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Immediate Transfusion in African Children with Uncomplicated Severe Anemia

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ABSTRACT

BACKGROUND

The World Health Organization recommends not performing transfusions in African children hospitalized for uncomplicated severe anemia (hemoglobin level of 4 to 6 g per deciliter and no signs of clinical severity). However, high mortality and readmission rates suggest that less restrictive transfusion strategies might improve outcomes.

METHODS

In this factorial, open-label, randomized, controlled trial, we assigned Ugandan and Malawian children 2 months to 12 years of age with uncomplicated severe anemia to immediate transfusion with 20 ml or 30 ml of whole-blood equivalent per kilogram of body weight, as determined in a second simultaneous randomization, or no immediate transfusion (control group), in which transfusion with 20 ml of whole-blood equivalent per kilogram was triggered by new signs of clinical severity or a drop in hemoglobin to below 4 g per deciliter. The primary outcome was 28-day mortality. Three other randomizations investigated transfusion volume, postdischarge supplementation with micronutrients, and postdischarge prophylaxis with trimethoprim–sulfamethoxazole.

RESULTS

A total of 1565 children (median age, 26 months) underwent randomization, with 778 assigned to the immediate-transfusion group and 787 to the control group; 984 children (62.9%) had malaria. The children were followed for 180 days, and 71 (4.5%) were lost to follow-up. During the primary hospitalization, transfusion was performed in all the children in the immediate-transfusion group and in 386 (49.0%) in the control group (median time to transfusion, 1.3 hours vs. 24.9 hours after randomization). The mean (±SD) total blood volume transfused per child was 314±228 ml in the immediate-transfusion group and 142±224 ml in the control group. Death had occurred by 28 days in 7 children (0.9%) in the immediate-transfusion group and in 13 (1.7%) in the control group (hazard ratio, 0.54; 95% confidence interval [CI], 0.22 to 1.36; P=0.19) and by 180 days in 35 (4.5%) and 47 (6.0%), respectively (hazard ratio, 0.75; 95% CI, 0.48 to 1.15), without evidence of interaction with other randomizations (P>0.20) or evidence of between-group differences in readmissions, serious adverse events, or hemoglobin recovery at 180 days. The mean length of hospital stay was 0.9 days longer in the control group.

CONCLUSIONS

There was no evidence of differences in clinical outcomes over 6 months between the children who received immediate transfusion and those who did not. The triggered-transfusion strategy in the control group resulted in lower blood use; however, the length of hospital stay was longer, and this strategy required clinical and hemoglobin monitoring. (Funded by the Medical Research Council and Department for International Development; TRACT Current Controlled Trials number, ISRCTN84086586.)

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*A complete list of the investigators in the TRACT Group is provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.

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Severe anemia (hemoglobin level <6 g per deciliter) is a leading cause of hospital admission among children in sub-Saharan Africa.[1,2] Outcomes remain unsatisfactory, with high reported in-hospital mortality (9 to 10%)[2,3] and 6-month mortality (12%)[4] and high rates of readmission.[4] Given the major burden of pediatric anemia on health services, coupled with scarce resources of donated blood (<5 units donated per 1000 population per year, despite substantial external funding),[5] the guidelines of the World Health Organization (WHO) encourage approaches for restrictive transfusion — specifically, not performing transfusion in children in stable condition who have a hemoglobin level of 4 to 6 g per deciliter.[6] The underpinning evidence on which the WHO guidelines are based is weak,[7] and adherence to the guidelines is poor[8,9] and hampered by inconsistent recommendations regarding the hemoglobin threshold for transfusion in patients with malaria. There is a lack of guidance on postadmission strategies for clinical and hemoglobin monitoring to identify children who have new signs of clinical severity that warrant transfusion.[6]

In the Transfusion and Treatment of Severe Anemia in African Children Trial (TRACT), we compared four interventions. Here, we compare immediate transfusion with no immediate transfusion, in which transfusion was triggered by the development of new signs of clinical severity or a drop in the hemoglobin level to below 4 g per deciliter, in children with uncomplicated severe anemia.[10]

METHODS

TRIAL DESIGN

We performed an open-label, multicenter, factorial, randomized, controlled trial at three hospitals in Uganda and one hospital in Malawi. In the part reported here, children 2 months to 12 years of age were eligible if they were hospitalized for uncomplicated severe anemia (defined as a hemoglobin level of 4 to 6 g per deciliter and no signs of clinical severity [i.e., no evidence of reduced level of consciousness, respiratory distress, acute hemoglobinuria,[11] or reported sickle cell disease]). Children who had known chronic disease (kidney or liver failure, malignant conditions, or congenital heart disease) or who were admitted for burns, trauma, or surgery were excluded, as were children who had previous transfusions during the same hospitalization or who were exclusively breast-fed. Further details are provided in the Methods section in the Supplementary Appendix, available with the full text of this article at NEJM.org.

The children were randomly assigned in a 1:1 ratio to undergo immediate transfusion or no immediate transfusion (control group). However, because we also evaluated the effects of transfusion volume (see the accompanying article by Maitland et al.[12] in this issue of the *Journal*), the children in the immediate-transfusion group underwent a second randomization in which they were assigned in a 1:1 ratio to receive 20 ml of whole blood (or 10 ml of packed or settled cells[13]) or 30 ml of whole blood (or 15 ml of packed or settled cells[13]) per kilogram of body weight. The children underwent simultaneous factorial randomization to receive adjunctive micronutrient supplementation or iron folate alone (usual care) for 3 months after discharge and to receive prophylaxis with trimethoprim–sulfamethoxazole (donated by Cipla) or no trimethoprim–sulfamethoxazole for 3 months after discharge (not reported here).

In the current report, the data from the children in the immediate-transfusion group who received 20 ml or 30 ml of whole-blood equivalent (whole blood or packed or settled cells) per kilogram were pooled for prespecified comparisons of the randomization groups. Children with signs of clinical severity, a hemoglobin level of less than 4 g per deciliter (profound anemia), or both at screening were also randomly assigned to receive 20 ml or 30 ml of whole-blood equivalent per kilogram; the results of this second randomization are reported in the accompanying article by Maitland et al.[12] The ethics committees of Imperial College London (London), Makerere University (Kampala, Uganda), and the College of Medicine (Blantyre, Malawi) approved the protocol, which is available at NEJM.org. All the authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol, and all the authors participated in writing the manuscript.

SCREENING AND RANDOMIZATION

At screening, the hemoglobin level was measured in children with signs or symptoms of severe anemia (e.g., severe pallor[14]) with the use of the

HemoCue system,[15] and a clinical assessment was performed. Written informed consent was obtained from the parents or guardians before randomization. When written informed consent could not be obtained, the ethics committees approved oral assent, with delayed written informed consent provided as soon as practical.[16] Randomization was stratified according to trial center alone, since no child in this randomization had severity features. The statistician in London generated and kept the sequential randomization list, which was computer-generated with the use of variably sized permuted blocks. Randomization was performed with the use of consecutively numbered packets that contained randomized links to opaque, sealed envelopes, a process that ensured concealment of the trial-group assignments. Further details are provided in the Methods section in the Supplementary Appendix.

PROCEDURES

Children were treated in general pediatric wards; ventilatory facilities were unavailable. Each trial center was provided with basic infrastructure support for emergency care; patient monitors; and bedside hemoglobin, glucose, and lactate point-of care tests. Local blood-transfusion services provided blood free of charge; the blood was prescreened for transfusion-transmissible infections and was prepared with the use of standard procedures, but without leukocyte reduction.[17] Second transfusions, if indicated among the children in the immediate-transfusion group, were performed with the originally assigned transfusion volume. Additional transfusions with 20 ml of whole-blood equivalent per kilogram (irrespective of the randomly assigned transfusion volume) were performed in the children in the immediate-transfusion group who had already received two transfusions if they continued to meet the criteria for transfusion or in the children in the control group if new signs of clinical severity developed or if they had a drop in the hemoglobin level to below 4 g per deciliter. Furosemide or other diuretics were not prescribed. Other treatments, including antimalarial and antibiotic agents, were administered according to national guidelines.

Bedside observations were performed at admission, every 30 minutes for the first 2 hours, and then 4, 8, 16, 24, and 48 hours after initiation of the first transfusion (immediate-transfusion group) or after randomization (control group). The hemoglobin level was assessed with the use of the HemoCue system every 8 hours during the first 24 hours and then at 48 hours or if triggered by clinical deterioration. The children were actively monitored for serious adverse events, particularly suspected cardiac or pulmonary overload or transfusion-related events; monitoring was performed according to the modified guidelines recommended by the Serious Hazards of Transfusion initiative in the United Kingdom.[18] After discharge, the children were clinically assessed and the hemoglobin level measured at 28, 90, and 180 days after randomization. Children exited the trial at 180 days. The clinicians were aware of the treatment-group assignments, but the laboratory tests were performed in a blinded manner.

OUTCOMES

The primary outcome was mortality at 28 days after randomization. Secondary outcomes were mortality at 48 hours, 90 days, and 180 days; development of new profound anemia (hemoglobin level <4 g per deciliter) during the primary hospitalization or severe anemia (hemoglobin level <6 g per deciliter) after discharge; hospital readmission; the percentage of children who had correction of anemia (defined as hemoglobin recovery to a level >9 g per deciliter[19] according to the WHO guidelines[6]); suspected transfusion reactions (febrile reactions and transfusion-related acute lung injury); serious adverse events; and cost and cost-effectiveness. Adverse events were graded according to the Common Toxicity Criteria for Adverse Events, version 4.0.[20] An independent end-point review committee reviewed the cause of death, suspected transfusion reactions, suspected respiratory and neurologic events, and allergic reactions in a blinded manner.

STATISTICAL ANALYSIS

We determined that 1553 children would need to be enrolled for the trial to have 80% power to detect a 50% relative difference in 28-day mortality, from 9.0%[2,3] in the control group to 4.5% in the immediate-transfusion group, assuming that 6% of the children would be lost to follow-up by 6 months (allowing for different timing of the primary outcomes in the other randomizations), at a two-sided alpha level of 0.013 (four

comparisons across randomizations, as detailed in the Methods section in the Supplementary Appendix). An independent data monitoring committee reviewed the interim data at three annual meetings with the use of the Haybittle–Peto criterion (P<0.001). The randomization groups were compared according to the intention-to-treat principle with the use of log-rank tests or competing-risks methods for time-to-event outcomes, exact tests for binary outcomes, and generalized-estimating equations with independent working correlation for global tests of repeated measures. The primary analyses of each outcome were stratified according to the same stratification factor used in randomization. In the economic analysis, costs (in U.S. dollars in 2018) and health outcomes (in life-years gained) over a period of 180 days were estimated with the use of health care utilization rates and unit costs for each country. Analyses were performed with the use of Stata software, version 15.1 (StataCorp), and R software, version 3.5.1 (R Foundation for Statistical Computing). The 95% confidence intervals were not adjusted for multiple testing. Further details of the statistical analysis are provided in the Methods section in the Supplementary Appendix.

RESULTS

PATIENTS

Between September 17, 2014, and May 15, 2017, a total of 1565 children underwent randomization, with 778 children assigned to the immediate-transfusion group (390 were assigned to receive 20 ml and 388 to receive 30 ml of whole-blood equivalent per kilogram) and 787 to the control group; all children who underwent randomization were included in all analyses (Fig. 1). The characteristics of the children at baseline were balanced between the randomization groups (Table 1, and Table S1 in the Supplementary Appendix). A total of 984 children (62.9%) had *Plasmodium falciparum* malaria, but human immunodeficiency virus infection, culture-proven bacteremia, and severe malnutrition were uncommon (<4%). Although children with known sickle cell disease were ineligible, the condition was identified in 7 children after randomization. At trial completion, batch genotyping confirmed sickle cell disease in 340 of 1549 children (21.9%).

ADHERENCE

Transfusion was performed during the primary hospitalization in 778 of the 778 children (100%) in the immediate-transfusion group and in 386 of the 787 children (49.0%) in the control group. The median times to transfusion after randomization were 1.3 hours (interquartile range, 0.9 to 1.7) in the immediate-transfusion group and 24.9 hours (interquartile range, 9.2 to 49.8) in the control group (Fig. S1 and Table S2 in the Supplementary Appendix). The major trigger for transfusion among the children in the control group was a drop in the hemoglobin level to below 4 g per deciliter (295 of 386 [76.4%]); 57 children (14.8%) had a new sign of clinical severity, and 7 (1.8%) received a new diagnosis of sickle cell disease. Of the 386 transfusions performed in the control group, 3 (0.8%) were performed before 48 hours and 24 (6.2%) after 48 hours in children who had a hemoglobin level of 4 to 6 g per deciliter at the last measurement and no new recorded signs of severity. Only 5 children (0.6%) in the control group who met the transfusion criteria did not receive one.

A total of 766 children (98.5%) in the immediate-transfusion group and 379 (98.2%) in the control group received their first transfusion with a volume of whole-blood equivalent that was within 3 ml per kilogram above or below their assigned transfusion volume. The first transfusion was with whole blood in 395 children (50.8%) in the immediate-transfusion group and in 218 (56.5%) in the control group. The median storage age of the blood was 12 days (interquartile range, 6 to 19) in the immediate-transfusion group and 11 days (interquartile range, 6 to 18) in the control group. A total of 748 children (96.1%) in the immediate-transfusion group and 346 (89.6%) in the control group received a single transfusion; in the first 48 hours, the maximum number of transfusions performed was four in the immediate-transfusion group and two in the control group (Table S2 in the Supplementary Appendix). During the primary hospitalization, the mean (±SD) total volume of whole-blood equivalent transfused per child was 314±228 ml in the immediate-transfusion group and 142±224 ml in the control group.

MORTALITY

Vital status was known for 1556 children (99.4%) at day 28 (primary outcome) and for 1494 children

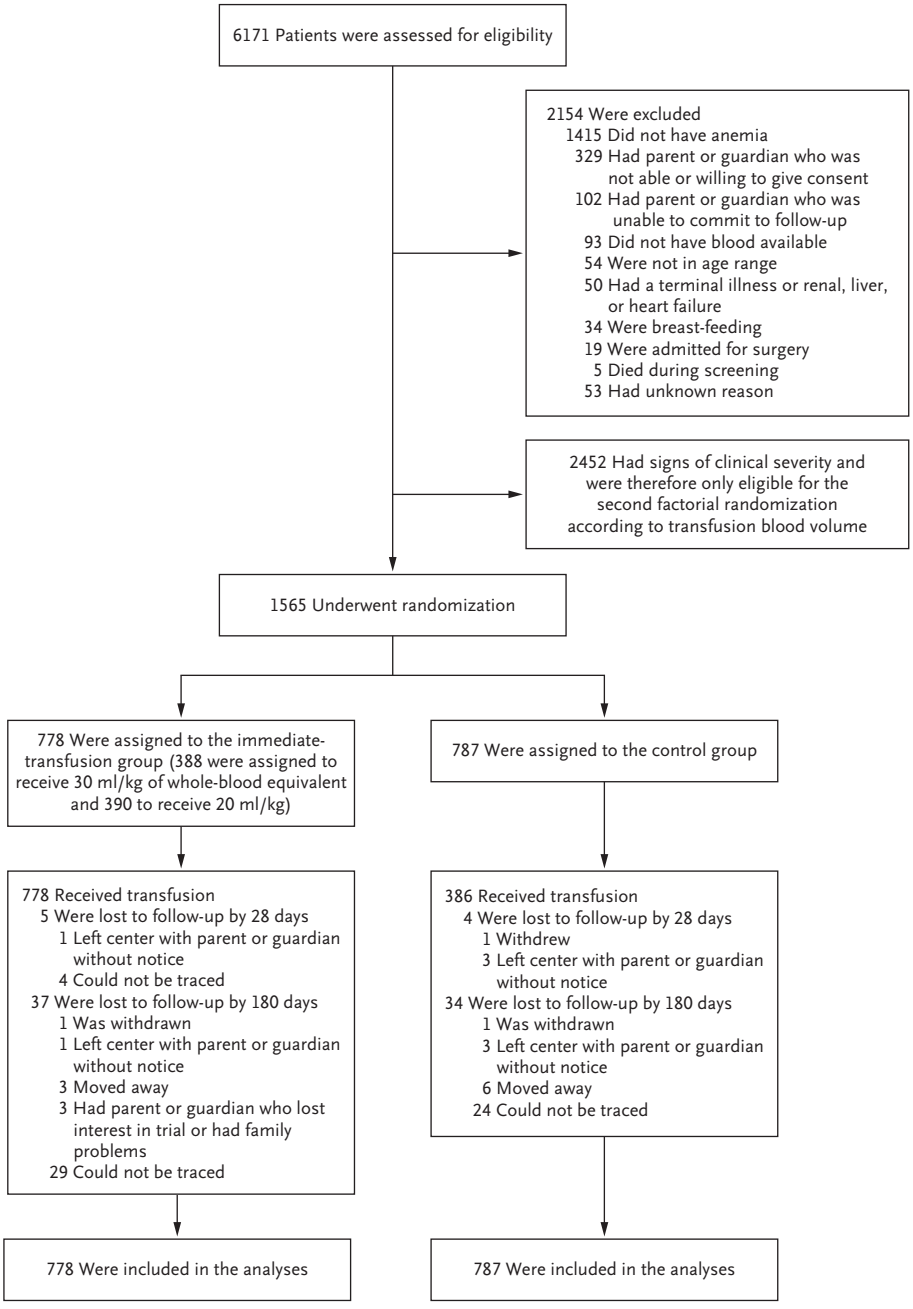

Figure 1. Screening, Randomization, and Follow-up.

In the control group (no immediate transfusion), transfusion with 20 ml of whole-blood equivalent per kilogram of body weight was triggered by the development of new signs of clinical severity, which included impaired consciousness (prostration or unconsciousness), increased difficulty in breathing (respiratory distress), hemoglobinuria (grade 6 or higher) in the current illness, or a hemoglobin level of less than 4 g per deciliter. The data regarding the children who were lost to follow-up are presented for days 0 through 28 and days 0 through 180 days (i.e., the data regarding children lost to follow-up by 28 days are a subset of the data of those lost to follow-up by 180 days). Screening did not take place on the days when there was no available blood for transfusion.

Table 1. Characteristics of the Children at Baseline.*

Characteristic	Immediate-Transfusion Group (N=778)	Control Group (N=787)	Total (N=1565)
Median age (IQR) — mo	27 (13–50)	26 (12–50)	26 (12–50)
Male sex — no. (%)	440 (56.6)	442 (56.2)	882 (56.4)
Median hemoglobin level (IQR) — g/dl	5.2 (4.5–5.7)	5.1 (4.6–5.7)	5.1 (4.6–5.7)
Median weight (IQR) — kg	10.3 (8.4–14.0)	10.5 (8.1–14.5)	10.4 (8.2–14.2)
Median circumference of mid upper arm (IQR) — cm	14.2 (13.3–15.1)	14.2 (13.4–15.5)	14.2 (13.4–15.2)
Median heart rate (IQR) — beats/min	144 (130–157)	145 (131–156)	144 (130–157)
History of fever in current illness — no. (%)	749 (96.3)	757 (96.2)	1506 (96.2)
Median axillary temperature at screening (IQR) — °C†	37.1 (36.7–37.8)	37.1 (36.6–37.8)	37.1 (36.7–37.8)
Fever — no. (%)	252 (32.4)	269 (34.2)	521 (33.3)
Hypothermia — no. (%)	27 (3.5)	25 (3.2)	52 (3.3)
Median blood pressure (IQR) — mm Hg			
Systolic	92 (85–98)	92 (85–99)	92 (85–99)
Diastolic	56 (49–63)	55 (49–63)	56 (49–63)
Median oxygen saturation (IQR) — %	98 (97–99)	98 (96–99)	98 (97–99)
Median respiratory rate (IQR) — breaths/min	38 (32–44)	38 (32–46)	38 (32–46)
Shock — no. (%)‡	100 (12.9)	112 (14.2)	212 (13.5)
Severe dehydration — no. (%)§	38 (4.9)	29 (3.7)	67 (4.3)
HIV positivity — no./total no. (%)	15/736 (2.0)	17/736 (2.3)	32/1472 (2.2)
Malaria slide or RDT positivity — no. (%)	497 (63.9)	487 (61.9)	984 (62.9)
Positive blood culture — no./total no. (%)	29/702 (4.1)	33/696 (4.7)	62/1398 (4.4)
Median C-reactive protein level (IQR) — mg/dl	54.2 (19.1–100.2)	55.8 (18.9–107.4)	54.9 (19.0–101.3)
Lactate level — mmol/liter	2.4 (1.7–3.2)	2.3 (1.7–3.2)	2.3 (1.7–3.2)
Previous blood transfusion in current illness — no. (%)	11 (1.4)	7 (0.9)	18 (1.2)
Blood transfusion ever	194 (24.9)	150 (19.1)	344 (22.0)
Sickle cell disease identified after randomization — no. (%)¶	0	7 (0.9)	7 (0.4)
Sickle cell disease identified by batch genotyping after the end of the trial — no./total no. (%)‖	172/772 (22.3)	168/777 (21.6)	340/1549 (21.9)

* There were no significant between-group differences in the baseline characteristics except for oxygen saturation (P=0.005) and blood transfusion ever (P=0.006). HIV denotes human immunodeficiency virus, IQR interquartile range, and RDT rapid diagnostic test.
† Axillary temperature was measured with a digital thermometer. Fever was defined as a temperature higher than 37.5°C, and hypothermia as a temperature lower than 36.0°C.
‡ Shock was defined as any one of the following: capillary refill time of more than 2 seconds, a lower-limb temperature gradient (a positive temperature gradient was indicated if the peripheral limb was cooler than the thigh), or weak pulse.
§ Severe dehydration was defined by skin turgor or sunken eyes.
¶ In this population of children who were hospitalized for uncomplicated severe anemia, sickle cell disease was identified in 7 children in the control group during their primary hospitalization on the basis of further questioning by the caregiver after the obtaining of consent and randomization (4 children) and after the development of clinical symptoms (3 children).
‖ The results of batch genotyping of admission blood samples after the end of the trial were missing for 16 children.

(95.5%) at day 180 (end of follow-up). By day 28, death had occurred in 7 children (0.9%) in the immediate-transfusion group (6 [0.8%] who received 20 ml and 1 [0.1%] who received 30 ml of whole-blood equivalent per kilogram) and in 13 children (1.7%) in the control group (hazard ratio, 0.54; 95% confidence interval [CI], 0.22 to 1.36; P=0.19) (Table 2 and Fig. 2A, and Fig. S2 in the Supplementary Appendix). Of the 13 children in the control group who died, 10 had received a transfusion a median of 9.0 hours (interquartile range, 6.8 to 30.6) after randomization

Table 2. Primary, Secondary, and Other Outcomes.*

Outcome	Immediate-Transfusion Group (N=778)	Control Group (N=787)	Total (N=1565)	Hazard Ratio (95% CI)†	P Value
Death — no. (%)					
At 48 hours‡	0	2 (0.3)	2 (0.1)		
At 28 days: primary outcome	7 (0.9)	13 (1.7)	20 (1.3)	0.54 (0.22–1.36)	0.19
At 90 days‡	24 (3.1)	31 (3.9)	55 (3.5)	0.78 (0.46–1.32)	
At 180 days‡	35 (4.5)	47 (6.0)	82 (5.2)	0.75 (0.48–1.15)	
Correction of anemia — no. (%)‡	399 (51.3)	43 (5.5)	442 (28.2)	11.73 (8.69–15.84)§	
Development of new profound anemia during the primary hospitalization — no. (%)‡	11 (1.4)	309 (39.3)	320 (20.4)	0.03 (0.02–0.05)§	
Development of severe anemia after discharge — no. (%)‡	106 (13.6)	142 (18.0)	248 (15.8)	0.73 (0.56–0.94)§	
Readmission to hospital — no. (%)‡	123 (15.8)	113 (14.4)	236 (15.1)	1.09 (0.84–1.40)§	
Serious adverse event‡					
At least one event — no. of patients (%)	152 (19.5)	151 (19.2)	303 (19.4)	1.02 (0.82–1.28)	0.85
No. of events	198	201	399		
Type of serious adverse event					
Anemia¶					
At least one event — no. of patients (%)	78 (10.0)	83 (10.5)	161 (10.3)		0.74‖
No. of events	97	107	204		
Malaria					
At least one event — no. of patients (%)	54 (6.9)	51 (6.5)	105 (6.7)		0.76‖
No. of events	61	56	117		
Sepsis					
At least one event — no. of patients (%)	22 (2.8)	28 (3.6)	50 (3.2)		0.47‖
No. of events	27	33	60		
Hemoglobinuria					
At least one event — no. of patients (%)	24 (3.1)	15 (1.9)	39 (2.5)		0.15‖
No. of events	27	16	43		
Suspected allergic reactions — no. (%)‡**	6 (0.8)	2 (0.3)	8 (0.5)		0.17‖
Suspected pulmonary overload, transfusion-related acute lung injury, or transfusion-related cardiac overload — no.‡	0	0	0		

* Correction of anemia was defined as hemoglobin recovery to a level greater than 9 g per deciliter during the primary hospitalization. Profound anemia was defined as a hemoglobin level of less than 4 g per deciliter. Severe anemia was defined as a hemoglobin level of less than 6 g per deciliter.
† Hazard ratios are for the immediate-transfusion group as compared with the control group. Confidence intervals have not been adjusted for multiple testing, and inferences drawn from the intervals may not be reproducible.
‡ This is a secondary outcome that was prespecified in the protocol. The P value is not reported except for adverse events.
§ This hazard ratio was estimated with the use of subhazard regression allowing for competing risks.
¶ The diagnosis of the serious adverse event of anemia (including anemia-related death) was made by the attending clinician (during the primary hospitalization and after discharge). There was no formal hemoglobin threshold required.
‖ The P value was calculated with the use of Fisher's exact test.
** The grades of suspected allergic reactions are provided in Table S6 in the Supplementary Appendix.

(Table S3 in the Supplementary Appendix). By day 180, death had occurred in 35 children (4.5%) in the immediate-transfusion group and 47 (6.0%) in the control group (hazard ratio, 0.75; 95% CI, 0.48 to 1.15). The causes of death and the results of subgroup analyses are pro-

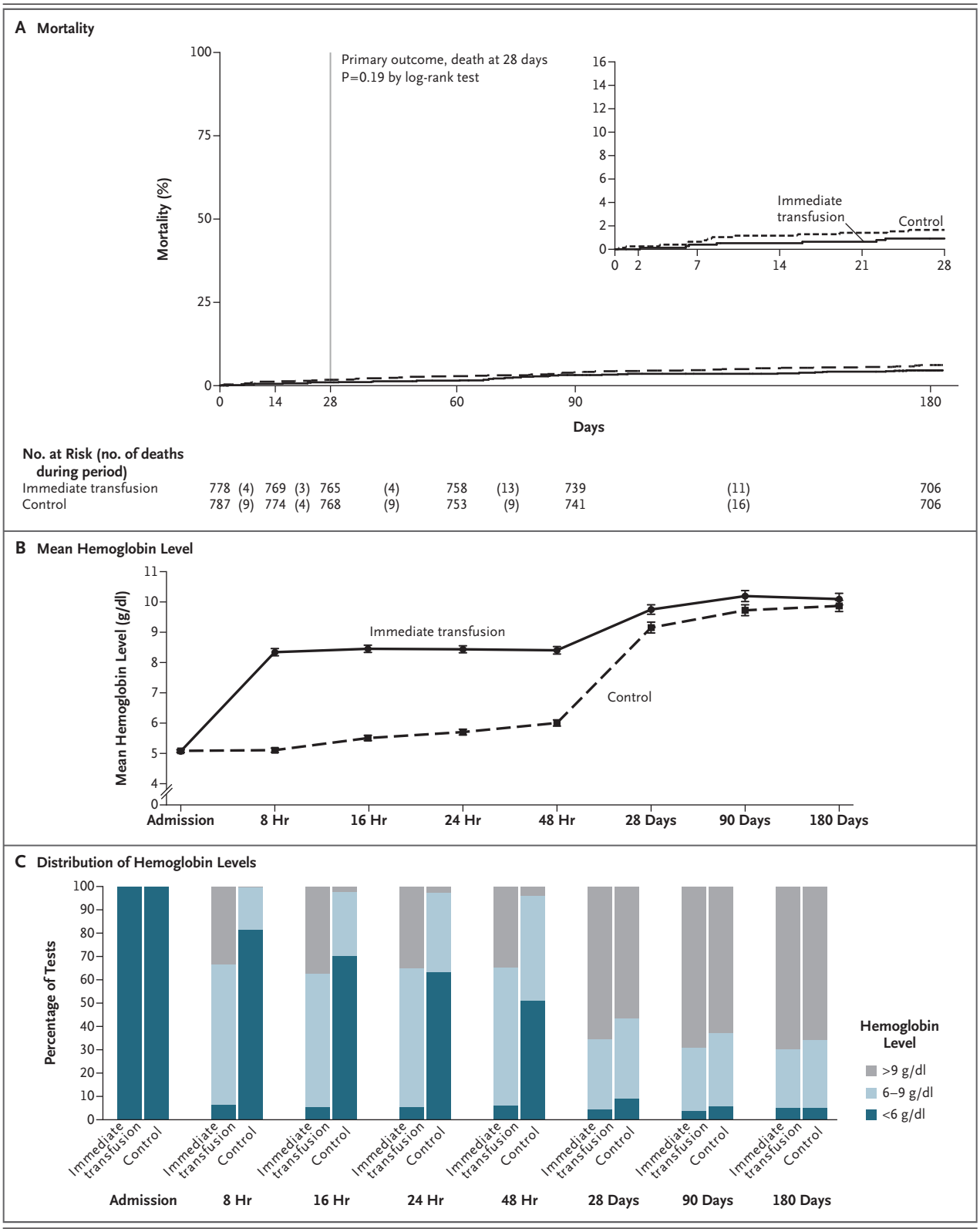
A Mortality
Primary outcome, death at 28 days
P=0.19 by log-rank test
Mortality (%)
Days
Immediate transfusion
Control
No. at Risk (no. of deaths during period)
Immediate transfusion 778 (4) 769 (3) 765 (4) 758 (13) 739 (11) 706
Control 787 (9) 774 (4) 768 (9) 753 (9) 741 (16) 706
B Mean Hemoglobin Level
Mean Hemoglobin Level (g/dl)
Immediate transfusion
Control
Admission
8 Hr
16 Hr
24 Hr
48 Hr
28 Days
90 Days
180 Days
C Distribution of Hemoglobin Levels
Percentage of Tests
Hemoglobin Level
>9 g/dl
6–9 g/dl
<6 g/dl

Figure 2 (facing page). Key Outcomes, Admission through 180 Days.

The time window for the 180-day visit was 120 to 240 days after randomization (99.3% of the children were seen after 170 days). The inset in Panel A shows the same data on an enlarged y axis. Panel B shows the mean hemoglobin level during the first 48 hours and through 180 days. Panel C shows distribution of hemoglobin levels of less than 6 g per deciliter, 6 to 9 g per deciliter, and higher than 9 g per deciliter according to the indicated time point. Additional details are provided in Table S4A and S4B in the Supplementary Appendix.

vided in the Results section in the Supplementary Appendix.

HEMOGLOBIN RECOVERY

As expected, increases in the hemoglobin level during the first 48 hours after randomization were substantially greater in the immediate-transfusion group than in the control group (Fig. 2B and 2C). At 48 hours, the mean hemoglobin level was higher by 2.42 g per deciliter (95% CI, 2.17 to 2.67) in the immediate-transfusion group than in the control group, with a mean hemoglobin level of 8.4±1.7 g per deciliter in the immediate-transfusion group, as compared with 7.0±1.7 g per deciliter among the 249 children in the control group who received a transfusion before 48 hours and 5.5±1.1 g per deciliter among the 535 children in control group who did not. In the control group, the children who received a transfusion 12 hours or more after randomization and those who received a transfusion within 12 hours had similar increases in the hemoglobin level at 48 hours (Fig. S3 in the Supplementary Appendix). During the primary hospitalization, hemoglobin recovery to a level greater than 9 g per deciliter occurred faster in the immediate-transfusion group than in the control group, and new profound anemia (hemoglobin level <4 g per deciliter) occurred less frequently in the immediate-transfusion group (Table 2, and Fig. S4 in the Supplementary Appendix). The differences in hemoglobin level between the randomization groups had attenuated substantially at 28 days (0.60 g per deciliter [95% CI, 0.35 to 0.86] higher in the immediate-transfusion group) and 90 days (0.48 g per deciliter [95% CI, 0.22 to 0.73] higher in the immediate-transfusion group). At day 180, there was no evidence of differences in the mean hemoglobin level between the two groups (0.23 g per deciliter [95% CI, −0.03 to 0.49] higher in the immediate-transfusion group) or in the percentages of children who had hemoglobin levels of 9 g per deciliter or lower or of less than 6 g per deciliter (Fig. 2B and 2C).

OTHER CLINICAL OUTCOMES

The median length of hospital stay was 3 days (interquartile range, 3 to 4) in the immediate-transfusion group and 4 days (interquartile range, 3 to 6) in the control group (hazard ratio for time to discharge, 1.62; 95% CI, 1.46 to 1.80) (Fig. S5 in the Supplementary Appendix), with a mean of 4.0 and 4.9 hospitalization days, respectively, during the primary hospitalization. By day 180, a total of 123 children (15.8%) in the immediate-transfusion group and 113 children (14.4%) in the control group had been readmitted to the hospital (hazard ratio for readmission, 1.09; 95% CI, 0.84 to 1.40) (Table 2, and Fig. S6 in the Supplementary Appendix), mostly because of anemia, malaria, or sepsis. Serious adverse events occurred in 152 children (19.5%) in the immediate-transfusion group and in 151 children (19.2%) in the control group (P=0.85) (Table 2, and Table S5 in the Supplementary Appendix). Transfusion-specific serious adverse events included non–life-threatening allergic events in 6 children in the immediate-transfusion group and 2 children in the control group (Table S6 in the Supplementary Appendix).

COSTS AND COST-EFFECTIVENESS

The main cost drivers were length of hospital stay (mean cost, $29.70 in the immediate-transfusion group and $34.30 in the control group), blood transfusions (mean cost, $22.20 and $11.78, respectively [half of children in the control group received a transfusion]), and hemoglobin tests (mean cost, $8.46 and $8.41, respectively); the total unadjusted costs per child were $72.09 in the immediate-transfusion group and $66.46 in the control group — $5.63 less in the control group (Tables S6 through S8 in the Supplementary Appendix). Sensitivity analyses suggested that the total unadjusted savings might increase to $22.80 if standard blood units (450 ml)

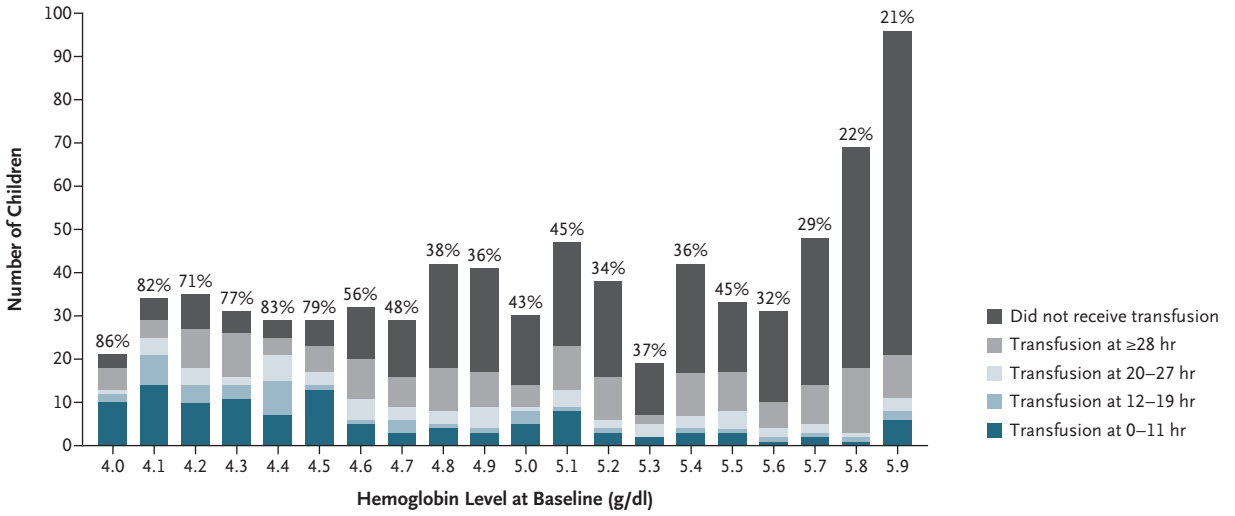

Figure 3. Transfusion Status among the Children in the Control Group, Stratified According to Baseline Hemoglobin Level.
The percentages above the bars represent the percentage of children who received a transfusion among those who had the indicated hemoglobin level at baseline.

were used, if blood costs were higher, or both. Total unadjusted costs were similar if no hemoglobin tests were performed in the immediate-transfusion group and two hemoglobin tests were performed in the control group within 48 hours from randomization (Table S10 in the Supplementary Appendix). Life-years gained over a period of 180 days were similar in the immediate-transfusion group (0.487) and the control group (0.482). Overall, the triggered-transfusion strategy used in the control group was less costly than the immediate-transfusion strategy, although the triggered-transfusion strategy was estimated to be less effective (Table S11 in the Supplementary Appendix).

PREDICTORS OF TRANSFUSION IN THE CONTROL GROUP

The time to transfusion was assessed among 776 children in the control group, with the exclusion of 11 children who were identified after randomization as having severity criteria at admission (7 had sickle cell disease [all of whom received a transfusion], and 4 had preexisting hemoglobinuria [3 of whom received a transfusion]). A total of 348 children (44.8%) received a transfusion by 96 hours. The hemoglobin level at admission was the strongest predictor (Table S12 in the Supplementary Appendix); 79.3% of the children who had a hemoglobin level of 4.5 g per deciliter or lower received a transfusion, and 35.4% of those who had a hemoglobin level higher than 4.5 g per deciliter received a transfusion (Fig. 3). Performing transfusion in all the children who had a hemoglobin level of 4.5 g per deciliter or lower (23.1% of the children in the control group) would have covered 142 (40.8%) of the triggered transfusions performed. There was no evidence that undiagnosed sickle cell disease had an effect on whether children received a transfusion. Predictors of transfusion for a hemoglobin level of less than 4 g per deciliter were similar to predictors of transfusion for any reason (data not shown).

DISCUSSION

Although mortality was too low to either show or refute any benefits from immediate transfusion, our large, multicenter trial showed that among children with uncomplicated severe anemia, the immediate-transfusion strategy resulted in fewer children who had development of profound anemia (hemoglobin level <4 g per deciliter), which is an absolute indication for transfusion, and more children who had early hemoglobin

recovery (to a level >9 g per deciliter) than the triggered-transfusion strategy. However, these findings in the immediate-transfusion group did not translate into fewer readmissions (15.1% of the children) or fewer serious adverse events related to anemia (10.3% of the children).

A key limitation of this trial was the lower overall mortality (2%) than the 9% predicted according to other studies of uncomplicated severe anemia in African children, which showed consistently higher mortality.[3,21,22] One reason may be that screening was halted when no donor blood units were available; thus, in contrast to previous reports,[8,21,22] no child in the trial died while waiting for a transfusion. Hemoglobin monitoring during the trial may have also improved outcomes. Hemovigilance detected very few adverse reactions to transfusion. Clinical and hemoglobin monitoring (every 8 hours during the first 24 hours and then at 48 hours or if triggered by clinical deterioration) identified new severity criteria that warranted transfusion in the control group, leading to 49.0% of the children in the control group receiving a potentially lifesaving transfusion (93.5% of whom received a transfusion according to the protocol), although the transfusions were performed substantially later than had they been in the immediate-transfusion group. The WHO guidelines were based largely on observational studies[7,21,22] and recommend not performing transfusion in patients with uncomplicated severe anemia. The guidelines, however, do not address either clinical or hemoglobin monitoring during hospitalization or anticipate the development of complicated severe anemia after admission. In this trial, we did not withhold transfusion in the patients in the control group who had development of complicated severe anemia, because this would be unethical and inconsistent with good clinical practice. However, our approach also may have led to lower mortality than originally hypothesized. Therefore, the control group in TRACT reflected a pragmatic strategy of conserving blood for the children who were identified after admission as being at high risk. The low mortality in the control group suggests that clinical and hemoglobin monitoring may be important in reducing poor outcomes, as compared with not performing transfusion at all. However, the trial retained good power to assess the rates of readmissions. Strategies to prevent readmissions should therefore be a key focus in future interventional trials to reduce morbidity in this high-risk group.

The guidelines that have received worldwide consensus regarding transfusion in children in stable condition in intensive care units recommend transfusion in those who have a hemoglobin level of less than 7 g per deciliter[23] but explicitly highlight the need for further trials, particularly those involving children who have a hemoglobin level of 5 to 7 g per deciliter.[7] Children in high-income countries probably have steady-state hemoglobin levels of 11 to 14 g per deciliter, whereas African children in areas where malaria and α^+-thalassemia are common[24] typically have hemoglobin levels of 9 to 11 g per deciliter.[4,25] The effect of lower thresholds for immediate transfusion in Africa may therefore reflect differences in steady-state hemoglobin levels. We cannot exclude a small mortality benefit with immediate transfusion among the children in our trial; however, 7 of the 13 deaths in the control group occurred in children who received a transfusion within 10 hours after randomization, and we found no evidence of differences in morbidity between the two groups. Given the burden of pediatric severe anemia in sub-Saharan Africa, the strategy of immediate transfusion in children with uncomplicated severe anemia has the potential to overburden the blood-transfusion services, as compared with close monitoring and targeted transfusion.

Nevertheless, the length of hospital stay was longer among the children in the control group than among those in the immediate-transfusion group, with potential implications for out-of-pocket costs for parents. Hemoglobin monitoring also uses resources (financial and staff), although at a lower rate than blood transfusion (the estimated costs were approximately $20 per blood unit vs. approximately $1 per hemoglobin test). Overall, the triggered-transfusion strategy resulted in a lower cost than the immediate-transfusion strategy but was also slightly less effective, which makes triggered transfusion with clinical and hemoglobin monitoring the cost-effective option.

An important limitation in this trial was the lack of hemoglobin measurements after 48 hours from admission and specifically at discharge.

Other limitations of this trial include the substantial uncertainty regarding the costs of blood units, which vary according to country, the size and type of blood units (Table S7 in the Supplementary Appendix),[26] and the costs of hemoglobin monitoring. Our within-trial economic analysis did not evaluate longer-term risks and benefits, which could change the value-for-money estimates. Ideally, greater efforts should be put into achieving an adequate and reliable blood supply. However, health services should consider the option of regular measurements of hemoglobin for monitoring and continuing the restrictive transfusion strategy in the WHO guidelines to avert the more substantial costs to the blood-transfusion services of providing immediate blood transfusion to all children who have a hemoglobin level of 4 to 6 g per deciliter.

The strengths of this trial include the broad eligibility criteria, which enhanced generalizability; the inclusion of a large subgroup of children with malaria; and high adherence to the assigned transfusion strategy (94%) and follow-up (>95%). The burden of hidden sickle cell disease, which was identified in 21.7% of the children with uncomplicated severe anemia after the end of this trial, should prompt universal screening of admitted children with severe anemia.[27] It is reassuring that undiagnosed sickle cell disease did not predict transfusion in the control group, which indicates that sickle cell disease without life-threatening complications can be managed without immediate transfusion.

Overall, there was no evidence of differences in clinical outcomes between the children who received immediate transfusion and those who did not. The triggered-transfusion strategy in the control group resulted in 60% lower blood use; however, the length of hospital stay was 20% longer, and this strategy required clinical and hemoglobin monitoring. Although we cannot rule out the possibility of a small mortality benefit with immediate transfusion, mortality was very low with both strategies, and immediate transfusion failed to lower the rate of readmission during the following 6 months, which remained high in both groups.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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