# Clinical Guidelines And Primary Care

*Alfred O. Berg, MD, MPH, Series Editor*

# Sickle Cell Disease: Screening, Diagnosis, Management, And Counseling In Newborns And Infants

*Alfred O. Berg, MD, MPH*

Sickle cell disease affects approximately 50,000 persons in the United States. Family physicians caring for large populations of African-Americans see sickle cell disease regularly: about 8 percent of African-Americans carry the sickle trait, and about 1 in 375 (265 per 100,000) African-American children are affected by sickle cell disease.[1] Individuals of Mediterranean, Caribbean, South and Central American, Arabian, or East Indian ancestry experience intermediate, but much lower, prevalences of sickle cell and related hemoglobinopathies, which range from 10 to 90 per 100,000 population. Family physicians caring for mostly white populations will rarely see a case, however; prevalence of sickle cell disease among whites is about 1 in 60,000 population.[2] Sickle cell disease is nonetheless one of the most common genetic diseases in the United States and the most common hemoglobinopathy.

Mortality in patients with sickle cell disease peaks in children aged 1 to 3 years, principally because of sepsis caused by *Streptococcus pneumoniae*. A new clinical policy on screening and diagnosis has been prompted by recent research showing that prophylactic penicillin therapy reduces the incidence and severity of pneumococcal sepsis and that early intervention for other infections and conditions is effective.

With publication in April 1993 of its sickle cell clinical practice guideline,[3] quick reference guide,[4] and parent guide,[5] the Agency for Health Care Policy and Research (AHCPR) completed its sixth guideline in a series that has also covered acute pain, pressure ulcers, urinary incontinence, cataracts, and depression. Principal recommendations are that all newborns should be screened for sickle cell disease with high-quality methods and that physicians should be responsible for appropriate diagnosis; the prescription of prophylactic penicillin; appropriate well-baby care; and parental instruction, education, and counseling. The intended audiences for this guideline are health care providers, policy makers, and the public.

Information for my review was gathered from the published guideline,[3] quick reference guide,[4] and parent guide[5]; from examination of primary articles (most referenced in the guide); and from interviews with several individuals associated with the panel's work.

## Summary of Guideline Development

Information about how the guideline was constructed is sketchy. Jarrett Clinton, MD, Administrator of AHCPR, states in the Foreword that the panel employed an expert evidence-based methodology and expert clinical judgment. AHCPR intends to publish technical reports detailing the process used in developing each of its guidelines. It is unfortunate that, to date, none of the technical reports (including that for the sickle cell) has been published. Accordingly, much of the material presented below is derived from reading between the lines of the published document and from discussions with individuals involved in the process.

### *Selection of the Panel*

The panel comprised 13 members: 11 who specialize in some aspect of sickle cell disease, a consumer representative whose child has sickle cell disease, and a practicing family physician. The panel was supported by a methodologist and a research coordinator. Four additional consultants were named, but their roles are not clear.

Submitted, revised, 10 November 1993.

From the Department of Family Medicine, University of Washington School of Medicine, Seattle. Address reprint requests to Alfred O. Berg, MD, MPH, Department of Family Medicine, University of Washington SA-01, Seattle, WA 98195.

### *Conduct of the Panel*

The methods used by the panel are specified in very general terms. No information is provided about the conduct of the meetings or the process used to arrive at the recommendations. At the conclusion of the panel's process, materials were submitted to 22 peer reviewers and 15 pilot testers. The introduction simply states that most recommendations from this process were incorporated into the final document, but no specifics are provided.

### *Review of Evidence*

Using an outline prepared by the panel, staff at the National Library of Medicine located more than 7000 possibly relevant publications, of which more than 2000 were selected for more in-depth review. Then, hundreds of these were used by the panel. A public forum was held in Washington, DC, to solicit additional materials and viewpoints. The standard review of the evidence recommended by AHCPR would include preparing evidence tables; grading the quality of individual research reports; predicting specific health outcomes; preparing balance sheets listing benefits and harms; and providing information about the rationale for final recommendations, including the strength with which the panel made the recommendations.

## Content of the Guideline

This review focuses only on the clinical practice guideline, not on the quick reference guide or the parent education booklet. As noted, the technical report is unpublished and thus not available for review.

The core of the clinical practice guideline is divided into four chapters covering recommendations for screening, laboratory methods, medical management, and education in counseling. A glossary, annotated clinical algorithm, listing of states and their screening policies, and sources for educational materials round out the guideline.

It is not stated explicitly, but the boldface recommendations that introduce major sections in the guideline appear to be the panel's formal recommendations (reproduced in Tables 1–4). There are many other recommendations provided throughout the text that appear to be made with less emphasis.

### *Screening*

The panel recommends that all newborns be screened for hemoglobinopathies (Table 1). This

**Table 1. Guideline: Population to be Screened.***

| |
|---|
| All newborns should be screened for sickle cell disease by accurate laboratory techniques. The purpose of such screening is to reduce morbidity and mortality from sickle cell disease. Screening also can identify infants with sickle cell trait, as well as homozygotes and heterozygotes for other hemoglobin variants. Screening of populations with a low prevalence of Hb S is cost-effective when the screening is integrated into a laboratory that is also testing samples from a population with a high prevalence of Hb S. |

*Sickle cell disease: screening, diagnosis, management, and counseling in newborns and infants. Rockville, MD: Agency for Health Care Policy and Research, (AHCPR Pub. No. 93-0562), 1993;6:11.

recommendation is based on three arguments: (1) early prophylaxis with penicillin reduces morbidity and mortality for affected individuals; (2) it is not possible to determine a person's risk based on appearance, surname, or presumed ethnicity; and (3) screening should benefit all because it is supported by state funds. The second and third arguments rest on the validity of the first: there would be no need for screening anyone if intervention were ineffective.

Evidence supporting the efficacy of penicillin prophylaxis in infants with sickle cell disease is compelling and well summarized in the guideline. Findings from a large multicenter randomized controlled trial published in 1986 showed that penicillin prophylactically administered to infants and children with sickle cell disease dramatically reduced infections and death, leading to early termination of the study.[6] Subsequent studies have shown similar improved outcomes in children detected through screening as newborns.[7,8]

The second and third parts of the argument for screening can be reduced to issues of cost-effectiveness. If screening is efficacious, if one has unlimited resources, and if there are no adverse effects of screening, then universal screening makes sense even in populations at extraordinarily low risk. If resources are limited or there are adverse effects, then one must balance the benefits against the costs and harms. Although no data are presented, it seems safe to dispense with adverse effects of screening (other than costs): specimen collection is well accepted (filter paper blood spot), and available testing protocols have excellent specificity (few false positives).

Thus we are left with the issue of costs; the guideline briefly considers cost-effectiveness. Sophisticated techniques were used to estimate

population prevalences of sickle trait and disease, including hierarchic Bayesian meta-analysis (although the actual analysis is not available here). More detail about methods is presented in this section than in any other chapter. The prevalence data are fundamental to a valid cost-effectiveness analysis, but the panel's handling of the cost-effectiveness issue is problematic. Three studies are cited. The single published study showed that screening is cost-effective only in higher prevalence populations.[9] A second study available in abstract suggested that administrative and procedural costs associated with selective screening (and often overlooked) could make universal screening cost-effective.[10] A third study in press was commissioned by the panel and found that, using an economic technique known as "shadow pricing," the costs associated with universal screening for sickle cell disease were less than those associated with finding cases of PKU, costs already acceptable to society.[11] The panel thus concluded that because it is hard to tell who is at risk, and because the costs of screening are comparable with already acceptable costs, universal screening should be implemented. Currently, more than 40 states have some sort of screening program, many of them mandatory and universal.

It is disappointing that the panel was not able to address screening for sickle trait in older children and young adults. In the past arguments have been made that adolescents and young adults be offered screening to guide reproductive decisions. This highly controversial subject might have been advanced by an expert evidence-based review.

### *Laboratory Screening for Sickle Cell Disease*

The second chapter of the guideline deals largely with technical issues about screening programs, focusing on laboratory methods, organization, reporting, and quality control (Table 2). The data used to construct the recommendations are extensive, but the rationale boils down to common sense.

The information of greatest interest to family physicians in this chapter is presented in the tables showing sensitivity, specificity, and predictive values for the various available laboratory tests. With a proper in-house laboratory protocol and two-tier testing, false negatives and false positives should be virtually zero.

**Table 2. Guideline: Laboratory Screening for Sickle Cell Disease.***

| |
|---|
| The laboratory must use a screening procedure that will detect sickle hemoglobin in the newborn. The laboratory has a responsibility to transmit the infant's results to the infant's health care provider and hospital of birth. Test results must be reported in understandable language that includes the identified phenotype, diagnostic possibilities, and sources where additional information may be obtained. The laboratory also should inform the infant's mother of the screening result, unless prohibited by law. |
| **Sample collection**<br>Samples of dried blood on filter paper should be used for hemoglobinopathy screening in newborns because they can be incorporated as part of other neonatal screening programs. Liquid blood samples are an acceptable alternative.<br>The methodologies employed for screening newborns should have high rates of sensitivity and specificity for the identification of newborns with sickle cell disease and other clinically important hemoglobin disorders. |
| **Reporting**<br>The newborn sickle cell screening system is responsible for ensuring that the report of an infant identified as possibly having sickle cell disease is sent to the provider responsible for medical follow-up. The report must clearly indicate the likelihood that the infant may have sickle cell disease and stress the urgency for immediate follow-up. |
| **Quality assurance and quality control**<br>The laboratory must participate in a proficiency testing program and, when feasible, should retest at least a sample of all newborns screened to determine the sensitivity and specificity of its screening methodology. |

*Sickle cell disease: screening, diagnosis, management, and counseling in newborns and infants. Rockville, MD: Agency for Health Care Policy and Research, (AHCPR Pub. No. 93-0562). 1993;6:21-34.

### *Medical Management of Newborns and Infants with Sickle Cell Disease*

This chapter makes the argument that providers caring for children with sickle cell disease should know what they are doing (Table 3). The principal medical recommendations are for penicillin prophylaxis beginning at age 2 months (data in support of this discussed earlier) and for regular health maintenance, with special emphasis on the need for immunization against *Haemophilus influenzae* and *S. pneumoniae*. Supporting literature is well described, but problems with the efficacy of the pneumococcal vaccine are minimized.

### *Educating and Counseling Parents of Newborns with Sickle Cell Trait and Disease*

This chapter is long on advice and short on data. Research on the efficacy of educational and counseling interventions falls short of showing im-

**Table 3. Guideline: Medical Management of Newborns and Infants with Sickle Cell Disease.***

The health care provider who is notified that a newborn has a positive screening test for sickle cell disease has the responsibility of promptly establishing a definitive diagnosis. Parents of affected infants should be educated about the disease, the importance of ongoing care, and the critical role they can play in early detection and management of infections and complications.

**Penicillin prophylaxis**
Penicillin prophylaxis should begin by 2 months of age for infants with suspected sickle cell anemia, whether or not the definitive diagnosis has been established.

**Diagnosis and management of complications**
Health care providers must educate parents about the early signs and symptoms of illness in the infant with sickle cell disease that require medical attention. Also, health care providers must be aware of the urgency of promptly detecting and treating infections and other complications, including acute splenic sequestration, aplastic crises, stroke, hand-and-foot syndrome, and acute chest syndrome.

**Health maintenance**
The health care provider must recognize that the infant with sickle cell disease also requires the well-child care which is standard pediatric practice.

Infants with sickle cell disease should be immunized against *Haemophilus influenzae* at the age of 2 months.

*Sickle-cell disease: screening, diagnosis, management, and counseling in newborns and infants. Rockville, MD: Agency for Health Care Policy and Research, (AHCPR Pub. No. 93-0562), 1993;6:37-45.

proved outcomes, instead focusing on the easier-to-measure intermediate outcomes of improvements in parental attitudes and knowledge. The recommendations that education and counseling be provided by specially trained individuals and incorporate quality assurance (Table 4) are made without reference to any published literature.

### *Clinical Algorithm*

Finally, the guideline appends a clinical algorithm, beginning with universal screening and moving through treatment of a child seen for emergent care (Figure 1). The algorithm provides brief annotations, but many of the recommendations imbedded in the algorithm are made in addition to those in the guideline itself, and none is referenced.

## Comment

The sickle cell disease guideline published by AHCPR is one of their weakest products. Readers must take too much on faith. The documents published to date lack sufficient information about the process, making assessment of the recommendations difficult. The search strategies for relevant literature are not explicit. How the scientific merit of individual articles was judged is not mentioned. Evidence tables are not provided. The recommendations themselves are made without a clear rationale and without notation as to the quality of the evidence upon which they are based. In short, the strengths of an evidence-based expert process claimed in the introductory pages are not obvious.

### *Overall Assessment and Clinical Recommendation*

Given the lack of documentation about the process of producing the guideline, what can practicing physicians take from the recommendations? Three topics are highlighted:

*Screening*

The most controversial recommendation of the AHCPR panel is that for universal screening of newborns. As noted above, the argument for universal screening rests on hoped-for cost-effectiveness but is unsupported by published evidence. Many states have implemented screening programs, so that the decision for screening might already have been taken out of the hands of the individual physician. Whatever the scientific basis for these programs might be, it is not cogently presented in the guideline.

In those states where screening is mandatory, physicians must follow state requirements (Table 5). In states where screening is not mandatory, the family physician faces a choice, and the decision is not illuminated by publication of the AHCPR guideline. Certainly the safest strategy is to screen all newborns, but this strategy will appear progressively more illogical if the physician serves a population of patients with vanishingly low

**Table 4. Recommendation: Educating and Counseling Parents of Newborns with Sickle Cell Disease and Trait.***

**Qualifications for sickle cell educators**
Sickle cell trait education can be provided by individuals who have received proper specialized training.

**Counselor qualifications**
Adequate quality assurance is an essential aspect of genetic counseling.

*Sickle cell disease: screening, diagnosis, management, and counseling in newborns and infants. Rockville, MD: Agency for Health Care Policy and Research, (AHCPR Pub. No. 93-0562), 1993;6:47-55.

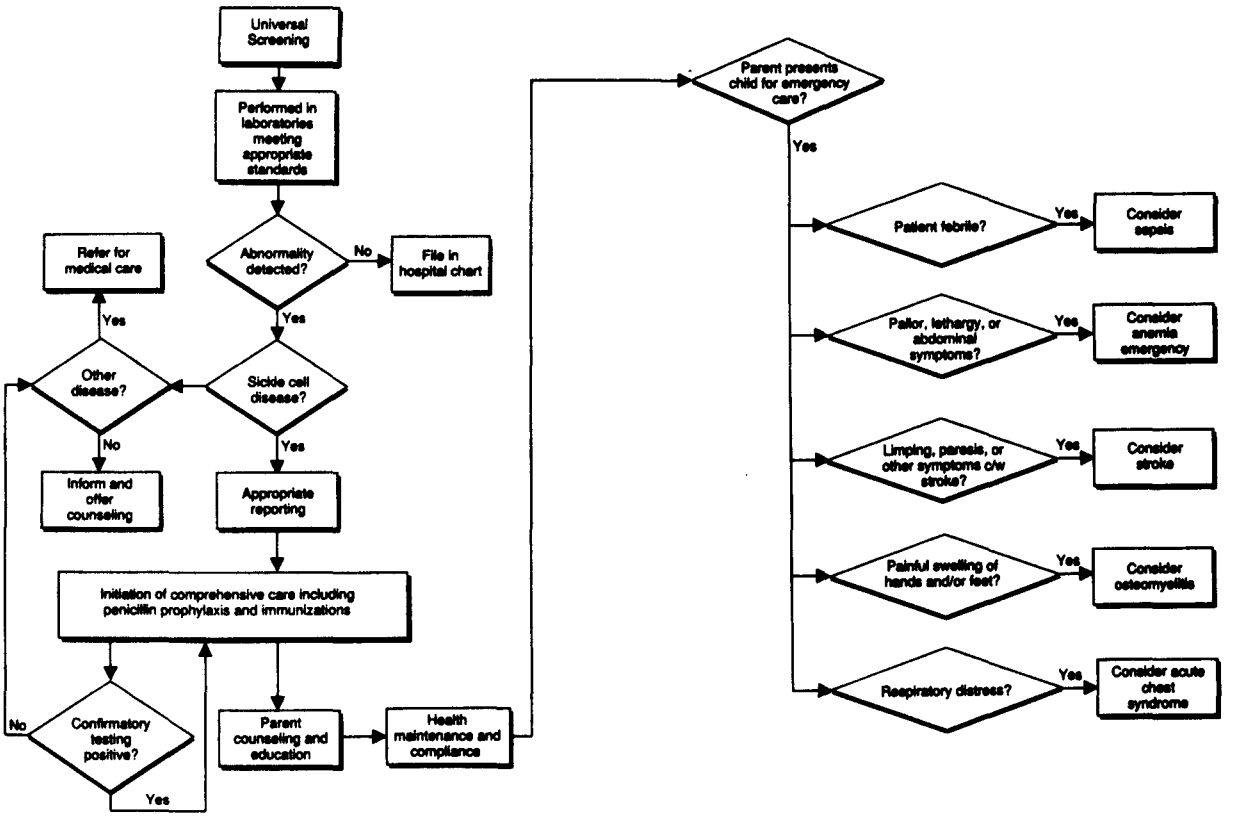


**Figure 1. Algorithm developed by the expert panel to display the organization, procedural flow, and decision points in identifying and caring for newborns and infants with sickle cell disease, sickle cell trait, and other hemoglobinopathies and educating and counseling their parents. Detailed annotations are provided in the *Guideline* (Sickle cell disease: screening, diagnosis, management, and counseling in newborns and infants. Rockville, MD: Agency for Health Care Policy and Research, AHCPR Pub. No. 93-0562, 1993; 6:82-3).**

prevalence (e.g., the 1 in 60,000 among whites). It is in low-prevalence populations that cost-effectiveness becomes relevant, and there are inadequate data on which to base a recommendation, notwithstanding the AHCPR panel's wishes otherwise. Unfortunately, this situation is one in which a valid scientific policy *is not possible*, because persuasive data do not exist. Family physicians must make their own decisions based on community standards, known characteristics of their patient population, hospital protocols, and other factors.

Finally, as noted earlier, it is disappointing that the panel was not able to address the issue of screening in older individuals. Here again, family physicians must make choices based on other factors.

*Parent Education and Counseling*

Regardless of the screening decision, family physicians should be prepared to educate and counsel parents about sickle cell trait and disease. As noted, the panel produced no evidence that such education and counseling improves clinical outcomes, but it is difficult to conclude from their findings that it can be ignored. Family physicians should provide appropriate information but be aware that their counsel might not be absorbed or followed. Family physicians caring for high-prevalence populations have an incentive for developing cost-effective educational and counseling strategies that produce the clinical outcomes that patients value.

Statements in the guideline that educators and counselors should have special training are, again, provided without supporting evidence. Certainly family physicians should be sure that the information they provide is accurate. Family physicians who rarely encounter these issues might wish to use some of the educational resources noted in the guideline or refer to an outside counseling service.

**Table 5. Neonatal Hemoglobinopathy Screening Policies and Primary Laboratory Methods in 53 US Jurisdictions as of Mid-1992.***

| Jurisdiction | Population Screened | Types of Screening |
|---|---|---|
| Alabama | Universal | Mandatory |
| Alaska | None | None |
| Arizona | Universal | Mandatory |
| Arkansas | Universal | Mandatory |
| California | Universal | Mandatory |
| Colorado | Universal | Mandatory |
| Connecticut | Universal | Voluntary |
| Delaware | Universal | Voluntary |
| District of Columbia | Universal | Voluntary |
| Florida | Universal | Mandatory |
| Georgia | Nonuniversal | Mandatory/voluntary |
| Hawaii | None | None |
| Idaho | None | None |
| Illinois | Universal | Mandatory |
| Indiana | Universal | Mandatory |
| Iowa | Universal | Mandatory |
| Kansas | Universal | Voluntary |
| Kentucky | Nonuniversal | Voluntary |
| Louisiana | Nonuniversal | Mandatory |
| Maine | None | None |
| Maryland | Universal | Voluntary |
| Massachusetts | Universal | Mandatory |
| Michigan | Universal | Mandatory |
| Minnesota | Universal | Mandatory |
| Mississippi | Universal | Mandatory |
| Missouri | Universal | Mandatory |
| Montana | None | None |
| Nebraska | None | None |
| Nevada | Universal | Mandatory |
| New Hampshire | Nonuniversal | Voluntary |
| New Jersey | Universal | Mandatory |
| New Mexico | Nonuniversal | Voluntary |
| New York | Universal | Mandatory |
| North Carolina | Nonuniversal | Voluntary |
| North Dakota | None | None |
| Ohio | Universal | Mandatory |
| Oklahoma | Universal | Voluntary |
| Oregon | None | None |
| Pennsylvania | Nonuniversal | Mandatory |
| Puerto Rico | Universal | Mandatory |
| Rhode Island | Universal | Mandatory |
| South Carolina | Universal | Mandatory |
| South Dakota | None | None |
| Tennessee | Universal | Mandatory |
| Texas | Universal | Mandatory |
| Utah | None | None |
| Vermont | Nonuniversal | Voluntary |
| Virginia | Universal | Mandatory |
| Virgin Islands | Universal | Voluntary |
| Washington | Universal | Mandatory |
| West Virginia | Nonuniversal | Voluntary |
| Wisconsin | Universal | Mandatory |
| Wyoming | Universal | Mandatory |

*Sickle cell disease: screening, diagnosis, management, and counseling in newborns and infants. Rockville, MD: Agency for Health Care Policy and Research, (AHCPR) Pub. No. 93-0562), 1993;6:87-9.

*Medical Management*

Here the evidence is on firm footing. Family physicians caring for a newborn with sickle cell disease should follow the AHCPR guideline for penicillin prophylaxis and assertive health maintenance, including *Hemophilus influenzae* type b (HIB) and pneumococcal vaccines. The material is well summarized in the text and outlined in the appended algorithm.

## Summary

The AHCPR guideline on sickle cell disease has several strengths and many weaknesses. For the practicing physician it is strongest in recommending medical management of infants with sickle cell disease but weakest on screening and education and counseling. The evidence-based methodology should have been presented in more detail. Until that occurs, family physicians are left with this guideline as a summary of expert opinions with variable documentation of the underlying science.

## References


1. Motulsky AG. Frequency of sickling disorders in US blacks. N Engl J Med 1973; 288:31-3.
2. Meany FJ, Riggle SM. Newborn screening report, 1990. Austin: Council of Regional Networks for Genetic Services (CORN), 1992.
3. Sickle cell disease: screening, diagnosis, management, and counseling in newborns and infants. (Clinical practice guideline no. 6.) Rockville, MD: Agency for Health Care Policy and Research, (AHCPR Pub. No. 93-0562), 1993.
4. Sickle cell disease: comprehensive screening and management in newborns and infants. (Quick reference guide for clinicians no. 6.) Rockville, MD: Agency for Health Care Policy and Research, (AHCPR Pub. No. 93-0562), 1993.
5. Sickle cell disease in newborns and infants. (A guide for parents.) Rockville, MD: Agency for Health Care Policy and Research, (AHCPR Pub. No. 93-0562), 1993.
6. Gaston MH, Verter JI, Woods G, Pegelow C, Kelleher J, Presbury G. Prophylaxis with oral penicillin in children with sickle cell anemia. A randomized trial. N Engl J Med 1986; 314:1593-9.
7. Vichinsky E, Hurst D, Earles A, Kleman K, Lubin B. Newborn screening for sickle cell disease: effect on mortality. Pediatrics 1988; 81:749-55.
8. Githens JH, Lane PA, McCurdy RS, Houston ML, McKinna JD, Cole DM. Newborn screening for hemoglobinopathies in Colorado. The first ten years. Am J Dis Child 1990; 144:466-70.

9. Tsevat J, Wong JB, Pauker SG, Steinberg MH. Neonatal screening for sickle cell disease: a cost-effectiveness analysis. J Pediatr 1991; 118:546-54.
10. Lane PA, Mauro RD, Houston ML, McKinna J. Universal screening for hemoglobinopathies is more cost-effective than screening targeted to high-risk infants. National Neonatal Screening Program. Raleigh, NC: Ninth National Screening Program Symposium, April, 1992. Abstract.
11. Sprinkle RH, Hynes DM, Konrad TR. A reconsideration of universal neonatal hemoglobinopathy screening in the United States. In press.