

PREDICTION OF ADVERSE OUTCOMES IN CHILDREN WITH SICKLE CELL DISEASE

SCOTT T. MILLER, M.D., LYNN A. SLEEPER, Sc.D., CHARLES H. PEGELOW, M.D., LAURA E. ENOS, M.S., WINFRED C. WANG, M.D., STEVEN J. WEINER, M.S., DORIS L. WETHERS, M.D., JEANNE SMITH, M.D., M.P.H., AND THOMAS R. KINNEY, M.D.*

ABSTRACT

Background The ability to identify infants with sickle cell anemia who are likely to have severe complications later in life would permit accurate prognostication and tailoring of therapy to match disease-related risks and facilitate planning of clinical trials. We attempted to define the features of such babies by following the clinical course of 392 children with sickle cell disease from infancy to about the age of 10 years.

Methods We analyzed the records of 392 infants who received the diagnosis of homozygous sickle cell anemia or sickle cell- β^0 -thalassemia before the age of six months and for whom comprehensive clinical and laboratory data were recorded prospectively; data were available for a mean (\pm SD) of 10.0 ± 4.8 years. Results obtained before the age of two years were evaluated to determine whether they predicted the outcome later in life.

Results Of the 392 infants in the cohort, 70 (18 percent) subsequently had an adverse outcome, defined as death (18 patients [26 percent]), stroke (25 [36 percent]), frequent pain (17 [24 percent]), or recurrent acute chest syndrome (10 [14 percent]). Using multivariate analysis, we found three statistically significant predictors of an adverse outcome: an episode of dactylitis (defined as pain and tenderness in the hands or feet) before the age of one year (relative risk of an adverse outcome, 2.55; 95 percent confidence interval, 1.39 to 4.67), a hemoglobin level of less than 7 g per deciliter (relative risk, 2.47; 95 percent confidence interval, 1.14 to 5.33), and leukocytosis in the absence of infection (relative risk, 1.80; 95 percent confidence interval, 1.05 to 3.09).

Conclusions Three easily identifiable manifestations of sickle cell disease that may appear in the first two years of life (dactylitis, severe anemia, and leukocytosis) can help to predict the possibility of severe sickle cell disease later in life. (N Engl J Med 2000; 342:83-9.)

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SINCE Herrick first described sickle cells in 1910,¹ much has been learned about the pathophysiology and molecular biology of sickle cell disease.² These advances have been accompanied by improvements in survival and the quality of life.³⁻⁵ Hydroxyurea therapy can substantially reduce the symptoms,⁶ and hematopoietic stem-cell transplantation can be curative.⁷ Ideally, the risks of these treatments should be commensurate with the risks of untreated sickle cell disease, and potentially cura-

tive treatments should begin before organ damage occurs. Although predictors of certain complications of sickle cell disease have been identified,^{2,3,8-13} there have been few attempts to identify patients at high risk for such complications during the first few years of life.¹⁴ Distinguishing such patients could help in prognostication and the selection of patients for high-risk therapies.

The Cooperative Study of Sickle Cell Disease^{15,16} included a cohort of infants with sickle cell anemia or sickle cell- β^0 -thalassemia who were enrolled before six months of age and monitored for complications. Laboratory tests were also performed during a mean (\pm SD) follow-up of 10.0 ± 4.8 years.¹⁷ We used these results to determine whether the features of the disease early in life could be used to predict its severity later in life.

METHODS

Patients

Recruitment procedures for the study have been described elsewhere.^{15,16} Consent for participation in the study was obtained from the patients' parents or guardians in accordance with the requirements and guidelines of the human subjects committee at each participating clinical center. From October 1978 through October 1988, 414 infants with homozygous sickle cell anemia or sickle cell- β^0 -thalassemia were enrolled in the study before they were six months old. Most of the infants were identified as newborns by screening programs. Of these 414 infants, 22 were excluded because they were followed for less than one year, leaving 380 patients with homozygous sickle cell anemia and 12 with sickle cell- β^0 -thalassemia. The mean age at entry into the study was 3.0 ± 1.5 months, and the mean duration of follow-up was 10.0 ± 4.8 years. Follow-up ended on August 31, 1998, and the data base was closed in August 1999.

An additional group of 105 patients with sickle cell anemia, plus 6 with sickle cell- β^0 -thalassemia, termed the validation cohort, were enrolled in the study from 1979 through 1981. These 111 children were enrolled at six months to two years of age and had complete clinical and laboratory data available. Their mean age at enrollment was 14.9 ± 5.4 months, and the mean duration of follow-up was 5.8 ± 1.3 years. Data on these patients were collected prospectively only after enrollment, but information was obtained at study entry about acute events that occurred earlier.

From the State University of New York–Downstate Medical Center, Brooklyn (S.T.M.); New England Research Institutes, Watertown, Mass. (L.A.S., L.E.E., S.J.W.); the University of Miami, Miami (C.H.P.); St. Jude Children's Research Hospital, Memphis, Tenn. (W.C.W.); St. Luke's–Roosevelt Medical Center, New York (D.L.W.); Harlem Hospital Center, New York (J.S.); and Duke University Medical Center, Durham, N.C. (T.R.K.). Address reprint requests to Dr. Miller at the State University of New York–Downstate Medical Center, 450 Clarkson Ave., Box 49, Brooklyn, NY 11203, or at stmseelig@aol.com.

*Participating institutions and investigators are listed in the Appendix.

Laboratory Methods

Hemoglobin typing was performed at the Centers for Disease Control and Prevention with the use of cellulose acetate and citrate agar electrophoresis,¹⁸ column chromatography (for the measurement of hemoglobin A₂), and alkali denaturation (for the measurement of fetal hemoglobin).¹⁹ The blot hybridization method was used to map the α -globin gene²⁰ in 321 patients (82 percent) and identify the β ^s-globin gene haplotypes²¹ in 304 patients (78 percent). Leukocyte counts were not corrected for the presence of nucleated red cells.²² The percentage of pocked (vesiculated) red cells (an indicator of splenic function) was calculated with the use of interference phase-contrast microscopy.²³ Hematologic data collected in two children after splenectomy were not included.

Definitions of Clinical Events

Stroke was defined as an acute neurologic syndrome due to vascular occlusion or hemorrhage in which neurologic symptoms or signs lasted more than 24 hours. Transient ischemic attacks and silent infarctions²⁴ were not included. All diagnoses of stroke were confirmed by three pediatric neurologists. A painful event was defined as pain in the arms and legs, back, abdomen, chest, or head that lasted at least two hours, led to a request for medical care, and was attributable to sickle cell disease. Dactylitis, the acute chest syndrome, the right upper quadrant syndrome, osteomyelitis, and appendicitis were not counted as painful events. The acute chest syndrome was defined as the presence of a new pulmonary infiltrate on a chest x-ray film, a defect on radionuclide imaging of the chest, or both, in association with an acute respiratory tract illness.

Dactylitis was defined as pain and tenderness, with or without swelling, in the hands, feet, or both. Acute splenic sequestration was defined as a decrease from base line in the hemoglobin level or hematocrit of at least 20 percent plus a simultaneous increase in the size of the spleen to at least 2 cm below the left costal margin.

Adverse Events

Four adverse events served as proxies for severe sickle cell disease: death known or believed to be related to sickle cell disease; stroke; an average of at least two painful events per year for the entire follow-up period, with at least two events per year for three consecutive years (referred to as frequent pain); and an average of at least one episode of acute chest syndrome per year for the entire follow-up period, with at least one episode per year for three consecutive years (referred to as recurrent acute chest syndrome). Pain and the acute chest syndrome were chosen not only because of the morbidity associated with them, but also because of the association of the acute chest syndrome with chronic lung disease²⁵ and of both complications with death during adulthood.³ Rates were calculated from enrollment through the end of follow-up or until the initiation of regular treatment with transfusions (in the case of 39 patients) or hydroxyurea therapy (in the case of 9 patients).

Statistical Analysis

The Cox proportional-hazards model was used to determine the age at which a severe outcome occurred.²⁶ All covariates were based on data collected up to the age of two years, the occurrence of an adverse event, or the initiation of regular transfusions, whichever occurred first.

Well-child visits were required every three months in the second year of life. We analyzed laboratory data collected during these routine visits from the ages of 11 to 25 months to determine steady-state values. The steady-state hemoglobin level and leukocyte count were based on measurements obtained during a median of four visits, the steady-state percentage of reticulocytes was based on measurements obtained during a median of three visits, and the steady-state platelet count was based on measurements obtained during a median of two visits. The steady-state fetal hemoglobin level was based on measurements obtained during a median of one visit made between the ages of 17 and 25 months. These mean laboratory values were first examined as continuous covariates to ex-

TABLE 1. INCIDENCE OF FIRST ADVERSE EVENTS.*

ADVERSE EVENT	NO. OF PATIENTS (%)	AGE AT TIME OF EVENT (YR)
≥2 Painful events/yr†	17 (24)	7.9±3.7
≥1 Episode of acute chest syndrome/yr†	10 (14)	3.5±1.0
Stroke	25 (36)	6.1±3.4
Death	18 (26)	5.1±3.7
Total	70 (100)	5.9±3.6

*Plus-minus values are means ±SD. These events served as proxies for severe disease.

†The average event rate was calculated for the entire follow-up period; in addition, the elevated rate had to be observed for three consecutive years.

plore potential linear and nonlinear relations. In order to identify the patients at highest risk for severe disease, we created indicators based on the mean laboratory values for the 75th, 90th, and 95th percentiles for the leukocyte count, hemoglobin level, and percentage of reticulocytes and the 5th, 10th, and 25th percentiles for total hemoglobin and fetal hemoglobin levels. On the basis of prior research,²³ we defined an early elevated pocked red-cell value as a value of at least 3.5 percent on at least one visit between birth and the age of 12 months; measurements were obtained during a median of four visits. Indicators for early dactylitis and splenic sequestration were created, with “early” defined as occurrences before one and before two years of age, respectively.

Variables with a P value of 0.20 or less on univariate analyses were evaluated in a multivariate model. The assumption used for the proportional-hazards model was found to be valid for the multivariate model.

After we developed a prognostic model based on findings in the original cohort of patients, we applied the model to data from the validation cohort to evaluate the predictive power of these findings. We fit a logistic-regression model using factors from the multivariate Cox model along with a covariate denoting the duration of follow-up for each patient. The sensitivity and specificity of the model were estimated for each cohort. We used the jackknife procedure²⁷ in the analysis of the original cohort to reduce the possibility of bias in the estimates of sensitivity and specificity.

RESULTS

Characteristics of the Patients

Of the 392 patients enrolled in the study, 70 (18 percent) had adverse outcomes that qualified their disease as severe (Table 1). In this group the mean duration of follow-up was 9.0±4.9 years, and in the remaining 322 patients, it was 10.2±4.7 years. Half the patients in the group with severe disease were boys. The most common adverse event that resulted in the classification of disease as severe was stroke (36 percent). The causes of death in this group of 70 patients were infection (56 percent), the acute chest syndrome (6 percent), splenic sequestration (6 percent), and other causes thought to be related to the disease (33 percent). The mean age at which infants were classified as having severe disease due to the acute chest syndrome was 3.5 years. Frequent attacks of the acute chest syndrome, however, did not predict the occurrence of other severe complications (stroke or pain) or death. For patients classified as having severe disease

TABLE 2. UNIVARIATE ANALYSIS OF THE RISK OF SEVERE SICKLE CELL DISEASE.*

VARIABLE†	NO. OF PATIENTS‡	RELATIVE RISK OF SEVERE DISEASE (95% CI)	PATIENTS WITH SEVERE DISEASE	PATIENTS WITHOUT SEVERE DISEASE
Hemoglobin level (g/dl)	357		8.5±1.3	9.1±1.3
≥7 g/dl	335	1.00§	56/64 (87.5)¶	279/293 (95.2)¶
<7 g/dl	22	2.64 (1.26–5.55)	8/64 (12.5)¶	14/293 (4.8)¶
Fetal hemoglobin (%)	174		14.7±6.3	17.4±8.0
Per each 5% absolute increase		0.80 (0.62–1.02)		
Leukocyte count (×10 ⁻³ /mm ³)	356		15.2±4.5	13.4±4.5
Per each 10-unit increase		2.17 (1.31–3.58)		
Reticulocytes (%)	348		11.6±6.7	9.3±5.7
Per each 5% absolute increase		1.37 (1.13–1.65)		
Platelets (×10 ⁻³ /mm ³)	184		402±123	372±104
Per each 100-unit increase		1.22 (0.93–1.59)		
Pocked-red-cell value before 1 yr of age	187			
<3.5%	135	1.00§	13/29 (44.8)¶	122/158 (77.2)¶
≥3.5%	52	3.59 (1.72–7.47)	16/29 (55.2)¶	36/158 (22.8)¶
Splenic sequestration before 1 yr of age	392			
No	381	1.00§	66/70 (94.3)¶	315/322 (97.8)¶
Yes	11	2.00 (0.73–5.50)	4/70 (5.7)¶	7/322 (2.2)¶
Dactylitis before 1 yr of age	392			
No	351	1.00§	55/70 (78.6)¶	296/322 (91.9)¶
Yes	41	2.67 (1.51–4.73)	15/70 (21.4)¶	26/322 (8.1)¶

*Plus-minus values are means ±SD. CI denotes confidence interval.

†Unless otherwise indicated, laboratory values are the means of those obtained during the second year of life.

‡Data were not available for all patients for the following reasons: data were not collected for all the years of the study, data were censored because of treatment or a severe outcome, and data were absent because of missed visits.

§This group served as the reference group.

¶The values shown are the number of patients with this characteristic and the total number of patients in each group. The value in parentheses is the percentage of patients with the characteristic.

||A unit was defined as 10³ cells per cubic millimeter.

because of frequent pain, the mean number of painful events during the entire follow-up period was 41.7±10.0, and for patients classified as having severe disease because of recurrent acute chest syndrome, the mean number of episodes was 16.9±9.2.

Laboratory Data

The mean steady-state hemoglobin level for the entire cohort was 9.0±1.3 g per deciliter (Table 2). The steady-state hemoglobin level was the value obtained during a routine visit during the second year of life, when the child had no acute medical problems. The steady-state hemoglobin levels correlated linearly and inversely with the severity of disease (P<0.001) (Table 2). The patients with severe anemia (defined as a hemoglobin level of less than 7 g per deciliter) were 2.64 times as likely to have severe disease as patients with hemoglobin levels of at least 7 g per deciliter (P=0.01).

The overall mean steady-state leukocyte count in the absence of infection was 13.7±4.5×10³ per cubic millimeter. Higher leukocyte counts were associated with severe disease (P=0.003). An elevation in

the proportion of pocked red cells to at least 3.5 percent before the first birthday was also strongly predictive of a severe course (P=0.001). The mean steady-state percentage of reticulocytes was 9.7±6.0 percent; higher values were associated with severe disease (P=0.001). The mean fetal hemoglobin value was 16.9±7.7 percent, but the percentage of fetal hemoglobin as a continuous covariate was not significantly related to disease severity (P=0.07), nor was a threshold of 20 percent fetal hemoglobin.^{28,29} The platelet count was not associated with severe disease.

Clinical Data

As compared with patients who did not have dactylitis before the age of one year, patients who had dactylitis before their first birthday were 2.67 times as likely to have severe disease (P<0.001). Of the 41 infants with early dactylitis, 80 percent had swelling of both hands and both feet; only 2 infants had no documented swelling. There was no association between the risk of severe disease and the occurrence of splenic sequestration before the age of one year (P=0.18).

TABLE 3. MULTIVARIATE ANALYSIS OF THE RISK OF SEVERE SICKLE CELL DISEASE.*

VARIABLE	RELATIVE RISK OF SEVERE DISEASE (95% CI)	P VALUE
Dactylitis before 1 yr of age		
Yes	2.55 (1.39–4.67)	0.002
No	1.00†	
Leukocyte count (per each 10-unit increase)‡	1.80 (1.05–3.09)	0.03
Hemoglobin level‡		
<7 g/dl	2.47 (1.14–5.33)	0.02
≥7 g/dl	1.00†	

*The analysis included data on 356 patients. CI denotes confidence interval.

†This group served as the reference group.

‡Values are based on mean steady-state levels measured during the second year of life.

Genetic Factors

One third of the tested children had α -thalassemia (two or three α -globin genes), and this trait was not significantly associated with the risk of severe disease (relative risk, 0.72; 95 percent confidence interval, 0.40 to 1.30; $P=0.27$). None of the most common β^s -globin gene haplotypes, *BEN/BEN* (35.5 percent), *BEN/CAR* (23.0 percent), *BEN/SEN* (10.2 percent), or *CAR/CAR* (5.9 percent), were significantly associated with the risk of severe disease, nor were indicators for the presence of any single haplotype (*BEN*, *CAR*, *SEN*, or *CAM*).

Multivariate Analysis

The multivariate model included three variables that were significantly associated with an adverse clinical

course: early dactylitis ($P=0.002$), leukocytosis ($P=0.03$), and a hemoglobin level of less than 7 g per deciliter ($P=0.02$) (Table 3). The percentage of reticulocytes ($P=0.08$), the occurrence of early splenic sequestration ($P=0.68$), and the percentage of fetal hemoglobin ($P=0.62$) did not significantly affect the multivariate model. There were no significant interactions among any of the variables in the final model.

Figure 1 shows the probability predicted by logistic-regression analysis that sickle cell disease would be severe by the age of 10 years on the basis of the three significant variables. The group at lowest risk, patients who did not have early dactylitis and who had a steady-state hemoglobin level of at least 7 g per deciliter and below-average leukocyte counts (less than 13.0×10^3 per cubic millimeter during the second year of life), constituted 44 percent of the cohort and had less than a 9 percent chance of having severe disease by the age of 10 years. The patients with the greatest probability of severe disease — at least twice the rate of severity in the entire cohort — constituted only 3 percent of the cohort. The high-risk group included patients with both early dactylitis and severe anemia or with one of these risk factors and a leukocyte count higher than approximately 20×10^3 per cubic millimeter (the 90th percentile). Logistic-regression analysis showed that the majority of patients (53 percent) were at medium risk (Fig. 1).

An elevated pocked-red-cell count before the age of one year was examined separately because pocked-red-cell values were not available for over half the patients (since such data were not collected after 1985). When elevation of the pocked-red-cell value at an early age was added to the prognostic model, none of the other variables were significant at the 0.05 level. It is possible that an elevated pocked-red-cell value

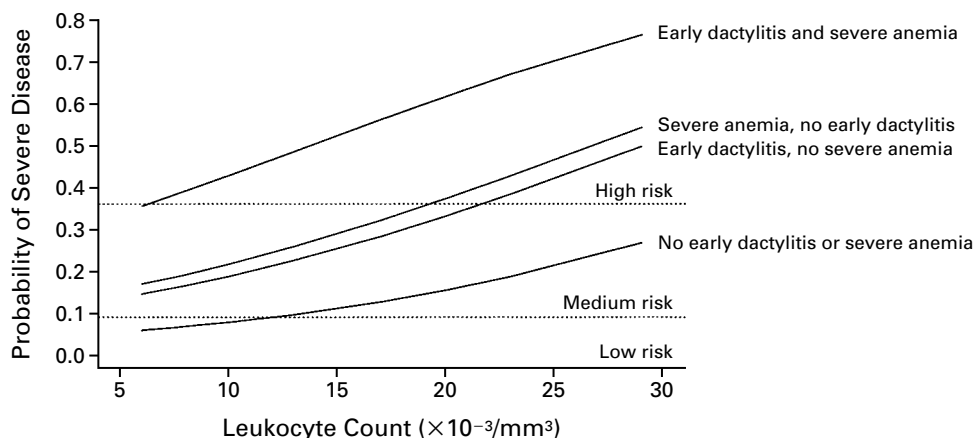


Figure 1. Estimated Probability of Severe Sickle Cell Disease by the Age of 10 Years According to the Leukocyte Count, Severe Anemia during the Second Year of Life, and the Occurrence of Dactylitis before the Age of 1 Year.

Severe anemia was defined as a hemoglobin level of less than 7 g per deciliter during the second year of life. In this cohort of patients, 3 percent were classified as being at high risk, 53 percent were classified as being at medium risk, and 44 percent were classified as being at low risk.

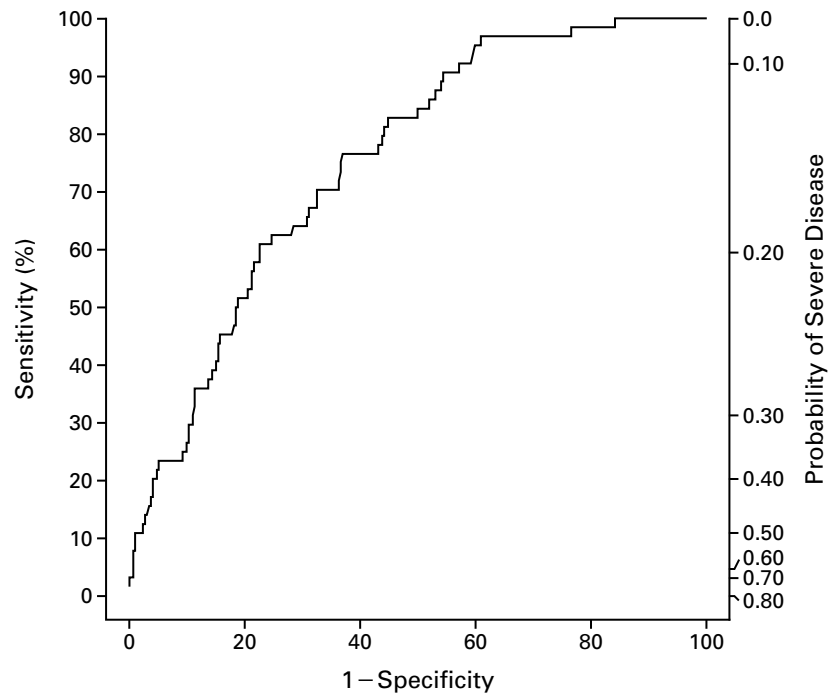


Figure 2. Receiver-Operating-Characteristic Curve for the Severity of Disease as Predicted by the Model. Data on 356 patients were included in the analysis. The x axis indicates the false positive rate, the y axis on the left indicates sensitivity (the proportion of patients who were correctly classified as having severe disease), and the y axis on the right indicates the threshold used to classify a patient as having severe disease.

before the age of one year is the strongest predictor of a severe course, but the incompleteness of the data on this factor precludes our drawing definitive conclusions.

Evaluation of the Model

A receiver-operating-characteristic curve was constructed on the basis of the final model in order to evaluate the usefulness of different classifications of severity (Fig. 2). Adopting a classification that was associated with a low false positive rate was of prime importance in order to minimize the likelihood that a patient who did not have severe disease would be referred for a high-risk therapy. The use of a predicted probability of severe disease of at least 36 percent, or twice the observed rate in our original cohort, as the criterion for severe disease was associated with a sensitivity of 23 percent and a specificity of 91 percent (i.e., a 9 percent false positive rate).

Validation of the Model

Fifteen members (13.5 percent) of the validation cohort had an adverse outcome (five died, five had a stroke, four had recurrent painful events, and one had recurrent acute chest syndrome), a rate similar to that of the original cohort ($P=0.27$). The validation cohort had rates of early dactylitis ($P=0.86$) and early

splenic sequestration ($P=0.74$) that were similar to those of the original cohort. Perhaps because hematologic measurements were obtained at older ages on average in the validation cohort than in the original cohort (although within the first and second years of life), the mean hemoglobin level (8.7 vs. 9.0 g per deciliter, $P=0.04$) and percentage of fetal hemoglobin (14.8 percent vs. 16.9 percent, $P=0.03$) were lower in this group, and the leukocyte count (15.0×10^3 vs. 13.7×10^3 per cubic millimeter, $P=0.04$) was higher. These differences may in part explain why our logistic-regression model did not result in estimates of relative risk that were similar to those obtained in the original cohort.

By using a predicted probability of 36 percent that a child would have a severe course (Fig. 2), we predicted that four members of the validation cohort would have a severe course, whereas three actually did so (positive predictive value, 75 percent). The negative predictive value — that is, the proportion of patients who did not have severe disease among those estimated not to have severe disease — was 89 percent (95 of 107). The use of this classification would result in the identification of only 20 percent of patients with severe disease (3 of 15); however, the rate of false positive results (1 of 96) would be low (1 percent).

DISCUSSION

In this observational study of children with sickle cell anemia, we found that dactylitis, a steady-state hemoglobin level of less than 7 g per deciliter, and leukocytosis in the absence of infection at an early age correlated significantly with adverse outcomes later in childhood. Early loss of splenic function, as indicated by an increase in the percentage of pocked red cells in the blood, may also be prognostically important. The relevant laboratory tests for predicting outcome — measurement of hemoglobin levels and white-cell count — are readily available,³⁰ but steady-state values must be obtained at a clinic visit when there are no acute complications or other illnesses.

A low hemoglobin level has previously been shown to correlate with an increased risk of death in childhood⁴ or adulthood³ and of stroke.⁸ However, higher hemoglobin levels correlate with increased risks of the acute chest syndrome⁹ and painful crisis.¹⁰ Although almost 40 percent of the children with severe disease in our study were so classified because of frequent episodes of pain and the acute chest syndrome, a low hemoglobin level was associated with the composite end point of severe disease. Perhaps low hemoglobin levels in infancy are determinants of severity in children, whereas the deleterious effects of an elevated hemoglobin level are cumulative.

An elevated leukocyte count was an independent predictor of the severity of disease in our analysis and was associated with the risk of stroke in a cohort of Jamaican patients.³¹ Whether leukocytes contribute to the pathogenesis of sickle cell disease, perhaps by releasing cytotoxic enzymes,³² is unknown. The adverse effect of neutrophils on vascular endothelium,³³ which is related in part to abnormal adhesion,³⁴ is of particular interest with regard to stroke and cerebrovascular disease in patients with sickle cell anemia.³⁵

A low fetal hemoglobin level was not independently associated with the risk of severe disease. This may be due to its correlation with total hemoglobin, or to a low statistical power of the study, since over half the cohort did not have values for fetal hemoglobin recorded at 17 to 25 months of age. Accelerated reduction in the fetal hemoglobin level during infancy has been associated with loss of splenic function²³ (reflected by a pocked-red-cell value of 3.5 percent or more), and the occurrence of this event before one year of age may be strongly associated with the risk of severe disease. However, the importance of this finding is reduced by the known variation between laboratories in the performance of this test³⁶ and by the fact that this test is not usually performed during routine visits. Neither the β^s -globin gene haplotype nor the presence of α -thalassemia³⁷ was associated with the risk of severe disease.

How should clinicians use this index? We must emphasize that there may be other factors that we did not examine or recognize that, if added to our model,

would enhance our ability to predict a severe outcome. To minimize the false positive rate, we suggest that children whose probability of severe disease is 36 percent or greater (i.e., at least twice that in the general population of children with sickle cell disease) be classified as having a high risk of severe disease. Although this conservative approach will not identify all children who are destined to have a severe course, its use will make it extremely unlikely that a child with mild disease will be considered for a potentially dangerous intervention, such as stem-cell transplantation.

The best use of this prognostic model is to estimate the level of risk, rather than strictly to classify a patient as having or not having severe disease. This approach may be useful in designing therapeutic clinical trials. Excluding children with relatively mild manifestations of disease will allow a larger treatment effect to be easily observed, thus reducing the number of subjects required in the study, and prevent low-risk children from receiving high-risk therapy.

Our model has been validated only retrospectively, and therefore it should also be validated by other means. We urge any who use the model as a means for justifying therapeutic intervention to do so only in controlled clinical trials, with thorough discussions among physicians, patients, and their families of the risks and benefits of both watchful waiting and the proposed intervention.

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APPENDIX

The following institutions and principal investigators participated in the study: L. McMahon (Boston Medical Center, Boston); O. Platt (Children's Hospital, Boston); K. Ohene-Frempong, F. Gill (Children's Hospital of Philadelphia, Philadelphia); E. Vichinsky, B. Lubin (Children's Hospital Medical Center of Northern California, Oakland); S. Leiken, J. Kelleher, G. Bray (Children's National Medical Center, Washington, D.C.); S. Piomelli (Columbia-Presbyterian Medical Center, New York); T. Kinney, R. Ware (Duke University Medical Center, Durham, N.C.); J. Smith, Y. Khakoo (Harlem Hospital, New York); R. Scott, O. Castro, C. Reindorf, C. Uy-Lee (Howard University, Washington, D.C.); R. Bellevue, L. Guarini (Interfaith Medical Center, Brooklyn, N.Y.); W. Mentzer, W. Lande (San Francisco General Hospital, San Francisco); W. Wang, J. Wilimas (St. Jude Children's Research Hospital, Memphis, Tenn.); D. Wethers, R. Grover (St. Luke's-Roosevelt Medical Center, New York); A. Brown, S. Miller (State University of New York Health Science Center at Brooklyn, Brooklyn); N. Talischy-Zahed (University of Illinois, Chicago); C. Pegelow (University of Miami, Miami); H. Zarkowsky, A. Schwartz, M. DeBaun (Washington University, St. Louis); R. Chilcote, J. Moorh, C. Dampier, U. Subramanian (Wylar Children's Hospital, Chicago); H. Pearson, A. Ritchey (Yale University, New Haven, Conn.); statistical coordinating centers — E. Chen, P. Levy, M. West, M. Espeland, D. Gallagher (University of Illinois School of Public Health, Chicago) and S. McKinlay, D. Gallagher, L. Sleeper, E. Wright, D. Brambilla (New England Research Institutes, Watertown, Mass.); program administrators for

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