43. Screening for Hemoglobinopathies

> ## RECOMMENDATION
>
> Neonatal screening for sickle hemoglobinopathies is recommended to identify infants who may benefit from antibiotic prophylaxis to prevent sepsis. Whether screening should be universal or targeted to high-risk groups will depend on the proportion of high-risk individuals in the screening area, the accuracy and efficiency with which infants at risk can be identified, and other characteristics of the screening program. All screening efforts must be accompanied by comprehensive counseling and treatment services. Offering screening for hemoglobinopathies to pregnant women at the first prenatal visit is recommended, especially for those at high risk. There is insufficient evidence to recommend for or against routine screening for hemoglobinopathies in high-risk adolescents and young adults, but recommendations to offer such testing may be made on other grounds (see *Clinical Intervention*.

Burden of Suffering

Hemoglobin S is formed as the result of a single-gene defect causing substitution of valine for glutamic acid in position 6 of the chain of adult hemoglobin. Persons homozygous for hemoglobin S (HbSS) have sickle cell anemia. Under conditions of low oxygen tension, hemoglobin S polymerizes, causing the red blood cells of persons with sickle cell anemia to assume a "sickled" shape. This deformity of red blood cells leads to the symptoms of sickle cell disease. Persons heterozygous for both hemoglobin S and hemoglobin C (HbSC) and persons heterozygous for both hemoglobin S and -thalassemia (HbS/ -thal) also may experience sickle cell disease, although their symptoms tend to be less severe than those of persons homozygous for hemoglobin S.[1] Sickle cell disease affects an estimated 50,000 Americans[2–4] and affects persons of many racial and ethnic backgrounds. Among infants born in the U.S., sickle cell disease occurs in 1 in every 375 African Americans, 1 in 3,000 Native Americans, 1 in 20,000 Hispanics, and 1 in 60,000 whites.[4]

Compared to blacks in the general population, the average life expectancy of patients with sickle cell anemia is decreased by 25–30 years.[5] Symptom severity and life expectancy vary considerably, with some patients

surviving beyond middle age and others dying during infancy or child-hood. Mortality in children with sickle cell disease peaks between 1 and 3 years of age, and is chiefly due to sepsis caused by *Streptococcus pneumoniae*.[1] Pneumococcal septicemia occurs at a rate of approximately 8 episodes per 100 person-years of observation in children under the age of 3 years with sickle cell disease.[6,7] The case-fatality rate can be as high as 35%.[8] After in-fancy, patients with sickle cell disease are usually anemic and may experi-ence painful crises and other complications, including acute chest syndrome, priapism, strokes, splenic and renal dysfunction, bone and joint disease, ischemic ulcers, cholecystitis, and hepatic dysfunction associated with cholelithiasis.[4,9] The causes of premature death in adults are varied, and include sudden death during acute pain episodes, stroke, infection, and chronic organ failure.[5] Treatment for sickle cell disease may be ex-pensive. This chronic illness places a large economic and psychosocial bur-den on patients and their caretakers.[9]

About 2 million Americans are heterozygous for hemoglobin S and he-moglobin A (normal adult hemoglobin). This carrier state has been termed sickle cell trait and is present in 8% of the African American pop-ulation.[3] Except for a slightly increased risk of exercise-related death under extreme conditions,[10] persons with sickle cell trait experience neg-ligible morbidity.[11,12] Parents who are both carriers have a 25% probabil-ity with each pregnancy of having a child with sickle cell disease. One in every 150 African American couples in the U.S. is at risk of giving birth to a child with sickle cell disease (about 3,000 pregnancies per year).[13,14]

Certain thalassemias may also be detected by screening for hemoglo-binopathies. Thalassemias result from genetic defects that cause reduced synthesis of the polypeptide globin chains that combine to form hemoglo-bin. The clinical severity of these syndromes is related to the degree of re-duction of α- or β-globin synthesis.

The β-thalassemias occur primarily among individuals of Mediter-ranean, African, or Southeast Asian origin. β-Thalassemia minor occurs in persons heterozygous for a gene causing reduction in β-globin synthesis. Life expectancy is normal, and the clinical severity of this state is related to the specific defect and its effect on β-chain synthesis. β-Thalassemia major occurs in persons homozygous for genetic defects in β-globin synthesis. β-Globin synthesis in these individuals is markedly reduced or absent. They suffer from severe anemia and are transfusion dependent. Modern trans-fusion protocols and iron chelation therapy have greatly improved prog-nosis and some patients survive beyond the third decade of life.[15] β-Thalassemia major affects fewer than 1,000 Americans.[16]

α-Thalassemias are common in persons of Southeast Asian descent and also occur in persons of African and Mediterranean origin. α-Thalassemias result from deletions of one or more of the four genes responsible for

-globin synthesis. Patients with a four-gene deletion develop hydrops fetalis secondary to severe anemia and die before or shortly after birth. Mothers of these infants are at risk for toxemia during pregnancy, operative delivery, and postpartum hemorrhage.[17] The three-gene deletion is referred to as hemoglobin H disease and affects about 1% of Southeast Asians.[18] Three- and four-gene deletions are rare in African Americans. Persons with hemoglobin H disease experience chronic hemolytic anemia that is exacerbated by exposure to oxidants and may require transfusion. Persons with a two-gene deletion have microcytic red blood cells and occasionally mild anemia. The one-gene deletion is a "silent" carrier state. These latter two conditions are often called -thalassemia trait. The exact prevalence of -thalassemia trait is uncertain, but it is estimated to be 5–30% among African Americans and 15–30% among Southeast Asians.[18–20]

Hemoglobin E trait is the third most common hemoglobin disorder in the world and the most common in Southeast Asia, where its prevalence is estimated to be 30%.[18] Although hemoglobin E trait is associated with no morbidity, the offspring of individuals who carry this hemoglobin variant may exhibit thalassemia major (hemoglobin E/ -thalassemia) if the other parent has -thalassemia trait and contributes that gene. This combination is the most common cause of transfusion-dependent thalassemia in areas of Southeast Asia.[18]

Accuracy of Screening Tests

Two-tier hemoglobin electrophoresis (cellulose acetate electrophoresis with confirmation by citrate agar electrophoresis) or thin-layer isoelectric focusing are widely used screening tests for hemoglobin disorders.[4,21] High-performance liquid chromatography (HPLC) is a newer technique that offers high resolution and is in use in at least one screening program.[22] Techniques employing monoclonal antibodies and recombinant DNA technology are not used widely.[23] Blood for screening is collected in heparinized tubes or, in the case of newborn screening, on filter paper (Guthrie paper blotter).[24]

Electrophoresis is highly specific in the detection of certain hemoglobin disorders, such as sickle cell disease. In one study, all 138 children with hemoglobin S identified by screening 3,976 African American newborns were found to have a sickling disorder when retested at age 3–5 years.[25] Another study of 131 infants detected by screening found only nine instances in which the sickling disorder required reclassification and no instance in which a child originally diagnosed as having sickle cell disease was found to have sickle cell trait.[26] Ten years' experience with universal screening of Colorado newborns (528,711 infants) using filter paper specimens and two-tier hemoglobin electrophoresis was reported in 1990.[27] Fifty infants with

sickle cell diseases (HbSS, HbSC, HbS/ -thal) and 27 infants with other hemoglobin disorders were identified. Initial screening failed to identify four infants with sickle cell disease, but three of these were diagnosed on routine follow-up testing of infants suspected of having sickle cell trait. There were 32 false-positive results, 27 of which were confirmed to have a hemoglobinopathy trait on follow-up testing. The remaining five had normal hemoglobin. The test characteristics of HPLC may be superior to those of two-tier electrophoresis. Data are yet to be published.

The yield in screening pregnant women for hemoglobin disorders depends on the risk profile of the population being tested. In one study, electrophoresis in combination with a complete blood count was performed on 298 African American and Southeast Asian prenatal patients. Ninety-four women (31.5%) had a hemoglobin disorder (including sickle cell disease, sickle cell trait, hemoglobin E, -thalassemia trait, -thalassemia trait, hemoglobin H, and hemoglobin C).[19] In a larger study in a different community, similar tests were performed on 6,641 prenatal patients selected without regard to race or ethnic origin.[28] One hundred eighty-five women (3%) had sickle cell trait, 68 (1%) had hemoglobin C, 30 (0.5%) had -thalassemia trait, and 17 (0.3%) had other disorders (hemoglobin E, -thalassemia trait, hemoglobin H, hemoglobin E/ -thalassemia disease). These results were obtained by combining electrophoresis with red cell indices. When low mean corpuscular volume (MCV) was used as the only screening test to detect thalassemia, the yield was 0.3–0.5%.[29]

Prenatal diagnosis of sickle cell disease and other hemoglobinopathies in the fetus has been aided by advances in techniques of obtaining and analyzing specimens. Early tests involved the analysis of fetal blood obtained by fetoscopy or placental aspiration.[30] Genetic advances, however, have provided a safer[14] and more practical method in which amniocytes are obtained by amniocentesis and gene mutations are identified directly through recombinant DNA technology.[13] These techniques are highly accurate (error rate less than 1%) in detecting sickle cell disease and certain forms of thalassemia.[14,30–33] The principal disadvantage of using amniocentesis to obtain specimens is that it cannot be performed safely until about 16 weeks' gestation, thus delaying diagnosis and potential intervention until late in the second trimester. Chorionic villus sampling (CVS) is a means of obtaining tissue for DNA analysis as early as 10–12 weeks of gestation and is an established technique for prenatal diagnosis (see Chapter 41).[34,35]

Effectiveness of Early Detection

Screening for hemoglobin disorders is usually discussed with respect to two target populations: neonates and adults of reproductive age. Newborns

with sickle cell disease benefit from early detection through the early institution of prophylactic penicillin therapy to prevent pneumococcal sepsis. A multicenter, randomized, double-blind, placebo-controlled trial demonstrated that the administration of prophylactic oral penicillin to infants and young children with sickle cell disease reduced the incidence of pneumococcal septicemia by 84%.[36] Other benefits of identifying newborns with sickle cell disease include prompt clinical intervention for infection or splenic sequestration crises and education of caretakers about the signs and symptoms of illness in these children. A 7-year longitudinal study reported lower mortality in children with sickle cell disease identified in the newborn period than in children diagnosed after 3 months of age (2% vs. 8%), but the investigators did not account for confounding variables in the control group.[37] A briefer longitudinal study (8–20 months) reported no deaths in 131 newborns detected through screening.[26] In the Colorado experience described above, 47 of the 50 newborns with sickle cell disease identified through screening remained in the state beyond 6 months of age. None of the 47 died during the period of observation.[27]

Screening older children and adolescents is designed to detect carriers with sickle cell trait, -thalassemia trait, and other hemoglobin disorders that have escaped detection during the first years of life. Identification of carriers before childbearing allows them to make informed reproductive choices by receiving genetic counseling about partner selection and the availability of diagnostic tests in the event of pregnancy. There is some evidence that individuals who receive certain forms of counseling retain this information and may encourage other individuals, such as their partners, to be tested.[28,38–40] A prospective study of 142 persons screened for -thalassemia trait found that 62 (43%) encouraged other persons to be screened.[38] Compared with controls, those who had received counseling demonstrated significantly better understanding of thalassemia when tested immediately after the session. There is no direct evidence, however, that individual genetic counseling by itself significantly alters reproductive behavior or the incidence of births of infants with hemoglobin disorders.[9,41]

Detection of carrier status during pregnancy provides prospective parents with the option of testing the fetus for a hemoglobinopathy. If the test is positive, they have the time to discuss continuation of the pregnancy and to plan optimal care for their newborn. Parents appear to act on this genetic information. About half of pregnant women with positive tests for thalassemia refer their partners for testing and, if the father is positive, about 60% consent to amniocentesis.[28] If sickle cell disease is diagnosed in the fetus, about 50% of parents elect therapeutic abortion.[32,42] In a recent study, 18,907 samples from pregnant women were screened for abnormal hemoglobin including thalassemias and hemoglobin S. In 810 (4.3%), an abnormal hemoglobin was identified; 66% occurred in mothers unaware

that they carried an abnormal hemoglobin, and 80% occurred in mothers unaware that they were at risk for giving birth to a child with a serious hematologic disorder. Eighty-six percent of mothers who received counseling said they wanted their partner tested and 55% of partners were tested. Seventy-seven pregnancies were identified as being at risk because the partner also was a carrier of an abnormal hemoglobin. Of these 77 pregnancies, the gestation was too advanced for prenatal diagnosis in 12 cases and the condition for which the pregnancy was at risk was too mild for this service to be offered in 12 others. Prenatal diagnosis was offered in the remaining 53 pregnancies and accepted by 25 couples (47%). Of 18 amniocenteses actually performed, 5 fetuses were found to have clinically significant hemoglobinopathies and one of these pregnancies was terminated.[43]

There is evidence from some European communities with a high prevalence of -thalassemia that the birth rate of affected infants has declined significantly following the implementation of routine prenatal screening,[30] and there are data suggesting a similar trend in some North American communities that have introduced community education and testing for thalassemia.[16] Time series studies do not, however, prove that such trends are due specifically to the effects of prenatal screening.

Recommendations of Other Groups

Screening for sickle cell disease in all newborns, regardless of their race or ethnic origin, has been recommended by a National Institutes of Health consensus conference[8] and by a guideline panel convened by the Agency for Health Care Policy and Research.[4] Screening infants from high-risk groups (e.g., those of African, Caribbean, Latin American, Southeast Asian, Middle Eastern, or Mediterranean ethnicity) has been recommended by the World Health Organization,[44] the British Society for Haematology,[45] the American Academy of Family Physicians (AAFP),[46] and the Canadian Task Force on the Periodic Health Examination.[47] The recommendations of the AAFP are currently under review. The American Academy of Pediatrics[48] and Bright Futures[49] recommend routine screening for hemoglobinopathies as required by individual states. At present 29 states, Puerto Rico, and the District of Columbia mandate screening all newborns for hemoglobinopathies, and 12 states offer screening as an option.[50]

The American College of Obstetricians and Gynecologists,[51] the British Society for Haematology,[45] and the Canadian Task Force[47] recommend selective prenatal screening and counseling of pregnant women from high-risk ethnic groups. The Canadian Task Force[47] recommends that parents with established positive carrier status be offered prenatal DNA analysis of

amniocentesis or CVS tissue sampling. No major organizations recommend routine screening of adolescents and young adults for carrier status.

Discussion

Hemoglobinopathies occur among all ethnic and racial groups. Efforts at targeting specific high-risk groups for newborn screening inevitably miss affected individuals due to difficulties in properly assigning race or ethnic origin in the newborn nursery. In one study of more than 500,000 newborns, parental race as requested on a screening form was found to be inaccurate or incomplete in 30% of cases.[27] Proponents of selective screening of high-risk populations emphasize that, especially in geographic areas with a small population at risk, cost-effectiveness is compromised and considerable expense incurred in screening large numbers of low-risk newborns to identify the rare individuals with sickle cell disease or other uncommon hemoglobin disorders.[52] Studies supporting this argument have compared universal screening to no screening, not targeted screening. Recent research that accounts for the additional procedural and administrative costs of targeted screening suggests that universal screening may be the more cost-effective alternative.[4] Whether to screen all infants (universal screening) or only those infants from ethnic groups known to be at relatively high risk of having sickle cell disease (targeted screening) is therefore a policy question to be addressed by individual screening programs, taking into consideration cost-effectiveness analyses, disease prevalence, and available resources.

There has been considerable debate over the value of screening for hemoglobinopathies in persons of reproductive age. Critics cite evidence that sickle cell screening programs in the past have failed to adequately educate patients and the public about the significant differences between sickle cell trait and sickle cell disease. This has resulted in unnecessary anxiety for carriers and inappropriate labeling by insurers and employers.[53] In addition, there is no evidence that counseling, however comprehensive, will be remembered throughout the individual's reproductive life, influence partner selection, alter use of prenatal testing, or ultimately reduce the rate of births of affected children.[9,29] Proponents argue that these outcomes should not be used as measures of effectiveness since the goal of genetic counseling is to facilitate informed decision making by prospective parents.[9,20,29] In this regard, clinicians are responsible for making the individual aware of the diagnosis, the risk to future offspring, and the recommended methods to reduce that risk, regardless of the strength of the evidence that such counseling reduces the number of affected offspring.

CLINICAL INTERVENTION

Screening newborn infants for hemoglobinopathies with hemoglobin elec-trophoresis or other tests of comparable accuracy on umbilical cord or heelstick blood specimens is recommended ("A" recommendation). In ge-ographic areas with a very low incidence of hemoglobin disorders, selec-tive screening of newborns may be more efficient than universal screening. Infants with sickle cell disease must receive prompt follow-up, including oral penicillin prophylaxis, diagnostic testing, immunizations, and regular evaluations of growth and nutritional status. Their families should receive genetic counseling regarding testing of family members and risks to future offspring, information about the disease, education about early warning signs of serious complications, and referrals for peer support groups and sources of medical and mental health services.

Offering screening for hemoglobinopathies with hemoglobin elec-trophoresis or other tests of comparable accuracy to pregnant women at the first prenatal visit is recommended ("B" recommendation), especially for those who are members of racial and ethnic groups with a high inci-dence of hemoglobinopathies (e.g., individuals of African, Caribbean, Latin American, Mediterranean, Middle Eastern, or Southeast Asian de-scent). Carriers identified through testing should be urged to have the fa-ther tested and should receive information on the availability of prenatal diagnosis if the father is positive and the fetus is at risk of having a clini -cally significant hemoglobinopathy.

There is insufficient evidence to recommend for or against screening for hemoglobinopathies in adolescents and young adults from ethnic and racial groups known to be at increased risk for sickle cell disease, thalassemias, and other hemoglobinopathies in order for them to be able to make informed re-productive choices ("C" recommendation). Recommendations to offer such testing may be made on other grounds, including burden of suffering and patient preference. If provided, testing should be accompanied by counsel-ing, which should include a description of the significance of the disease, how it is inherited, the availability of a screening test, and the implications to individuals and their offspring of a positive result.

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