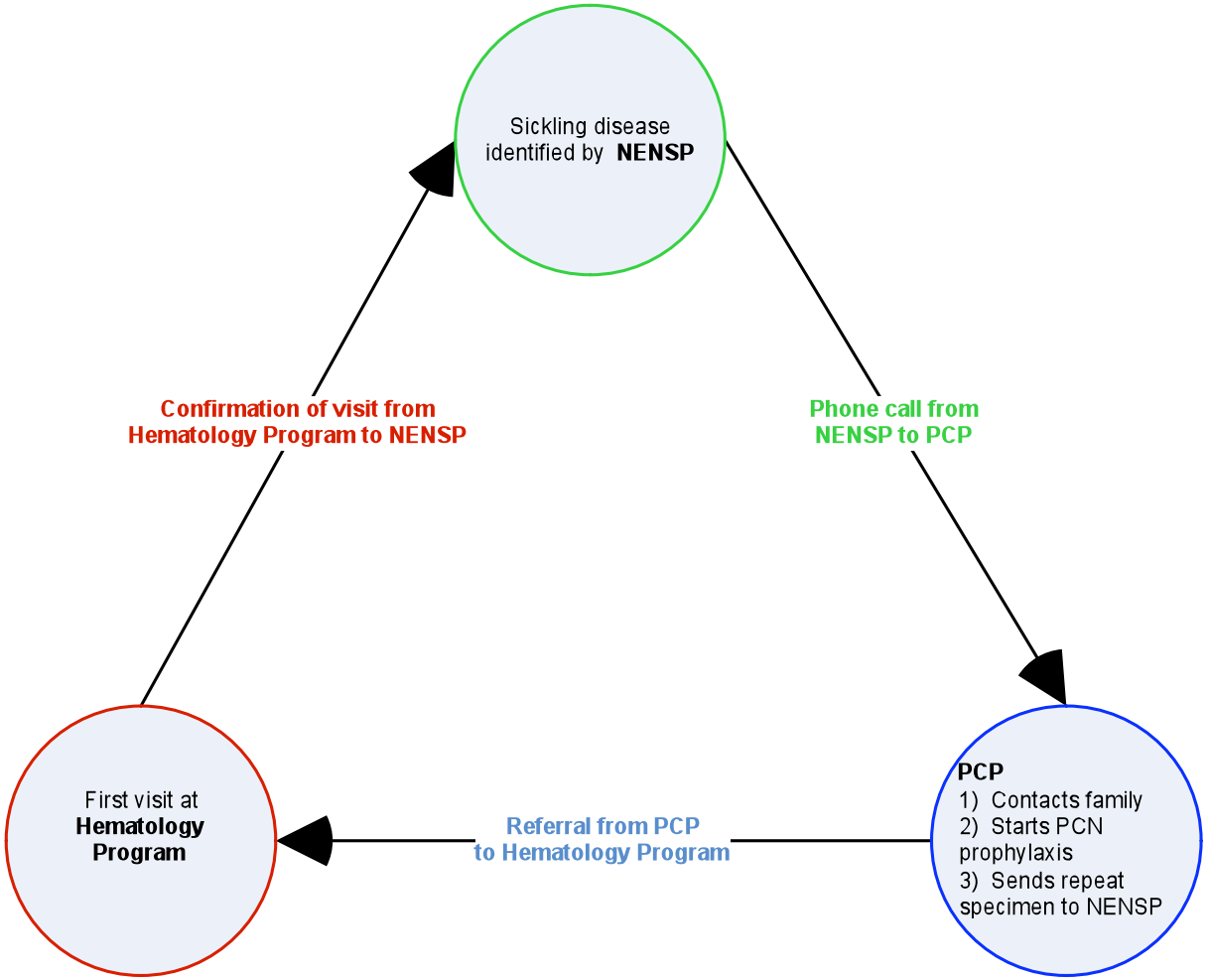
Review of Results: The New England Newborn Screening Program

FA	Normal for infant
FAS	Sickle cell trait
FS	Sickle cell disease: either Hb SS or HbS-beta^0 thalassemia
FSC	Sickle cell disease: HbSC
FSA	Sickle cell disease: Hb S-beta$^+$ thalassemia
FS + anything other than A (D, E..)	A potential variant of sickle cell disease

Reporting Sequence for Abnormal Results : Sickling Disorders



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Elements of Care

Background

- Comprehensive care starting in infancy has markedly decreased mortality for children with SCD
- Children and adolescents require additional specialty visits for evaluation, counseling, and education in addition to routine health maintenance visits with PCP
- Specialty visit frequency depends upon age, complications, educational needs, and therapeutic monitoring

Medications

Susceptibility to Bacteria

- Sickling results in functional asplenia which may begin in infancy
- Increased susceptibility to infections with encapsulated organisms
  - *Streptococcus pneumonae* (Pneumococcus)
  - *Haemophilus influenzae* (Hib)
  - *Neisseria meningitidis* (meningococcus)
- Presentation includes bacteremia/sepsis, meningitis, osteomyelitis, and pneumonia/acute chest syndrome

Need for Penicillin Prophylaxis

The New England Journal of Medicine

Volume 314:1593-1599. June 19, 1986. Number 25

Prophylaxis with oral penicillin in children with sickle cell anemia. A randomized trial.

MH Gaston, JI Verter, G Woods, C Pegelow, J Kelleher, G Presbury, H Zarkowsky, E Vichinsky, R Iyer, JS Lobel, and et al.

"We conclude that children should be screened in the neonatal period for sickle cell hemoglobinopathy and that those with sickle cell anemia should receive prophylactic therapy with oral penicillin by four months of age to decrease the morbidity and mortality associated with pneumococcal septicemia."

Antibiotics

Birth to 36 months	Penicillin VK 125 mg PO BID
36 months to 5 years	Penicillin VK 250 mg PO BID
> 5 years only if surgically splenectomized	Penicillin VK 250 mg PO BID

May use erythromycin ethyl succinate (20 mg/kg/d BID) for patients with penicillin allergy

Fever

- For sickle cell patients over age 2 months any temperature above 101.5º F (38.5º C) is an EMERGENCY
- All febrile sickle cell patients require prompt evaluation and treatment with parenteral antibiotics

Folic Acid

- Not necessary since US food supply is fortified
- Exceptions
  - Females of childbearing age
  - Pregnant females
  - Diet reportedly low in natural and enriched sources
  - Significant baseline hemolysis(reticulocyte count $\geq$10%)

Iron

- Sickle cell disease invariably results in anemia
- Coincidental iron deficiency is rare but possible
- Check Iron Stores prior to initiating supplemental iron (Fe, TIBC, Ferritin)
- Iron overload is uncommon in sickle cell anemia unless affected patients receive numerous red blood cell transfusions (>20 in lifetime)
- Transfusional iron overload results in complex multi-system morbidity requiring chelation therapy

Home Pain Management Plan

- NSAID (*ibuprofen*)
- NSAID + oral short-acting opioid (*oxycodone,codeine*)
- NSAID + long-acting opioid (*MS Contin*™, *Oxycontin*™) with short acting opioid for breakthrough
- Ensure family has understanding of plan and adequate supply of medication

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Hydroxyurea (HU)

- Chemotherapeutic agent which increases levels of fetal hemoglobin
- Approved for use in adults with sickle cell disease
- Widely used in older children
- Most common side-effect is reversible neutropenia
- Potential for carcinogenicity must be extremely low
- Possible teratogenicity requires excellent attention to contraception

HU in Adults

- Has been shown to reduce morbidity and mortality
- Requires frequent lab monitoring and dose adjustments
- Sexually active patients must use effective form of birth control

HU in Children

- Initial studies have shown clinical benefit
- Minimal data on long term effects on growth and development for the youngest children, especially under 5 years of age
- Should only be prescribed by a hematologist familiar with its use in children

Immunizations

Background

- Penicillin prophylaxis in non-splenectomized may be discontinued at age 5 years
- Keeping an up-to-date record of immunizations
- Especially important to verify immunization status before surgical splenectomy
- Influenza carries significant risk of pulmonary complications

Pneumococcal

- PCV7
  - 7-Valent Pneumococcal Conjugate Vaccine
  - Prevnar™
- PPV23
  - 23-Valent Pneumococcal Polysaccharide Vaccine
  - Pneumovax™
- Together these vaccines cover 87% of pneumococcal bacteremia and meningitis in the US

PCV7- Prevnar

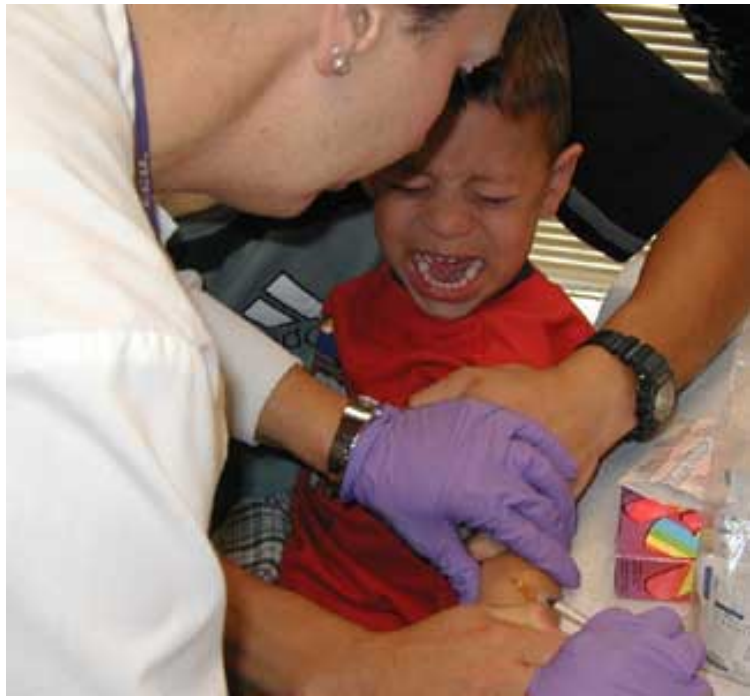
- Infants and young children follow childhood immunization schedule
- Catch-up all children and adolescents with SCD by giving at least 2 doses 6-8 weeks apart

PPV23- Pneumovax

- Starting at age 24 months
- Repeat in 3-5 years depending upon age at original vaccination
- If missing PCV7 and PPV23, give all doses of PCV7 first

Hib

- As per childhood immunization schedule
- Catch-up all children and adolescents with SCD by giving 1- 2 doses 6-8 weeks apart



Meningococcal

- May be given after age 24 months
- Need before splenectomy
- Booster before residential living situation (dorm)
- Recommended by AAP Red Book, but not standard in all hematology programs

Influenza

- Patients
  - For all patients after age 6 months
  - Ideally given before December 1st
- Household Contacts
  - Especially for families of infants and for siblings in out-of-home care or school
- Live-virus (Flu-Mist™)
  - Insufficient data re: use of intranasal live-virus vaccine in sickle cell patients

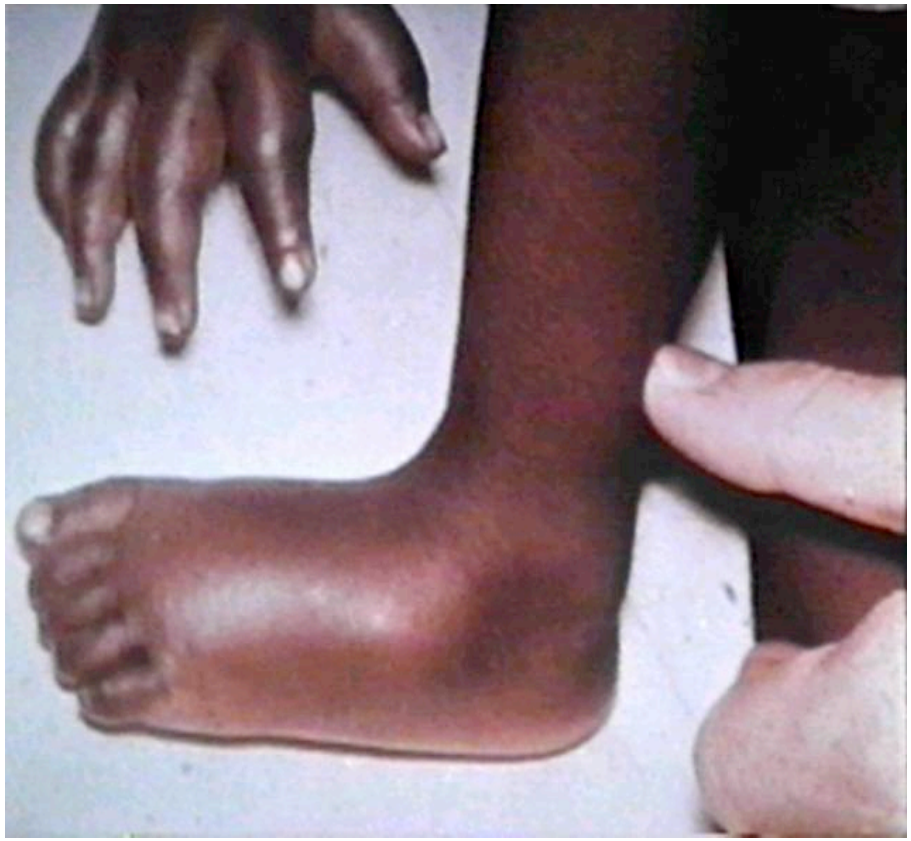
Physical Exam

Heart Murmur

- Expect flow murmur and enlarged heart in patients with significant anemia
- Heart failure uncommon in pediatrics
- Concern for pulmonary hypertension in the older adolescents and those with underlying pulmonary compromise
- Patients with transfusion-related iron overload require yearly evaluation

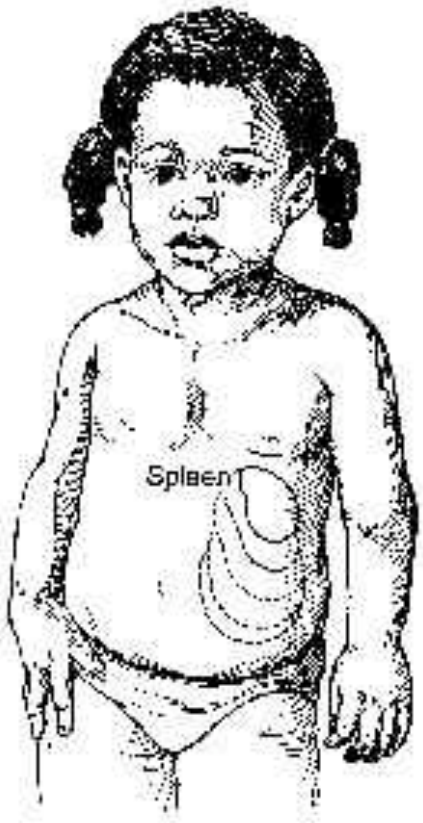
Vaso-occlusive Crises

- Emphasis on preventing painful episodes
- Many episodes of pain may be treated as an outpatient
- Fluids, warmth, medication, and rest the affected area



Splenic Sequestration

- Acute, life-threatening anemia if red cells are trapped within the spleen
- Chronic hypersplenism with reduced hemoglobin and platelet counts
- All physical exams should include documentation of spleen size
- Parents may be taught to palpate and measure spleen
- Occurs in younger children with HbSS, but also in older children and adults with HbSC

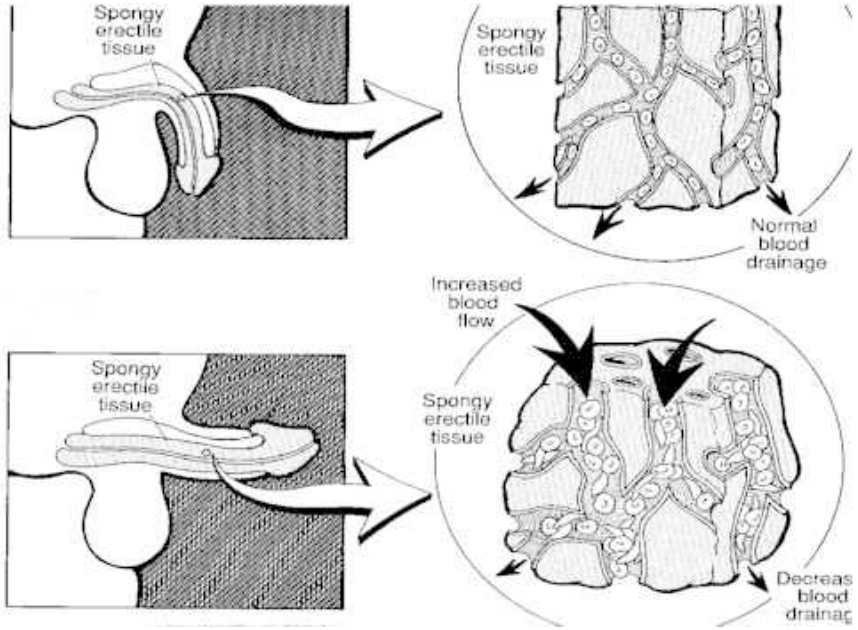


Kidneys: Pediatric Patients

- Concentrating defect (*Isosthenuria*)
- Nocturnal enuresis may start from childhood
- Predisposes to dehydration
- Families may limit fluids in attempt to decrease wetting, but this intensifies dehydration and may cause pain

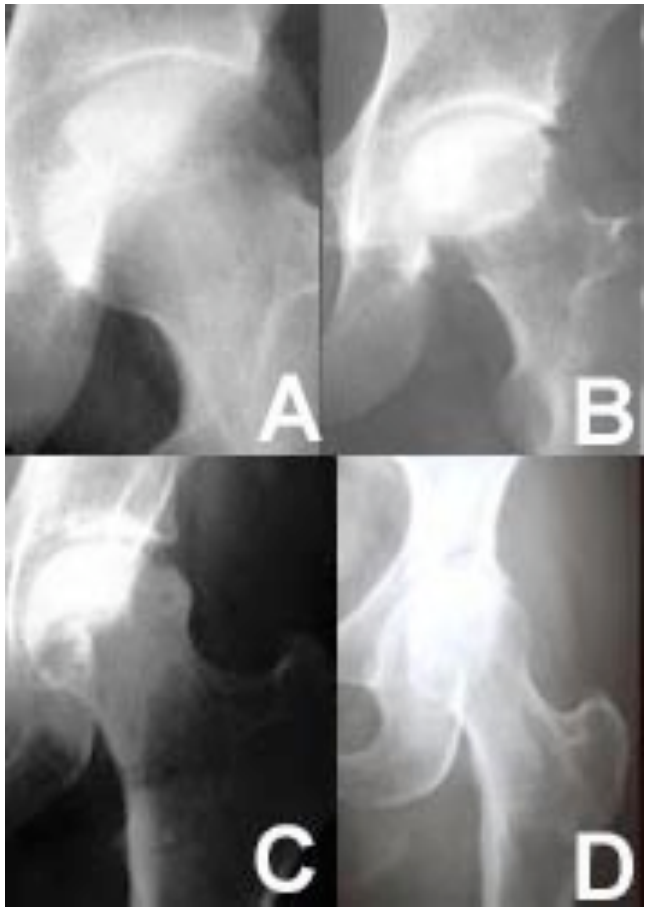
Priapism

- Vaso-occlusion obstructs penile venous draining
  - prolonged
  - stuttering
- Episode lasting several hours requires urologic intervention
- Severe or repeated events can cause fibrosis and impotence



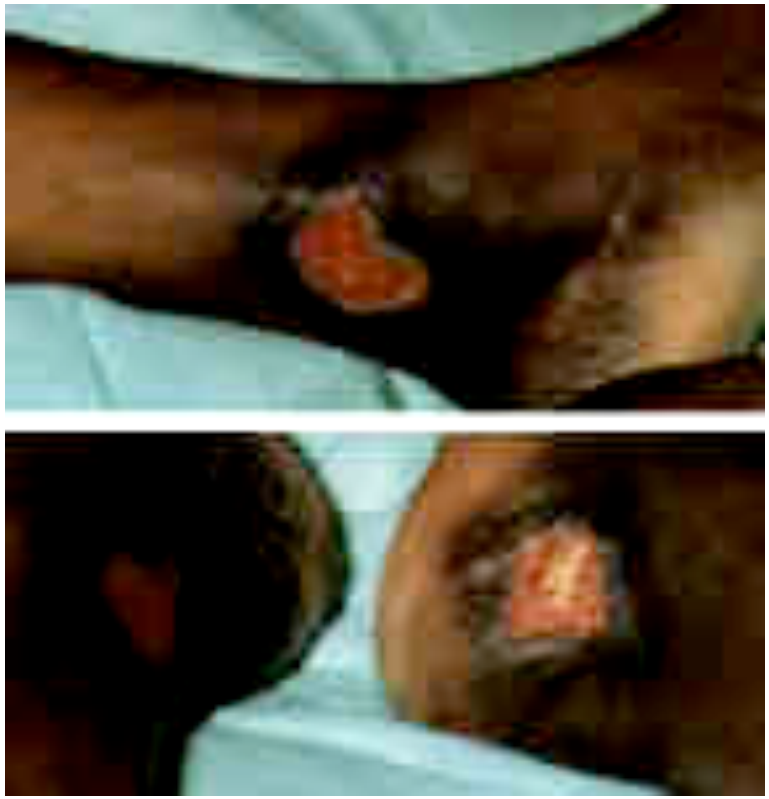
Hips and Joints

- Painful destruction of femoral or humeral heads
- Treatment depends upon extent and skeletal maturity
- May require surgical intervention, especially in late adolescence and adulthood
- May eventually require joint replacement

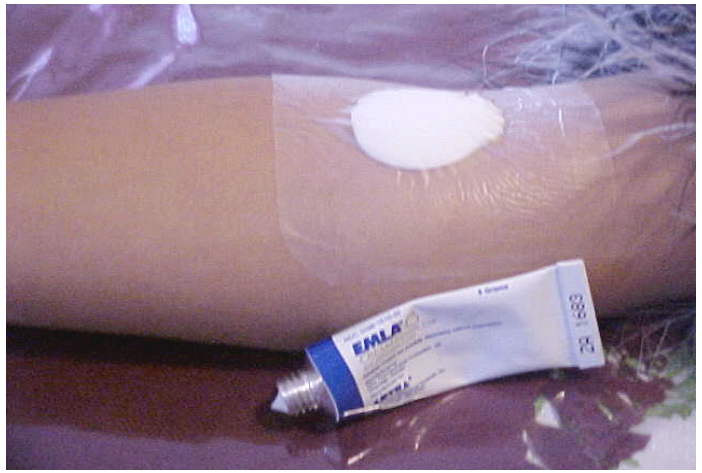


Leg Ulcers

- 10-20% of HbSS patients develop leg or ankle ulcers after age 10
- Unclear etiology, but anemia, hypoxia, infarction of surrounding skin and trauma contribute
- May persist for years and be painful
- Treatment is individualized



Laboratory monitoring



Background

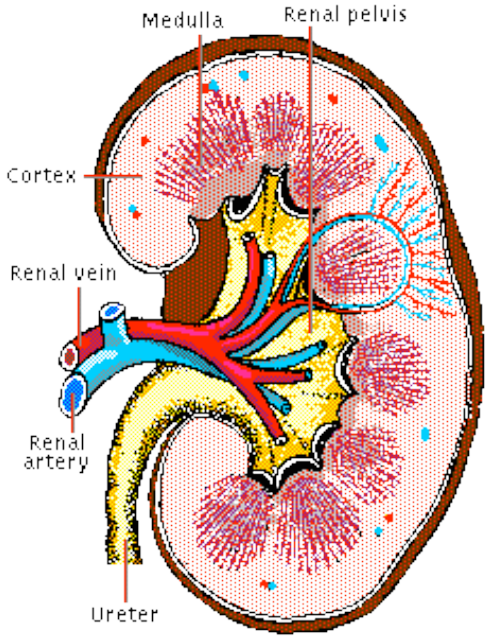
- Laboratory screening when well is required to establish baseline hematological parameters and to detect impending complications
- Every family should know their child's baseline hemoglobin/hematocrit as well as the presence of any allo or auto antibodies
- Renal function testing becomes more important in adolescence and adulthood to detect glomerular injury

Recommendations

Diagnostic	Repeat newborn screen result Qualitative hb electrophoresis at age 1
Antigen typing	RBC antigen after age 1 and before 1st transfusion
CBC with diff and retic	1-2x/year
LFTs/Bili/Renal	Annual
UA	Annual once school-age

Kidneys: Adolescents and Adults

- Hematuria from papillary necrosis
- Acute renal failure as component of MSOF
- Chronic renal failure from glomerular abnormalities
- Start screening for proteinuria in adolescence

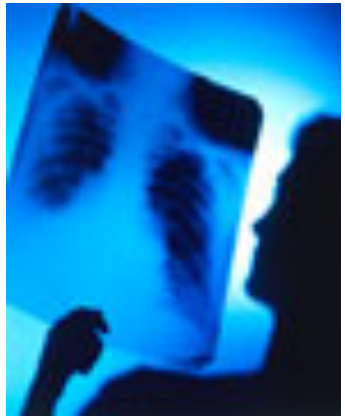


Microsoft Illustration

Routine Screenings

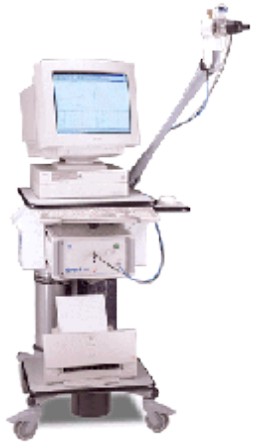
Pulmonary Complications

- Pulmonary events are leading causes of mortality and morbidity for adolescent and adult patients
- Risk increases with age
- Recurrent acute chest syndrome (ACS) and baseline reactive airway disease may predispose patients to continued pulmonary compromise



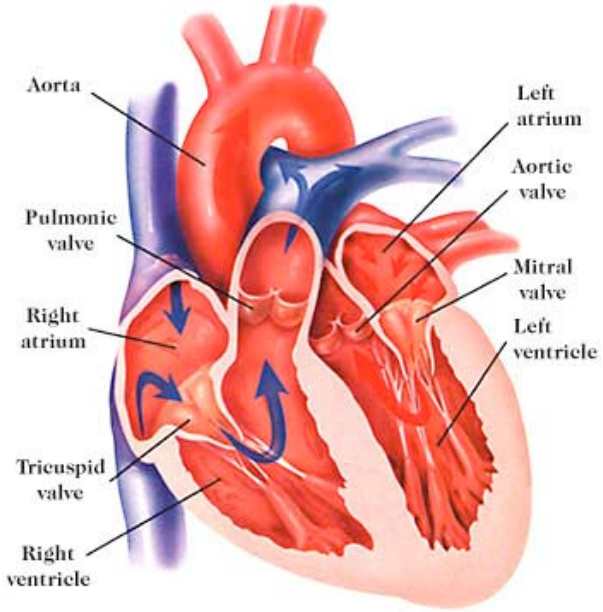
Pulmonary Care

- Goals are to evaluate and maximize pulmonary function
- Patients with any degree of reactive airway disease should have an Asthma Action Plan with strong emphasis on preventing future attacks with maintenance medications
- Patients with impaired function require intensive management from both primary and specialty care



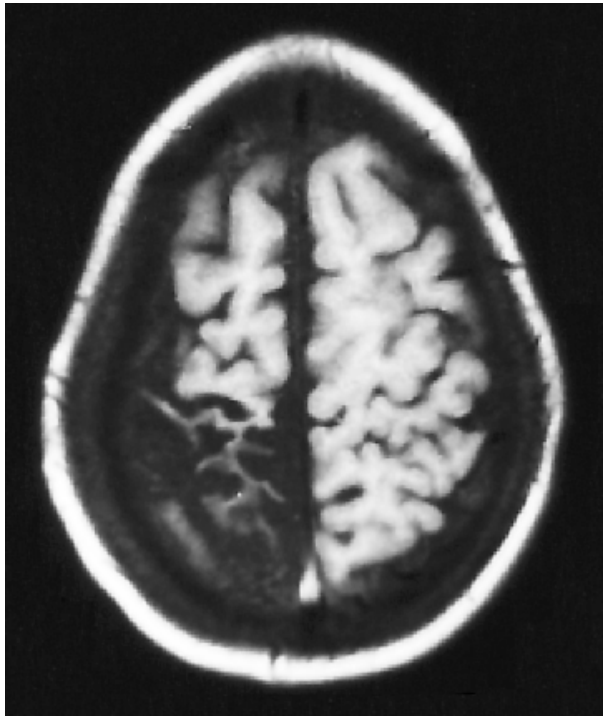
Cardiac Evaluation

- Association of pulmonary hypertension with death in adult patients
- Screening echocardiogram for older adolescents and those with pulmonary disease
- Addition screening depends upon pulmonary status and iron balance



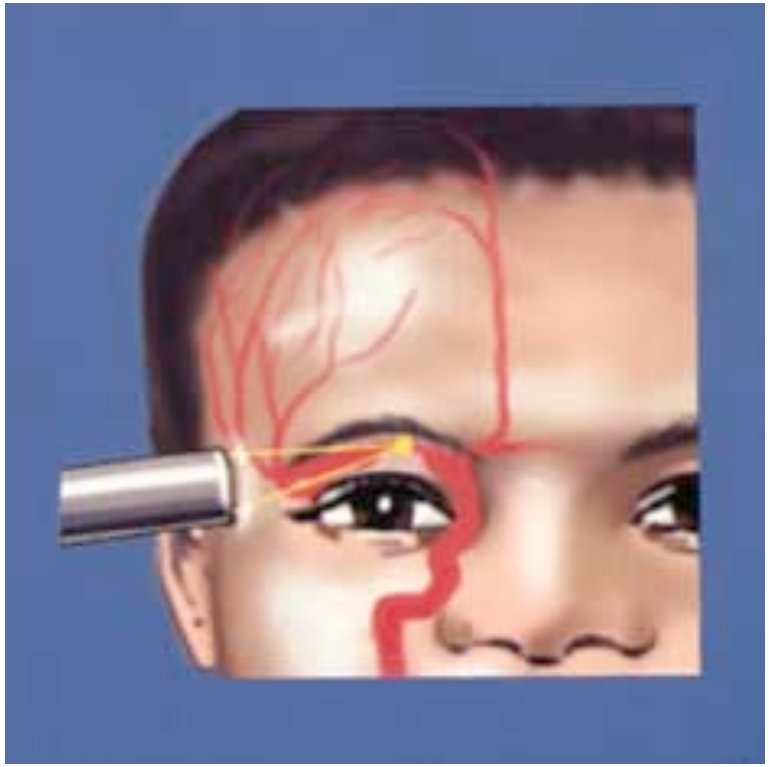
Stroke

- Stroke occurs in 10 % of sickle cell patients
- Most common in patients with HbSS and Hb S-β^0 thalassemia diseases between the ages of 3 and 10 years
- STOP study demonstrated that
  - Patients could be screened for increased stroke risk
  - Subsequent blood transfusions could prevent stroke



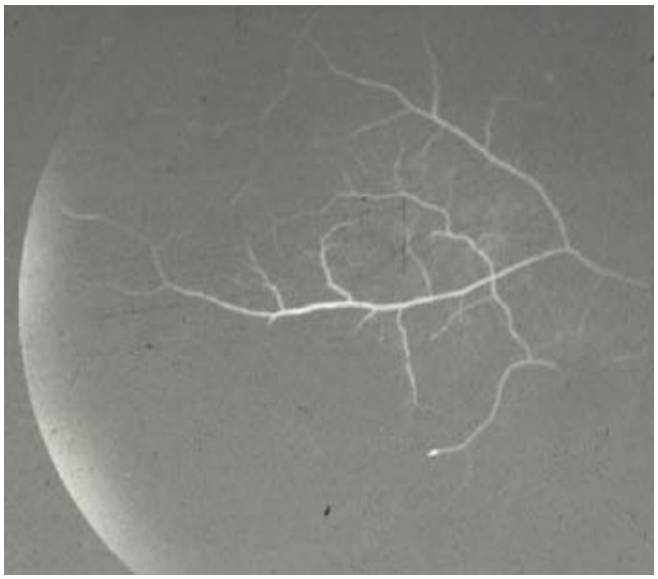
TCD Screening for Stroke Risk

- Stroke risk screened using TCD (transcranial Doppler ultrasound)
- Increased risk is indicated by elevated velocities of blood flow through cerebral arteries
- Now standard care for HbSS and HbS-β^0 thalassemia diseases from ages 3 to 16 years



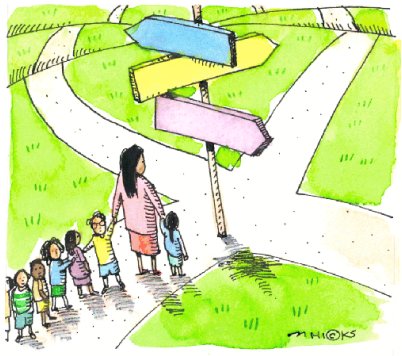
Vision Loss and the Retina

- Asymptomatic proliferative retinopathy may progress to retinal detachment
- Timely recognition and treatment may preserve vision
- All patients should have annual dilated opthamologic exam starting at age 10 years
- Especially important for patients with Hb SC disease

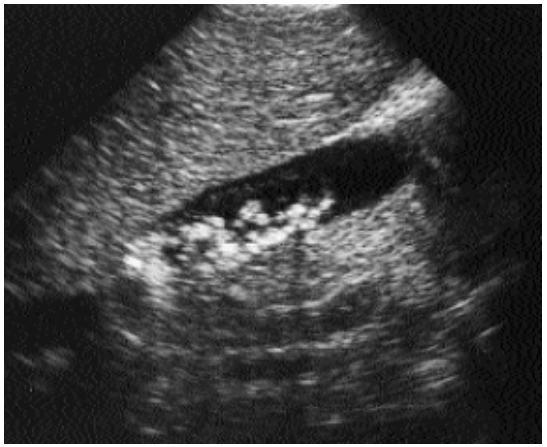


Neuropsychological

- Useful for patients after stroke, or with school/ developmental concerns
- May access services of EI or SPED/766
- Tutoring important for those with missed school days
- Families may need help advocating for services



Chronic Hemolysis



- Chronic hemolysis causes hyperbilirubinemia and gallstones
- Scleral icterus: need to know baseline
- Gallstones: 30% will have stones by adulthood, but do not need removal unless symptomatic
- Screening of asymptomatic patients not necessary

Screening Recommendations

Pulmonary	SaO_2 every visit PFTs at school age & adolescence, Consider echo for PHTN
TCD	Q 6 – 12 months from ages 3 to 16 for HbSS and HbS β^0 thal
Dilated opthamology	Yearly after age 10
Neuropsychology	After CVA or if concerns

Pregnancy and Contraception

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Genetic Counseling

- Sickle cell does not impair in fertility!
- Review inheritance of sickle cell disease and trait
  - Include role of beta-thal trait and other abnormal hemoglobins
- Provide information on prenatal diagnosis
- For females review pregnancy-related complications and need for close prenatal monitoring

HU Concerns

- Hydroxyurea is FDA pregnancy category X and should be considered a potential teratogen
- Male and female patients on HU should use effective methods of birth control
- Female patients of reproductive age may be required to use hormonal methods of contraception in order to receive HU

Contraception

- Estrogen containing contraceptives are not contraindicated in patients with SCD in absence of other risk factors
  - Smoking
  - HTN
  - Hx of clot
- Injected progesterone based contraceptives (Depo-Provera™) have been shown to ameliorate painful crises in initial studies

Pregnancy and Termination

- All pregnant patients with SCD must be referred to a high-risk OB with experience caring for patients with SCD and cared for in conjunction with an experienced hematologist
- Therapeutic abortion should not be performed by using hypertonic saline solution, this may induce sickling

Conclusion

- A comprehensive medical home for children and adolescents with sickle cell diseases requires both primary and specialty care
- Coordinated care with an emphasis on prevention of complications should serve to lessen the morbidity and mortality from this disease
- As children with sickle cell become adolescents they should be educated about their condition in preparation for transition into adult medical care

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