

HEMOGLOBINOPATHIES

Kansas Newborn Screening Program

Doc. Name: HGB

Version 2.0

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SICKLE CELL ANEMIA AND OTHER HEMOGLOBINOPATHIES

Introduction

Neonatal diagnosis and early appropriate treatment of sickle cell anemia (SS disease) and other clinically significant hemoglobinopathies have drastically lowered morbidity and mortality among affected infants.

Children with homozygous sickle cell anemia (SS disease) have inherited the gene for hemoglobin S, sickle hemoglobin, from each parent. The birth incidence rate of sickle cell anemia in the African American population is about 1:400; it is greater than 1:5000 in the general population.

There are other clinically significant sickling conditions which result when a child has inherited a sickle gene from one parent and a gene for some other hemoglobin variant from the other parent (e.g., a beta thalassemia gene or a gene for Hemoglobin C, D, E, or other variant). These mixed heterozygous conditions, including the relatively common hemoglobin SC disease, as a group, tend to be clinically less severe than homozygous sickle cell anemia, though severe medical complications may occur in each of them in some individuals.

Clinical Features

Sickle cell syndromes, particularly SS disease, are variable in their clinical manifestations and may involve multiple organ systems. The early manifestations, which may be life threatening, include fever and susceptibility to overwhelming infection, splenic sequestration, severe anemia and aplastic crisis. Other complications of sickle cell syndromes include osteomyelitis, vaso-occlusive pain syndromes, acute chest syndrome, cerebrovascular accident (stroke), priapism, pyelonephritis, retinopathy and others. Mortality rates, which have been reported to be as high as 25% in the first 3 years of life prior to initiation of newborn screening programs, have fallen to less than 10% in states where appropriate newborn screening is offered.

Other significant hemoglobinopathies including hemoglobin C disease and various thalassemias also have variable manifestations which range from very mild chronic anemia to clinical states of severe dyserythropoiesis requiring a lifetime of transfusion support.

Laboratory Tests

The initial screening test involves an estimation of the relative concentration of the various hemoglobins via thin layer isoelectric focusing. This test is sensitive and specific, even in the newborn period. It is performed on a small amount of hemoglobin dissolved from the dried blood spot from the newborn screening filter paper. See Table 5 for normal values and laboratory criteria for requesting repeat samples.

TABLE 5
Normal Values and Laboratory Criteria for Requesting Repeat Samples

| ANALYTE | NORMAL RESULTS | RESULTS REQUIRING PHONE FOLLOW-UP | RESULTS REQUIRING MAIL FOLLOW-UP |
|----------------------------------|----------------|--|--|
| Hemoglobin Iso-Electric Focusing | Hgb FA | Probable Disease (No Adult Hemoglobin Present) (FS, FSC, FC, etc.) | Probable Heterozygous Trait (FAS, FAC, FAE, FAV, etc.) |

All phoned results are followed by faxed or mailed confirmation. All tests are screening tests. Abnormal results need full evaluation before a diagnosis is confirmed.

Confirmatory Testing

Newborn screening tests are not diagnostic and **MUST** be confirmed on a liquid blood specimen. Solubility testing (Sickle-dex) is not an appropriate test to use on infants.

Different newborn screening findings in hemoglobin patterns are possible (Table 6). "FA" is considered "normal" when abnormal hemoglobin is not found.

Treatment

Early education of families about the disorders, use of prophylactic antibiotics, provision of emergency care for fever and infections, and assurance of appropriate immunizations including pneumococcal vaccine have resulted in a dramatic decline in early mortality from sickle cell anemia, Hemoglobin SC disease, and Sickle Beta Thalassemia. Various other treatments, including judicious use of blood products, are useful in some affected children. Continuing family education, specialized genetic counseling, and support groups have proven to be helpful to most families. See Table 6 for examples of some hemoglobinopathies.

It is strongly recommended that prior to repeating the newborn screen practitioners should confer with one of the consultants. The consultant may recommend repeating the State Newborn Screen, or they may suggest labs to draw and analyze in a practitioner's local lab. The consultant may wish to see the newborn in the office and do the lab work and assessment there. Whatever the case, we want to prevent unnecessary lab draws or inappropriate testing on these infants. In summary,

please contact the consultant in your vicinity prior to drawing the repeat blood work.

TABLE 6
Some Hemoglobinopathies

| RESULTS | LIKELY CAUSE | ACTION |
|------------------------|---|---|
| FS (absence of A) | Sickle Cell Anemia OR Sickle Beta Thalassemia | Contact MD by phone with recommendations for diagnosis and treatment |
| FSC (absence of A) | Sickle C Hemoglobin Disease (Hemoglobin SC disease) | |
| FC (absence of A) | Hemoglobin C Disease | |
| FE (absence of A) | Homozygous Hemoglobin E OR Hemoglobin E-Beta Thalassemia | |
| FAS | Hemoglobin S Trait S Beta Thalassemia Sickle Cell Anemia following transfusion | Report by letter regarding retesting and significance |
| FSA | S Beta Thalassemia Sickle cell anemia following transfusion | |
| FAC | Hemoglobin C Trait Hemoglobin C Disease following transfusion | |
| FA+slow band ("X") | Most commonly hemoglobin E, O, D, or G trait | |
| FA+fast band (Bart's)# | Bart's hemoglobin is a marker for an alpha thalassemia condition | |
| F only | Preterm infant or Beta Thalassemia major | Contact MD by phone with recommendations regarding testing and significance |
| Predominance of A | Transfused Infant Patient outside of neonatal age range | Report by letter regarding retesting and significance |

Carrier Detection Makes Hemoglobin Screening Different

The screening assay for hemoglobin will identify carriers (heterozygotes or children with so called sickle trait) as well as those affected with disease. Many more children will be identified with trait than with disease not only for sickle cell syndromes, but also for other variant hemoglobins. Several principles are clear and important when handling this genetic information:

- The family is entitled to the information and it is private. The Kansas Newborn Screening Program will inform the primary care practitioner and the family of all abnormal results. The primary care practitioner is obliged to assist in informing and counseling the family.
- The parents are at increased risk, at least 1/4 compared to 1/400, of having a subsequent child affected with a hemoglobin disorder because at least one of the parents is now known (indirectly) to be a heterozygote. The family should be offered testing and genetic counseling. If the family declines participation, this should be documented.
- The newborn screening test is only a screen and is NOT a definitive diagnostic procedure.

A large variety of hemoglobinopathy carrier states have been identified ("traits"). Most hemoglobin traits have little or no direct clinical significance for the patient. The family, however, must be fully informed of their significance and offered testing as well as genetic counseling.

Screening Practice Considerations

Newborn screening for hemoglobinopathies is performed on the first specimen and any repeats, however they are not diagnostic.

Some hemoglobinopathies, particularly the Beta thalassemias, are not reliably detected through newborn screening and a normal screening test report does not eliminate the possibility that a patient might have a hemoglobinopathy. Further testing or consultation should be sought if there is clinical suspicion.

Infant Transfusion

Transfusion of red blood cells prior to drawing the newborn screening specimen will invalidate the hemoglobinopathy screen. Hemoglobin patterns of affected infants may be masked by donor cells if the infant is transfused. It is recommended that the practitioner obtain the screening specimen **BEFORE TRANSFUSION** whenever possible to assure early diagnosis of disease states.

If the infant is transfused prior to obtaining the specimen a repeat specimen should be performed at least eight weeks after the transfusion.

Medical Consultants

Medical consultants are available to provide consultation for the follow-up, evaluation, and long-term management of children identified with hemoglobinopathies.

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Office: 316-293-2667

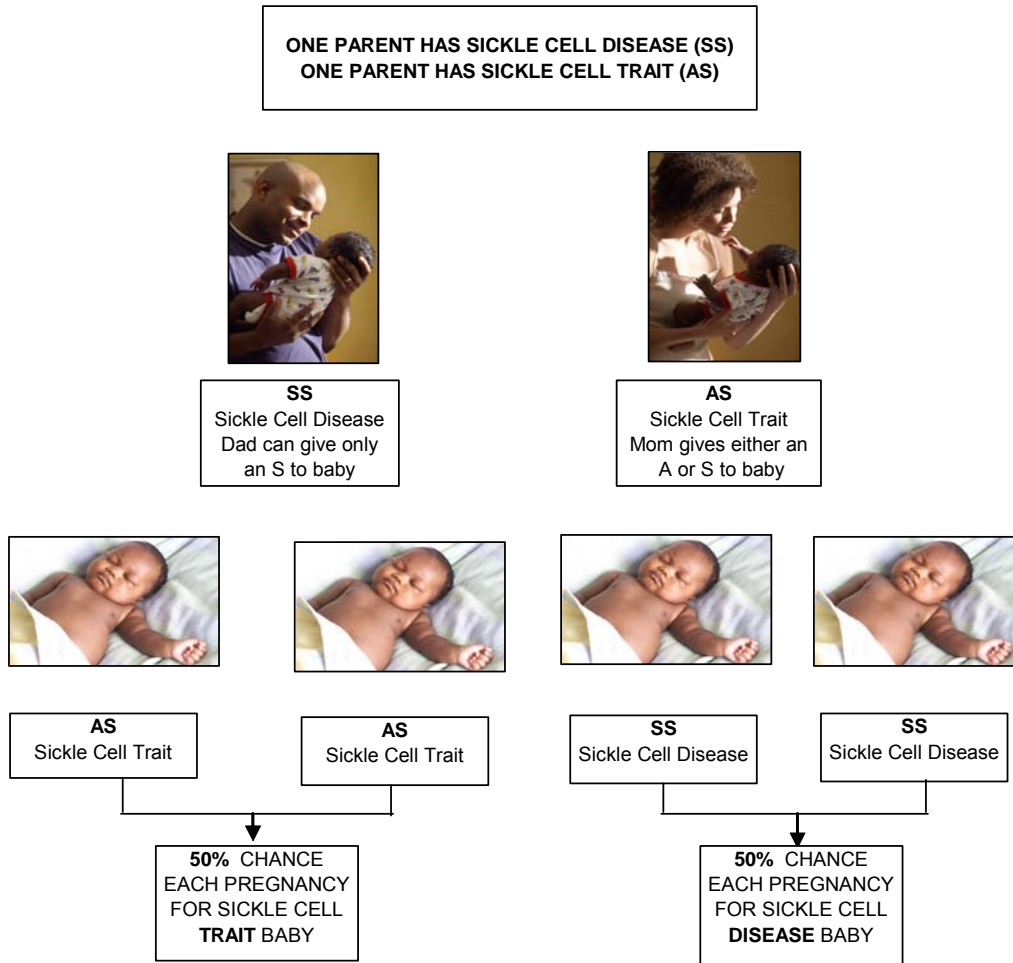
Dr. Jakica Tancabelic
KU Dept of Pediatrics/ Div. Hematology/Oncology
Kansas City, KS
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**Procedure for Newborn Screening Follow-Up Activities
Sickle Cell and Other Hemoglobinopathies**

- 1) Newborn Screening follow-up team reviews the laboratory reports that are faxed overnight from the lab or records the information provided per telephone call from the laboratory on a white phone information sheet.
- 2) If the hemoglobin result is FA: the results are considered **normal**.
 - a) Follow-up team does not receive results.
 - b) Lab will fax or mail results to doctor listed on NBS card.
- 3) If the hemoglobin results are A, AA2, FAA2, AF, or AFA2: the results are considered **normal**.
 - a) Follow-up team receives results, but no follow-up is needed.
 - b) Lab will fax or mail results to doctor listed on NBS card with notation that results need to be evaluated by physician as baby may have been transfused.
- 4) If the hemoglobin result has hemoglobin "F", "A", and another hemoglobin (in that order) the results are considered a **hemoglobin trait**. (Ex: FAC, FAS, FA#, etc.)
 - a) Lab will fax follow-up team with baby's information and test results.
 - b) Follow-up team will enter data into Access database under HGB.
 - c) Follow-up team will print Hgb Misc Trait First letter and mail to healthcare provider.
 - d) Follow-up team will print Hgb Parent Letter Trait and Hgb parent information sheet and mail to baby's parents to inform them that their child has an abnormal result.
NOTE: If infant is in the NICU, no parent letter is sent.
 - e) Lab will fax or mail results to doctor listed on NBS card.
 - f) Follow-up team will enter lab information into WebIZ and set a follow-up reminder for 10 months from date of birth. NOTE: Name changes are documented on the lab report. Surname changes are also documented in WebIZ as an alias.
 - g) When complete, paperwork is filed by infant's date of birth.
- 5) If the hemoglobin result has no "A" hemoglobin (i.e. FS, FC, FE, etc.), the results are considered **presumptive**.
 - a) Lab will contact follow-up team via phone with baby's information and test results. Follow-up team will document information on white phone slip.
 - b) Follow-up team will print out baby's information from DHEL database on a green sheet of paper, attach the white phone information sheet and write "Hgb" with result on green sheet.
 - c) Follow-up team will enter data into Access database under HGB.
 - d) Follow-up team will call healthcare provider listed on report and:
 - i) Verify that they are seeing the baby.
 - ii) Inform them of results.
 - iii) Ask them to notify parents and arrange appointment with specialist for a blood test.

- iv) Confirm doctor's fax number.
- v) Inform them that a letter will be faxed to their office with the results and instructions.
- e) Follow-up team will print the Disease Presumptive First Letter and physician report forms and fax (or mail, if no fax) to healthcare provider.
- f) Follow-up team will print Hgb Parent Letter Presumptive and Hgb parent information sheet and mail to baby's parents to inform them that their child has an abnormal result. NOTE: If infant is in the NICU, no parent letter is sent.
- g) Follow-up team will enter data into Excel spreadsheet "Presumptive Totals" located on the "H" drive.
- h) Lab will fax or mail results to doctor listed on NBS card.
- i) Follow-up team will enter lab information into WebIZ and set a follow-up reminder for 6 months from date of birth. NOTE: Name changes are documented on the copy of the lab report. Surname changes are also documented in WebIZ as an alias.
- j) When complete, paperwork is filed by infant's date of birth.

ODDS FOR BABY FROM ONE PARENT WITH SICKLE CELL TRAIT AND ONE PARENT WITH SICKLE CELL DISEASE

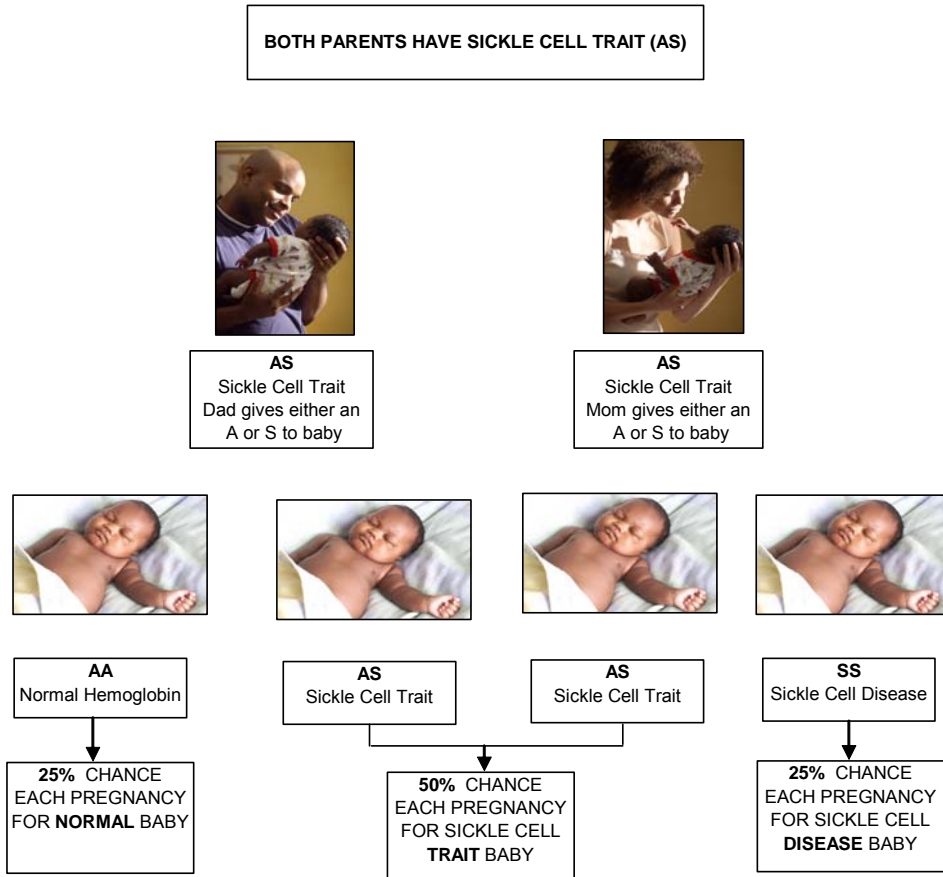


If one parent has sickle cell trait, they are type AS with one Hemoglobin A gene and one Hemoglobin S gene. If the other parent has sickle cell disease, they are type SS with two Hemoglobin S genes. Since each parent gives only one gene to their baby, the trait parent can give either the A gene or S gene to their baby while the disease parent can only give an S gene to their baby. The diagram below shows what the baby might get from each parent and the baby's type.

| | | Mom's genes | |
|-------------|---|-------------|----|
| | | A | S |
| Dad's genes | S | SA | SS |
| | S | SA | SS |

The baby can be: SA = Sickle Cell Trait (50% chance)
 SS = Sickle Cell Disease (50% chance)

ODDS FOR BABY FROM TWO SICKLE CELL TRAIT PARENTS



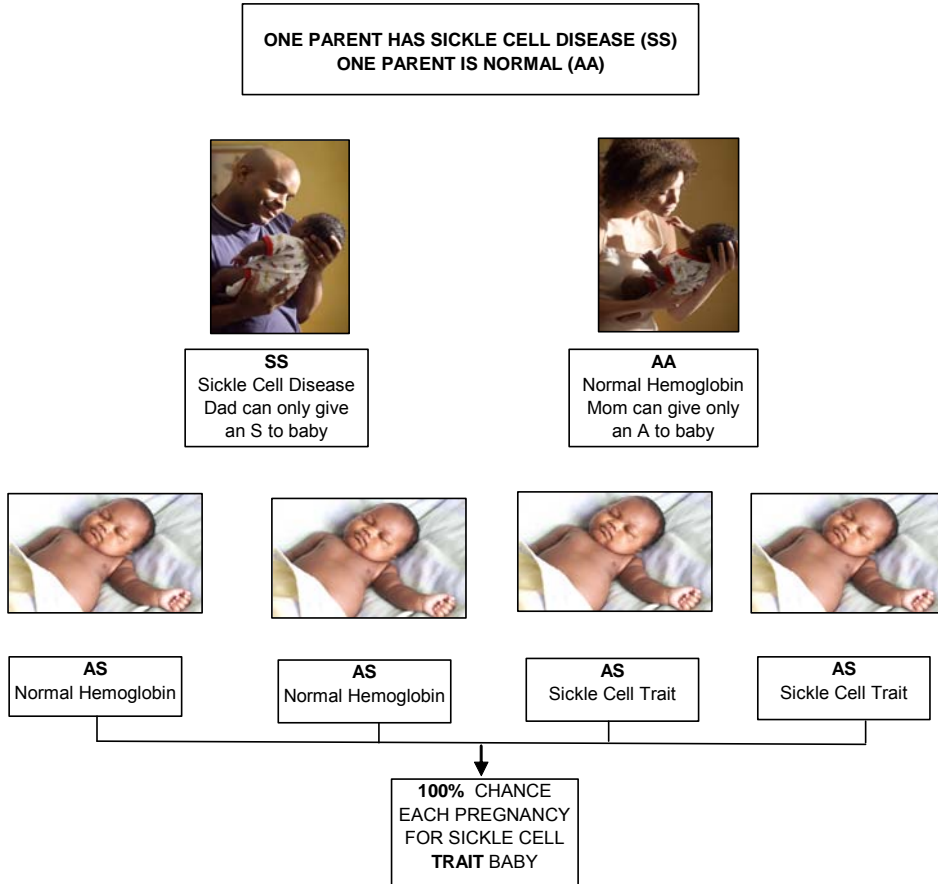
When both parents have sickle cell trait, they each are type AS with one Hemoglobin A gene and one Hemoglobin S gene. Since each parent gives only one gene to their baby, they each can give either the A gene or S gene to their baby. The diagram below shows what the baby might get from each parent and the baby's type.

| | | Mom's genes | |
|-------------|---|-------------|----|
| | | A | S |
| Dad's genes | A | AA | AS |
| | S | SA | SS |

The baby can be:

- AA = Normal (25% chance)
- SA or AS = Sickle Cell Trait (50% chance)
- SS = Sickle Cell Disease (25% chance)

ODDS FOR BABY FROM ONE PARENT WITH SICKLE CELL DISEASE AND ONE PARENT WITH NORMAL HEMOGLOBIN

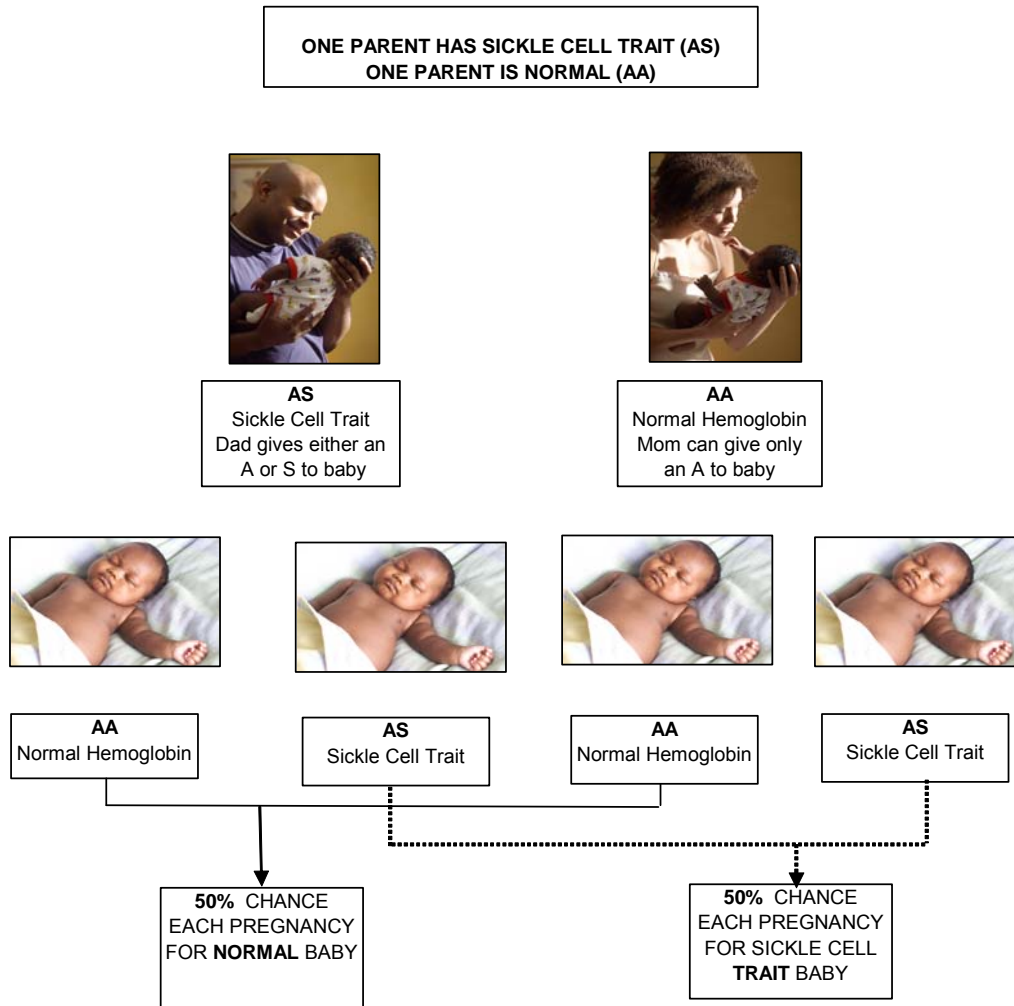


If one parent has normal hemoglobin, they are type AA with two Hemoglobin "A" genes. If the other parent has sickle cell disease, they are type SS with two Hemoglobin "S" genes. Since each parent gives only one gene to their baby, the normal parent can only give an "A" gene to their baby while the disease parent can only give an "S" gene to their baby. The diagram below shows what the baby might get from each parent and the baby's type.

| | | Mom's genes | |
|-------------|---|-------------|----|
| | | A | A |
| Dad's genes | S | SA | SA |
| | S | SA | SA |

The baby can be only SA = Sickle Cell Trait (100% chance)

ODDS FOR BABY FROM ONE PARENT WITH SICKLE CELL TRAIT AND ONE PARENT WITH NORMAL HEMOGLOBIN



If one parent has sickle cell trait, they are type AS with one Hemoglobin "A" gene and one Hemoglobin "S" gene. If the other parent has normal hemoglobin, they are type AA with two Hemoglobin "A" genes. Since each parent gives only one gene to their baby, the trait parent can give either the "A" gene or "S" gene to their baby while the normal parent can only give an "A" gene to their baby. The diagram below shows what the baby might get from each parent and the baby's type.

| | | Mom's genes | |
|-------------|---|-------------|----|
| | | A | A |
| Dad's genes | A | AA | AA |
| | S | SA | SA |

The baby can be either: AA = Normal hemoglobin (50% chance)
 SA = Sickle Cell Trait (50% chance)



NEWBORN SCREENING ACT SHEET

SCREEN FOR: HEMOGLOBINS F, A & S

CONDITION: SICKLE CELL CARRIER (TRAIT)
(Hb AS)

DIFFERENTIAL DIAGNOSIS: The hemoglobins are listed in order (F>A>S) of the amount of hemoglobin present. This result is different than FS which is consistent with sickle cell anemia or FSA which is consistent with sickle beta-plus thalassemia.

METABOLIC DESCRIPTION: Generally benign genetic carrier state (trait) characterized by the presence of fetal hemoglobin (F) and hemoglobin A and S.

ACTION TO BE TAKEN:

- Contact the family to inform them of the screening result to offer education and reassurance that infants and young children do not have clinical problems related to the carrier state for hemoglobin S.
- Repeat screen or confirm result by alternate assay.
- Offer family members referral for hemoglobinopathy testing and genetic counseling.
- Report findings to newborn screening program.

CONFIRMATION OF DIAGNOSIS: Hemoglobin separation by electrophoresis, isoelectric focusing or HPLC showing FAS pattern. Family or DNA studies may be used to confirm genotype.

CLINICAL EXPECTATIONS: Infants are usually normal at birth. Prognosis is good, with a normal life expectancy. Carriers are at risk for having children affected by sickle cell disease. Older children and adults may have hematuria. Splenic infarction and an increased risk of sudden death associated with severe hypoxia, extreme physical exertion and dehydration have been reported.

REPORTING: Report diagnostic result to family and Kansas NBS program.

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KANSAS DEPARTMENT OF HEALTH AND ENVIRONMENT

NEWBORN SCREENING ACT SHEET

SCREEN FOR: HEMOGLOBINS F & S

CONDITION: SICKLE CELL ANEMIA (HbSS DISEASE OR HbS/BETA ZERO THALASSEMIA)

DIFFERENTIAL DIAGNOSIS: Homozygous sickle cell disease (Hb SS); sickle beta-zero thalassemia or sickle hereditary persistence of fetal hemoglobin (S-HPFH).

METABOLIC DESCRIPTION: A red blood cell disorder characterized by presence of fetal hemoglobin (F) and hemoglobin S in the absence of hemoglobin A. The hemoglobins are listed in order of the amount of hemoglobin present (F>S). This result is different from FAS which is consistent with sickle carrier.

ACTION TO BE TAKEN:

- Contact the family to inform them of the screening result.
- Contact a consultant in hemoglobinopathies; refer if needed.
- Evaluate infant and assess for splenomegaly.
- Initiate timely confirmatory/diagnostic testing as recommended by consultant.
- Initiate penicillin VK prophylaxis and other treatment as recommended by consultant.
- Educate parents/caregivers regarding the risk of sepsis, the need for urgent evaluation if fever of $\geq 38.5^{\circ}\text{C}$ (101°F) or signs and symptoms of splenic sequestration.
- Follow-up at six months of age.
- Report findings to newborn screening program.

CONFIRMATION OF DIAGNOSIS: Hemoglobin separation by electrophoresis, isoelectric focusing or HPLC showing FS pattern. Family or DNA studies may be used to confirm genotype. Sickledex is not appropriate for confirmation of diagnosis in infants.

CLINICAL EXPECTATIONS: Newborn infants are usually well. Hemolytic anemia and vaso-occlusive complications develop during infancy or early childhood. Complications include life-threatening infection, splenic sequestration, acute chest syndrome, pain episodes, aplastic crisis, dactylitis, priapism and stroke. Comprehensive care including family education, immunizations, prophylactic penicillin and prompt treatment of acute illness reduces morbidity and mortality. S-HPFH is typically benign.

REPORTING: Report diagnostic result to family and Kansas NBS program.

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KANSAS DEPARTMENT OF HEALTH AND ENVIRONMENT

NEWBORN SCREENING ACT SHEET

SCREEN FOR: HEMOGLOBINS F, S & A

CONDITION: HEMOGLOBIN S/BETA⁺ - THALASSEMIA
(HbSβ⁺ DISEASE)

DIFFERENTIAL DIAGNOSIS: Hemoglobin FSA pattern on newborn screen is highly suggestive of sickle beta plus thalassemia. The hemoglobins are listed in order (F>S>A) of the amount of hemoglobin present. This result is different than FAS which is consistent with sickle carrier (trait).

METABOLIC DESCRIPTION: Individuals with sickle beta⁺ Thalassemia, a form of sickle cell disease, are compound heterozygotes for the Hb S and beta-thalassemia mutations in the beta-globin genes.

ACTION TO BE TAKEN:

- Contact the family to inform them of the screening result.
- Perform a physical exam on the infant and assess for splenomegaly.
- Obtain a blood sample for confirmatory testing and a complete blood count with reticulocyte count.
- Contact a consultant in hemoglobinopathies for diagnostic evaluation and management.
- Initiate penicillin (Pen VK) prophylaxis and other treatment as recommended by consultant.
- Educate parents/caregivers regarding the risk of sepsis and advise that infant be immediately evaluated if fever of $\geq 38.5^{\circ}\text{C}$ (101°F) is present.
- Follow-up at six months of age.
- Report findings to newborn screening program.

CONFIRMATION OF DIAGNOSIS: Hemoglobin separation by electrophoresis, isoelectric focusing or HPLC showing FSA pattern. Family or DNA studies may be used to confirm genotype.

CLINICAL EXPECTATIONS: Infants are usually normal at birth. Later potential clinical problems include mild hemolytic anemia, life-threatening infection, vaso-occlusive pain episodes, dactylitis, and chronic organ damage. Prompt treatment of infection and splenic sequestration is associated with decreased mortality in the first three years of life.

REPORTING: Report diagnostic result to family and Kansas NBS program.

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KANSAS DEPARTMENT OF HEALTH AND ENVIRONMENT

NEWBORN SCREENING ACT SHEET

SCREEN FOR: HEMOGLOBINS F, S & C

CONDITION: HEMOGLOBIN SC DISEASE (HbSC)

DIFFERENTIAL DIAGNOSIS: Hemoglobin SC disease most likely.

METABOLIC DESCRIPTION: A red blood cell disorder characterized by presence of fetal hemoglobin (F) and hemoglobins S and C in the absence of hemoglobin A. The hemoglobins are listed in order of the amount of hemoglobin present (F>S>C). This result is different from FAS which is consistent with sickle carrier.

ACTION TO BE TAKEN:

- ➔ Contact the family to inform them of the screening result.
- ➔ Contact a consultant in hemoglobinopathies; refer if needed.
- ➔ Evaluate infant and assess for splenomegaly.
- ➔ Initiate timely confirmatory/diagnostic testing as recommended by consultant.
- ➔ Initiate treatment as recommended by consultant.
- ➔ Educate parents/caregivers regarding the risk of sepsis, the need for urgent evaluation if fever of $\geq 38.5^{\circ}\text{C}$ (101°F) or signs and symptoms of splenic sequestration.
- ➔ Follow-up at six months of age.
- ➔ Report findings to newborn screening program.

CONFIRMATION OF DIAGNOSIS: Hemoglobin separation by electrophoresis, isoelectric focusing or HPLC showing FSC pattern. Family or DNA studies may be used to confirm genotype.

CLINICAL EXPECTATIONS: Newborn infants are usually well. Hemolytic anemia and vaso-occlusive complications develop during infancy or early childhood. Complications include life-threatening infection, splenic sequestration, pneumonia, acute chest syndrome, pain episodes, aplastic crisis, dactylitis, priapism and stroke. Comprehensive care including family education, immunizations, prophylactic penicillin and prompt treatment of acute illness reduces morbidity and mortality.

REPORTING: Report diagnostic result to family and Kansas NBS program.

CONSULTANTS:

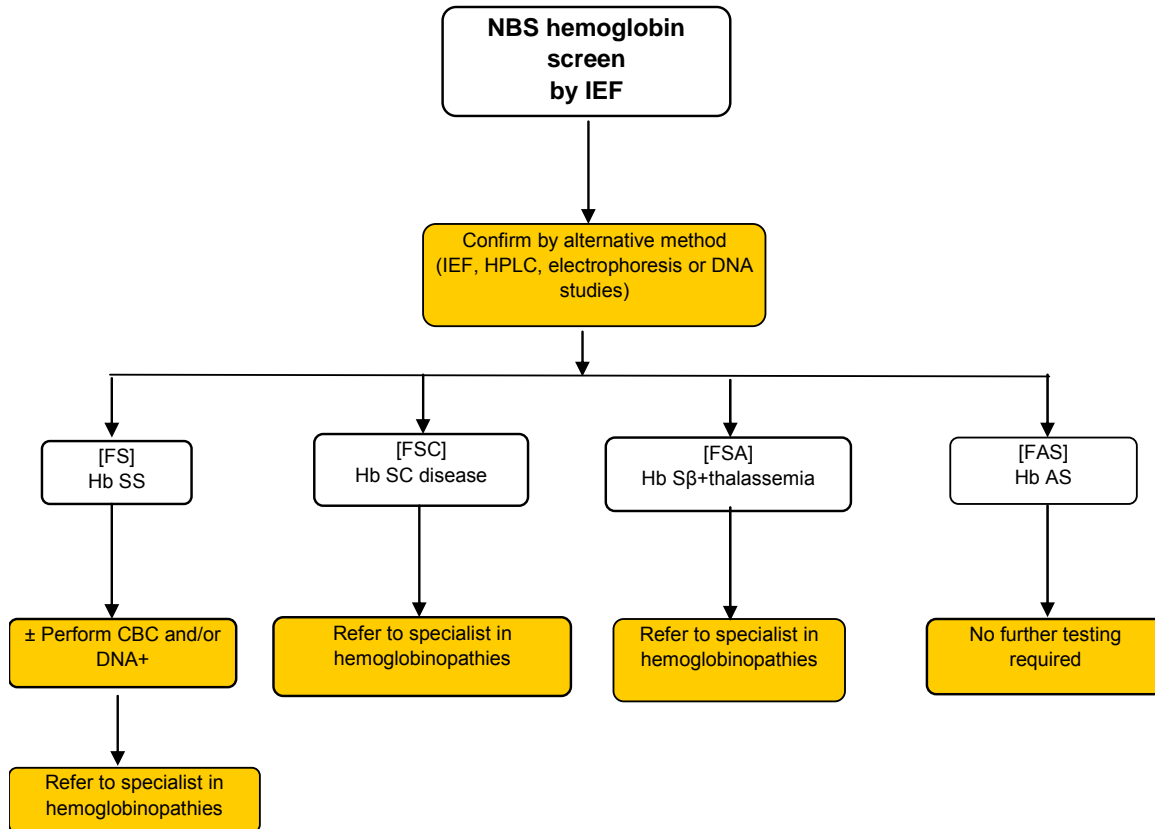
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HEMOGLOBIN SCREENING



Action steps are shown in gold (shaded) boxes; results are in plain boxes.

Abbreviations/Key

F, S, A and C = The hemoglobins seen in neonatal screening.

± = Repeat testing at 6 months age is required if genotyping to confirm the newborn screening result is not done.

DISCLAIMER: These algorithms and guidelines were adapted from the American College of Medical Genetics algorithm sheets. They are designed primarily as an educational resource for physicians to help them provide quality medical services. Adherence to these standards and guidelines does not necessarily ensure a successful medical outcome. These standards and guidelines should not be considered inclusive of all proper procedures and tests or exclusive of other procedures and tests that are reasonable directed to obtaining the same results. In determining the propriety of any specific procedure or test, the healthcare provider should apply his or her own professional judgment to the specific clinical circumstances presented by the individual patient or specimen. It may be prudent, however, to document in the patient's record the rationale for any significant deviation from these standards and guidelines

EXAMPLE OF PHYSICIAN'S LETTER FOR HEMOGLOBIN TRAITS



Mark Parkinson, Governor
Roderick L. Bremby, Secretary

DEPARTMENT OF HEALTH
AND ENVIRONMENT

www.kdheks.gov

Abnormal Hemoglobin Lab Report
Kansas Newborn Screening Program

Date

Doctor's Name
Address Line 1
Address Line 2

RE: Baby's Name
DOB: xx/xx/xxxx

MOTHER'S NAME: Mother's Name
MOTHER'S PHONE: xxx-xxx-xxxx

Specimen date: xx/xx/xxxx

Hemoglobins: Result
Expected result: FA

The newborn screening result above indicates an abnormal hemoglobin phenotype. The infant named is likely to have a hemoglobin TRAIT.

KDHE screens hemoglobin phenotype on newborn screen in order to identify those infants who may have a diagnosis of sickle cell disease or other rare hemoglobin disease. Many other infants with clinically benign hemoglobin traits are also identified.

Because the hemoglobin phenotype changes as the infant matures, it is possible that preterm babies may have an initial abnormal result that changes or becomes normal at a mature gestational age. (Transfusion of the infant prior to obtaining NBS invalidates the result and necessitates repeating the entire NBS.)

The hemoglobin phenotype lab result is reported in the order of largest percentage hemoglobin present to smallest percentage hemoglobin present. FOR EXAMPLE, for a hemoglobin phenotype FAS, the most abundant hemoglobin present is F (fetal), followed by A (adult), and the least percentage of hemoglobin present is S (sickle). The infant in this example would most likely have sickle cell trait.

RECOMMENDATIONS: There are three options you have as the primary care physician as to how to proceed.

- 1) Obtain a hemoglobin electrophoresis and CBC when the baby is about 9 to 12 months of age. We recommend you obtain these labs at the same time you would conduct your routine screening for lead and anemia. Obtain the results, confirm the diagnosis, and give appropriate counseling to the family. You are encouraged to visit the KDHE website at www.kdheks.gov/newborn_screening/info_professionals.htm or www.acmg.net/resources/policies/ACT/condition-analyte-links.htm

- 2) You may consult by phone with one of the physician listed below at any time during your evaluation for advice as to how to proceed with lab testing, diagnosis, and counseling.
- 3) Call a physician listed below to arrange a non-urgent appointment for the infant and family for confirmatory testing and genetic counseling.

You will receive a reporting form in approximately ten months. Please use this to report the electrophoresis results to the State of Kansas.

In accordance with Kansas Administrative Regulation 28-4-502, it is the responsibility of the attending physician or other birth attendant to obtain repeat specimens when needed to complete the screening process.

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Additional information is available on the Kansas Newborn Screening Website at:
http://www.kdheks.gov/newborn_screening/info_professionals.htm.

You may contact the Newborn Screening Program at (785) 291-3363 or 1-800-332-6262 if you have any questions or concerns.

EXAMPLE OF PHYSICIAN'S LETTER FOR PREMATURE INFANTS WITH F@ HEMOGLOBIN



Mark Parkinson, Governor
Roderick L. Bremby, Secretary

DEPARTMENT OF HEALTH
AND ENVIRONMENT

www.kdheks.gov

**Abnormal Hemoglobin Lab Report
Kansas Newborn Screening Program**

Date

Doctor's Name
Address Line 1
Address Line 2

RE: Baby's Name
DOB: xx/xx/xxxx

MOTHER'S NAME: Mother's Name
MOTHER'S PHONE: xxx-xxx-xxxx

Specimen date: xx/xx/xxxx

Hemoglobins: Result Expected result: FA

The newborn screening result above indicates an abnormal hemoglobin phenotype.

KDHE screens hemoglobin phenotype on newborns in order to identify those infants who may have a diagnosis of sickle cell disease or other rare hemoglobin disease. Many other infants with clinically benign hemoglobin traits are also identified.

Because the hemoglobin phenotype changes as the infant matures, it is possible that preterm babies may have an initial abnormal result that changes or becomes normal at a mature gestational age. (Transfusion of the infant prior to obtaining NBS invalidates the result and necessitates repeating the entire NBS.)

The hemoglobin phenotype lab result is reported in the order of largest percentage hemoglobin present to smallest percentage hemoglobin present. FOR EXAMPLE, for a hemoglobin phenotype FAS, the most abundant hemoglobin present is F (fetal), followed by A (adult), and the least percentage of hemoglobin present is S (sickle). The infant in this example would most likely have sickle cell trait.

RECOMMENDATION:

For premature neonates, born at or before 28 weeks gestation age, the neonatal screen should be repeated at 32 weeks gestational age in order to get the optimal results for the screen.

In accordance with Kansas Administrative Regulation 28-4-502, it is the responsibility of the attending physician or other birth attendant to obtain repeat specimens when needed to complete the screening process.

CONSULTANTS:

Jakica Tancabelic, M.D.
Pediatric Hematologist
KU Dept of Pediatrics
Kansas City, KS
Office: 913-588-6340

Rebecca Reddy, M.D.
Pediatrician
Pediatric Faculty Clinic
Wichita, KS
Office: 316-293-2667

Additional information is available on the Kansas Newborn Screening Website at:
http://www.kdheks.gov/newborn_screening/info_professionals.htm

You may contact the Newborn Screening Program at (785) 291-3363 or 1-800-332-6262 if you have any questions or concerns

EXAMPLE OF PHYSICIAN'S LETTER FOR HEMOGLOBIN DISEASE



Mark Parkinson, Governor
Roderick L. Bremby, Secretary

DEPARTMENT OF HEALTH
AND ENVIRONMENT

www.kdheks.gov

Abnormal Hemoglobin Lab Report Kansas Newborn Screening Program

Date

Doctor's Name
Address Line 1
Address Line 2

RE: Baby's Name
DOB: xx/xx/xxxx

MOTHER'S NAME: Mother's Name
MOTHER'S PHONE: xxx-xxx-xxxx

Specimen date: xx/xx/xxxx

Hemoglobins: Result Expected result: FA

The newborn screening result above indicates an abnormal hemoglobin phenotype. The infant named is likely to have a hemoglobin DISEASE.

KDHE screens hemoglobin phenotype on newborns in order to identify those infants who may have a diagnosis of sickle cell disease or other rare hemoglobin disease. Many other infants with clinically benign hemoglobin traits are also identified.

Because the hemoglobin phenotype changes as the infant matures, it is possible that preterm babies may have an initial abnormal result that changes or becomes normal at a mature gestational age. (Transfusion of the infant prior to obtaining NBS invalidates the result and necessitates repeating the entire NBS.)

The hemoglobin phenotype lab result is reported in the order of largest percentage hemoglobin present to smallest percentage hemoglobin present. FOR EXAMPLE, for a hemoglobin phenotype FAS, the most abundant hemoglobin present is F (fetal), followed by A (adult), and the least percentage of hemoglobin present is S (sickle). The infant in this example would most likely have sickle cell trait.

RECOMMENDATION:

This hemoglobin phenotype is consistent with a possible hemoglobin DISEASE. (Hemoglobin FS, FSC, FS@, FSA, FSD, or FSV are possible types of sickle cell disease.) Consultation with one of the physicians below is essential for diagnostic testing, genetic counseling and possible medical care. Please call to arrange an immediate appointment.

In accordance with Kansas Administrative Regulation 28-4-502, it is the responsibility of the attending physician or other birth attendant to obtain repeat specimens when needed to complete the screening process.

CONSULTANTS:

Jakica Tancabelic, M.D.
Pediatric Hematologist
KU Dept of Pediatrics
Kansas City, KS
Office: 913-588-6340

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Kansas Newborn Screening Program

Doc. Name: HGB

Version 2.0

Effective Date: 9/1/09

EXAMPLE OF HEMOGLOBINOPATHY PHYSICIAN'S REPORT



Mark Parkinson, Governor
Roderick L. Bremby, Secretary

DEPARTMENT OF HEALTH
AND ENVIRONMENT

www.kdheks.gov

HEMOGLOBINOPATHY NEWBORN SCREENING
PHYSICIAN REPORTING FORM

****Return this form When Follow-Up is Complete ****

Date

Doctor's Name
Address Line 1
Address Line 2

If this infant is not a current patient of this practice, record name and contact information for Primary Care Physician and return this form.

RE: Baby's Name
DOB: xx/xx/xxxx

Baby's name if different than listed

- DIAGNOSIS EXCLUDED:** Date Excluded: _____
 - Baby does **NOT** have a Hemoglobin Disorder
- DIAGNOSIS CONFIRMED:** Date Diagnosis Confirmed: _____
 - Baby has a Hemoglobin Disorder/Trait
 - o **Lab Results:** (please fill in and attach specialist's report)
Hemoglobin electrophoresis: _____ DNA or Additional lab results: _____
 - o Date treatment began: _____
 - Specific Hemoglobin Disorder (please check one)

| | |
|--|--|
| <input type="checkbox"/> Sickle cell anemia (S/S) | <input type="checkbox"/> Sickle C disease (S/C) |
| <input type="checkbox"/> Sickle E disease (S/E) | <input type="checkbox"/> Sickle D disease (S/D) |
| <input type="checkbox"/> Sickle Beta-thalassemia (S/Beta thal) | <input type="checkbox"/> Homozygous Beta-thalassemia |
| <input type="checkbox"/> Hemoglobin H disease (Hb H) | <input type="checkbox"/> Other (please specify): _____ |

FORM CONTINUES ON BACK

Kansas Newborn Screening Program

Specific Hemoglobin Trait (please circle one)

FAS FAC FAE FAD FAG

Other (please indicate type): _____

Baby referred to specialist

o Name of specialist: _____

UNABLE TO COMPLETE SCREENING PROCESS:

Parent notified of abnormal lab by registered letter and did not follow-up

o Date letter sent: _____

Parent notified of abnormal lab at office visit and did not follow-up

o Date of office visit: _____

Additional Comments:

Physician Signature _____

Date _____

When a hemoglobinopathy is confirmed, the Kansas Law 65-180 through 65-183 requires reporting by physician. Financial assistance for hemoglobinopathy clinic services and treatments may be available to the family upon application to the Children & Youth with Special Health Care Needs (CYSHCN) program. A CYSHCN application will be sent to the baby's address. Parents or physicians can call CYSHCN at 1-800-332-6262 or 1-785-296-1313 for more information.

Baby's most recent address:

Parent or Guardian _____

Address _____
Street/PO Box City State Zip



Hemoglobin Disorders (Hemoglobinopathies) Information for Healthcare Professionals

Hemoglobin disorders include (1) structural hemoglobin variants (S, C or E), which cause sickle cell disease and (2) thalassemias, resulting from defective alpha and beta globin production. Both types of disorders seemingly developed as a form of carrier resistance against malaria and are widespread in areas profoundly affected by malaria, predominantly Africa, Southeast Asia, the Mediterranean, and the Middle East. A detailed family history can facilitate the diagnostic process.

✓ Clinical Symptoms

Clinical symptoms of hemoglobinopathies, depending on the genotype, range from mild to severe. Sickle cell anemia (Hb SS, accounting for about 60% of all sickle cell disease) is the most severe presentation, though it rarely presents in the newborn period due to postnatal persistence of fetal hemoglobin. The red blood cells distort because they contain an abnormal type of hemoglobin (hemoglobin S), instead of the normal hemoglobin (hemoglobin A). Sickled blood cells are destroyed by the body faster than normal blood cells, which can lead to the body receiving an inadequate supply of oxygen. Also, sickled blood cells can become trapped in blood vessels, reducing or blocking blood flow. This can damage organs, muscles, and bones and may lead to life-threatening conditions. Sickle cell disease is most commonly found in populations of African descent. It is also relatively common in people from Central and South America, Saudi Arabia, India, and the Mediterranean. Infants with Hb SS disease are at risk for:

- anemia
- bacterial infection and fever
- painful swelling of the hands and feet
- acute chest syndrome (coughing, breathing problems, pain)
- stroke
- splenomegaly
- aplastic crisis

Sickle cell disease (Hb SC or Hb SB-thal) generally will have a milder presentation, though most children with sickle cell disease will have some degree of anemia and are at risk of developing any of the above symptoms.

The thalassemias are classified according to the ineffectively synthesized globin chains. There are two major forms of thalassemia: alpha thalassemia (alpha chain deficiency) and beta thalassemia (beta chain deficiency). Alpha thalassemia is most common in people of Southeast Asian, Indian, Middle Eastern and African descent. Beta thalassemia is most common in people from the Mediterranean and the Middle East, but is also found in Africans and Southeast Asians. Beta thalassemia mutations are population specific: each ethnic group has its own subset of common mutations.

Only the most severe forms of thalassemia will have a neonatal presentation. Alpha thalassemia major (hydrops fetalis) is generally incompatible with life. Fetuses with alpha-thal major will develop severe anemia, fluid accumulation in the tissues, and heart failure. Most are stillborn or die shortly after birth. Beta thalassemia major (also called Cooley anemia) results in life-threatening anemia. Individuals with beta thalassemia major require regular blood transfusions and chelation therapy to reduce iron overload.

✓ Incidence

Sickle cell disease (Hb SS, SC, or SB) occurs in approximately 1 in 400 births in the African American population. Thalassemia is rare in the U.S., but recent immigration patterns suggest that thalassemia is of increasing concern.

✓ Genetics and inheritance of hemoglobinopathies

Mutations in the *HBB* gene (hemoglobin beta chain) cause sickle cell disease and beta thalassemia. Mutations in *HBA1* and *HBA2* lead to alpha thalassemia. All of these conditions are inherited in an autosomal recessive manner. Pregnancies between two carriers have a 25% chance of producing an affected child, a 50% chance

of producing an unaffected carrier, and a 25% chance of producing an unaffected child who is not a carrier.

It is also important to be aware of compound heterozygous states, when children are born with two different forms of variant hemoglobin. Hemoglobin SC disease and Hemoglobin SB-thalassemia are examples of compound heterozygosity. In general, compound heterozygotes have less severe anemia than their homozygous counterparts, but will have more symptoms than those individuals who carry one normal gene.

✓ **Treatment**

Treatment for sickle cell disease is lifelong and should take place under the care of pediatric hematologists experienced with hemoglobin disorders. Prophylactic antibiotics are administered up to twice a day to prevent bacterial infection, and painful crises are managed with analgesia and hydration. It is important to keep immunizations current to prevent illness. Families should be trained to monitor and manage minor symptoms at home, and have a plan in place for times when medical attention becomes urgently needed.

Treatment for thalassemia (alpha and beta) may require occasional-to-regular blood transfusions, depending on the severity of symptoms, along with iron chelation therapy.

✓ **Screening Methodology /Confirmation of Diagnosis**

Primary newborn screening for hemoglobinopathies utilizes high performance liquid chromatography (HPLC) to determine the presence of variant hemoglobins. Follow-up evaluation of the newborn for symptoms and confirmatory testing by repeat HPLC or hemoglobin electrophoresis, CBC, parental testing and/or molecular DNA analysis should be performed as soon as possible. False positive and false negative results are possible in newborn screening. Specimens should be drawn before administration of medications or transfusions. False results can also occur if the specimen is mishandled or exposed to heat, or if screening is delayed.

✓ **What to do After Receiving Presumptive Positive Abnormal Hemoglobin Results**

- 1) **An abnormal Hb screen requires an immediate check on the clinical status of the baby.**
- 2) **Refer the infant to a pediatric hematologist, or to a dedicated sickle cell clinic.**
- 3) **Collection of a blood specimen for confirmatory testing.**
- 4) **Call KS Newborn Screening Program at 785-291-3363 with questions about results.**
- 5) **Report Clinical Findings to Newborn Screening Program at 785-291-3363.**

✓ **Communication of Results to Parents**

If a baby has a presumptive abnormal hemoglobin newborn screening result, additional testing needs to be performed to confirm a diagnosis. In accordance with Kansas Administrative Regulation 28-4-502, it is the responsibility of the attending physician or other birth attendant to obtain repeat specimens when needed to complete the screening process.

If a baby is diagnosed with a hemoglobin disorder, the following points should be conveyed to parents:

- ***Parents should understand that treatment is lifelong.***
- ***Parents should understand that treatment is not curative and that all morbidity cannot be prevented. Long-term management, monitoring and compliance with treatment recommendations are essential to the child's well-being.***
- ***Genetic counseling services may be indicated. A list of counselors and geneticists, whose services are available in Kansas, should be given to the parents if they have not already seen a geneticist.***

For consultation, contact:

Dr. Jakica Tancabelic
Pediatric Hematologist
KU Dept of Pediatrics
Kansas City, KS
Office: 913-588-6340

Dr. Rebecca Reddy
Pediatrician
Pediatric Faculty Clinic
Wichita, KS
Office: 316-293-2667

11/24/08

EXAMPLE OF HEMOGLOBIN TRAIT LETTER TO PARENTS



Mark Parkinson, Governor
Roderick L. Bremby, Secretary

DEPARTMENT OF HEALTH
AND ENVIRONMENT

www.kdheks.gov

Date

Parent's Name
Address Line 1
Address Line 2

RE: Baby's Name DOB: xx/xx/xxxx

Dear Parent:

Best wishes on the birth of your baby! Shortly after your baby was born, a small blood sample was taken for a test called the Newborn Screen. This test helps parents find out if their baby has certain health problems.

The result of your baby's blood test shows that more testing needs to be done for abnormal hemoglobin. ***This does not necessarily mean your child is ill.***

THIS IS WHAT YOU NEED TO DO:

1. Discuss this with your baby's doctor. Say that you have received a letter stating that your baby's Newborn Screen test was not normal. More testing should be done at 9-12 months of age, but your doctor may want to do other testing before that date.
2. We have < Name of Doctor > listed as your baby's doctor, and we have notified him/her of your baby's test result. If this is NOT your baby's doctor, please call the Newborn Screening Program at 785-296-0109 so we can contact the right doctor.

DO NOT DELAY. YOUR BABY'S HEALTH DEPENDS ON YOU.

If your baby does not have a doctor, or if you have questions about this letter, please call Kansas Newborn Screening at 785-296-0109.

Sincerely,

Jamey Kendall BSN, RN
Kansas Newborn Screening
Follow-up Coordinator

Linda A. Williams, MT(ASCP)
Kansas Newborn Screening
Follow-up Coordinator

EXAMPLE OF SICKLE CELL PARENT LETTER



Mark Parkinson, Governor
Roderick L. Bremby, Secretary

DEPARTMENT OF HEALTH
AND ENVIRONMENT

www.kdheks.gov

Date

Parent's Name
Address Line 1
Address Line 2

RE: Baby's Name DOB: xx/xx/xxxx

Dear Parent:

Best wishes on the birth of your baby! Shortly after your baby was born, a small blood sample was taken for a test called the Newborn Screen. This test helps parents find out if their baby has certain health problems. A baby can look healthy, but may have a harmful illness that can be found by doing this blood test.

The result of your baby's blood test shows that more testing needs to be done for a hemoglobin disease. ***This does not necessarily mean your child is ill.***

THIS IS WHAT YOU NEED TO DO NOW:

3. Call your baby's doctor. Say that you have received a letter stating that your baby's Newborn Screen test was not normal. Set up a time for your baby to have a second test done as soon as you can.
4. We have < Doctor's Name > listed as your baby's doctor, and we have notified him/her of your baby's test result. If this is NOT your baby's doctor, please call the Newborn Screening Program at 785-296-0109 so we can contact the right doctor.

DO NOT DELAY. YOUR BABY'S HEALTH DEPENDS ON YOU.

If your baby does not have a doctor, or if you have questions about this letter, please call Kansas Newborn Screening at 785-296-0109.

Sincerely,

Jamey Kendall BSN, RN
Kansas Newborn Screening
Follow-up Coordinator
Jamey Kendall BSN, RN
Newborn Screening Program Coordinator

Linda A. Williams, MT(ASCP)
Kansas Newborn Screening
Follow-up Coordinator

Kansas Newborn Screening Program



Hemoglobin Disorders (Hemoglobinopathies) Information for Parents

- **Overview**

Hemoglobin is a protein in the blood that carries oxygen from the lungs to all the tissues in the body. Most hemoglobin is made up of 2 parts, alpha globin and beta globin. The instructions for making the alpha globin and beta globin are contained in our DNA (which makes up our genes). There are many changes (or mutations) that can take place in these instructions. Often, these changes can result in a *hemoglobin variant*, which has no effect on the individual's health. Sometimes, however, the hemoglobin is changed enough that the health of the individual is affected.

- **What is a hemoglobinopathy?**

Hemoglobinopathy is a term describing a number of inherited disorders involving differences in the structure or amount of hemoglobin in the blood. If there is not enough hemoglobin in the body, or the hemoglobin is not formed correctly, oxygen cannot be carried through the body as efficiently. Abnormally low levels of healthy hemoglobin or red blood cells is called anemia. Depending on how much abnormal hemoglobin is being produced, symptoms can range from mild to life-threatening. Sickle cell anemia and thalassemia are examples of hemoglobinopathies.

- **How are hemoglobinopathies inherited?**

Hemoglobinopathies are inherited as autosomal recessive conditions. Most people have two complete sets of genes, one inherited from each of our parents. Genes are the instructions for growth and development of the body. In the case of recessive inheritance, two genes with mutations need to be inherited to have the condition. People with only one copy of a changed gene, also called a mutation, do not have the condition, but can pass the mutation on to their offspring. Individuals with one changed gene copy for a hemoglobin disorder are called *carriers*, or are said to have the *trait*. Hemoglobinopathies are inherited when both parents are carriers. With each pregnancy between two carriers, there is a 25% chance that the child will have a hemoglobin disorder, a 50% chance that the child will be an unaffected carrier, and a 25% chance that the child will not be a carrier nor have the disorder.

- ✓ **Types of hemoglobinopathies**

- ✓ **Sickle Cell Disease (Hemoglobin SS, SB⁰, SB⁺, or SC):** a serious condition in which most of the red blood cells are sickled (crescent-shaped), instead of their normal round shape. This sickle shape is the result of a mutation in the beta globin genes. The abnormal shape is less efficient at carrying oxygen. In addition, sickled cells have a tendency to get stuck in smaller blood vessels, causing blockages. People with sickle cell disease tend to get tired easily, have episodes of pain, called "sickle crises", and are prone to fevers and infections. Sickle cell anemia is more common in people of African descent.
- ✓ **Beta Thalassemia (Thalassemia Major/Intermedia/Minor):** a form of anemia in which the amount of beta hemoglobin is decreased. Depending on how serious the anemia is (Thalassemia Major), regular blood transfusions may be needed. It is more common in people with southern European (especially Greek and Italian), Middle Eastern, African and southeast Asian ancestry.
- ✓ **Alpha Thalassemia (Hemoglobin Barts):** occurs when one or more of the four genes responsible for alpha globin production is lost, resulting in a decrease in the amount of alpha globin. Depending on how many genes are missing, the individual can range from having no symptoms to severe, life-threatening anemia. Alpha thalassemia is most common among people of Asian descent.

- **Why is newborn screening done for hemoglobinopathies?**

Newborn screening is done so that babies with a hemoglobin disorder can be diagnosed quickly, and treatment, if needed, can be started.

- **Does a positive result from the Kansas Newborn Screening Lab mean that my baby has a hemoglobinopathy?**

No, not necessarily. Newborn screening tests the baby's level of different types of hemoglobin. The amount of these different types of hemoglobin in relation to each other may indicate that your child either is affected with a hemoglobin disorder or has the trait. Consultation with a specialist with experience in hemoglobin disorders can best determine if your baby needs treatment.

- **How common are hemoglobinopathies?**

Hemoglobinopathies are more common in certain ethnic groups, in particular, people of African, Asian, Arabic or Mediterranean descent. In the U.S., sickle cell anemia affects approximately 1 in every 250-600 African Americans. Beta thalassemia and alpha thalassemia are rare in the U.S., affecting less than 1 in 200,000 people. However, it is possible for two carriers of different hemoglobinopathies to have children with both traits; that is, two hemoglobin variants and no normal hemoglobin. This is called *compound heterozygosity*. The effect on the health of compound heterozygotes is variable, but can be significant.

- **What are the signs and symptoms of a severe hemoglobinopathy, such as sickle cell disease?**

Some of the more common signs and symptoms of a severe hemoglobinopathy include:

- fatigue, shortness of breath
- jaundice (yellow tint to skin and whites of eyes)
- slow growth, late puberty
- joint, bone and chest pain
- enlarged spleen and liver

- **How are hemoglobinopathies diagnosed?**

Hemoglobinopathies are diagnosed by a CBC (complete blood count) and gel electrophoresis testing to confirm the amounts of different kinds of hemoglobin. Follow up genetic testing on family members may also be performed.

- **Is there a cure for hemoglobin disorders?**

No, there is no cure, but new treatments and therapies have improved the quality of life for many patients with severe anemia, allowing them to live longer, more healthy lives.

- **How are hemoglobinopathies treated?**

- Many minor forms of thalassemia require no treatment.
- For more severely affected individuals, treatment may involve antibiotics to prevent infections, blood transfusions to increase the amount of normal hemoglobin in the body, and healthy nutrition to provide the best growth and development in the child.

Where can I get additional information?

1. American Sickle Cell Anemia Association (ASCAA)
<http://www.ascaa.org/>
2. Thalassemia Patients and Friends: <http://www.thalassemiapatientandsfriends.com/>

11/24/08