Transfusion Volume for Children with Severe Anemia in Africa


ABSTRACT

BACKGROUND
Severe anemia (hemoglobin level, <6 g per deciliter) is a leading cause of hospital admission and death in children in sub-Saharan Africa. The World Health Organization recommends transfusion of 20 ml of whole-blood equivalent per kilogram of body weight for anemia, regardless of hemoglobin level.

METHODS
In this factorial, open-label trial, we randomly assigned Ugandan and Malawian children 2 months to 12 years of age with a hemoglobin level of less than 6 g per deciliter and severity features (e.g., respiratory distress or reduced consciousness) to receive immediate blood transfusion with 20 ml per kilogram or 30 ml per kilogram. Three other randomized analyses investigated immediate as compared with no immediate transfusion, the administration of postdischarge micronutrients, and postdischarge prophylaxis with trimethoprim–sulfamethoxazole. The primary outcome was 28-day mortality.

RESULTS
A total of 3196 eligible children (median age, 37 months; 2050 [64.1%] with malaria) were assigned to receive a transfusion of 30 ml per kilogram (1598 children) or 20 ml per kilogram (1598 children) and were followed for 180 days. A total of 1592 children (99.6%) in the higher-volume group and 1596 (99.9%) in the lower-volume group started transfusion (median, 1.2 hours after randomization). The mean (±SD) volume of total blood transfused per child was 475±385 ml and 353±348 ml, respectively; 197 children (12.3%) and 300 children (18.8%) in the respective groups received additional transfusions. Overall, 55 children (3.4%) in the higher-volume group and 72 (4.5%) in the lower-volume group died before 28 days (hazard ratio, 0.76; 95% confidence interval [CI], 0.54 to 1.08; P = 0.12 by log-rank test). This finding masked significant heterogeneity in 28-day mortality according to the presence or absence of fever (>37.5°C at screening (P=0.001 after Sidak correction). Among the 1943 children (60.8%) without fever, mortality was lower with a transfusion volume of 30 ml per kilogram than with a volume of 20 ml per kilogram (hazard ratio, 0.43; 95% CI, 0.27 to 0.69). Among the 1253 children (39.2%) with fever, mortality was higher with 30 ml per kilogram than with 20 ml per kilogram (hazard ratio, 1.91; 95% CI, 1.04 to 3.49). There was no evidence of differences between the randomized groups in readmissions, serious adverse events, or hemoglobin recovery at 180 days.

CONCLUSIONS
Overall mortality did not differ between the two transfusion strategies. (Funded by the Medical Research Council and Department for International Development, United Kingdom; TRACT Current Controlled Trials number, ISRCTN84086586.)
Severe Anemia (Hemoglobin Level, <6 g per deciliter) is a leading cause of hospitalization and death in children in sub-Saharan Africa. The demand for blood transfusion is high, with most transfusions administered to young children and women. However, blood donation in most African countries is scarcely adequate; most countries collect fewer than 5 units per 1000 population. World Health Organization (WHO) guidelines, therefore, encourage rational blood use, recommending (on the basis of expert opinion) transfusion only for children with profound anemia (hemoglobin level, <4 g per deciliter) or life-threatening severe anemia (4 to 6 g per deciliter) and a uniform transfusion volume of 20 ml of whole blood or its equivalent per kilogram of body weight, irrespective of hemoglobin level. Outcomes remain unsatisfactory, with high reported in-hospital mortality (9 to 10%) and 6-month mortality (12%).

If standard formulae for transfusion volume are applied, the one-size-fits-all recommendation of 20 ml per kilogram appears to underestimate transfusion requirements by approximately 30%. A consensus guideline on transfusion in critically ill children noted a weak global evidence base and specifically highlighted a need to evaluate transfusion volumes and clinical outcomes. In addition to providing superior correction of anemia, higher transfusion volumes may reduce the need for second transfusions, thus saving resources and decreasing the risks associated with receiving blood from multiple donors.

The Transfusion and Treatment of Severe Anemia in African Children Trial (TRACT) investigated four interventions in African children with hemoglobin levels of less than 6 g per deciliter. Here, we report the results comparing the transfusion of 20 ml of whole-blood equivalent per kilogram with the transfusion of 30 ml per kilogram; a companion article from the trial about immediate as compared with no immediate transfusion also appears in this issue of the Journal.

**METHODS**

**TRIAL DESIGN AND OVERSIGHT**

We conducted an open-label, multicenter, factorial, randomized trial at three hospitals in Uganda and one in Malawi. Children 2 months to 12 years of age who had been admitted with severe anemia (hemoglobin level, <6 g per deciliter) were eligible to participate. Children who had known chronic disease (kidney or liver failure, malignant conditions, heart failure, or congenital heart disease) or who had already received a transfusion during the primary hospitalization and infants who had been exclusively breast-fed were children who had already received a transfusion during the primary hospitalization and infants who had been exclusively breast-fed. (For details, see the Methods section in the Supplementary Appendix, available with the full text of this article at NEJM.org.)

In the first stratum, children with complicated severe anemia (a hemoglobin level <4 g per deciliter, reduced consciousness, respiratory distress, acute hemoglobinuria, disclosed sickle cell disease, or a combination of these severity features) were randomly assigned in a 1:1 ratio to receive 30 ml of whole blood per kilogram (15 ml of packed or settled cells per kilogram) or 20 ml of whole blood per kilogram (10 ml of packed or settled cells per kilogram). In the second stratum, children with uncomplicated severe anemia (4 to 6 g per deciliter without signs of severity) were randomly assigned in a 1:1 ratio to immediate transfusion of whole-blood equivalent or no immediate transfusion (until or unless severity criteria were met). The patients in the immediate-transfusion group were then assigned, with the use of a factorial design, to receive either 30 ml per kilogram or 20 ml per kilogram. The groups that were assigned to immediate or no immediate transfusion are reported separately. Here, we do not report the results of randomized analyses of 3 months of postdischarge adjunctive micronutrient supplementation or prophylaxis with trimethoprim–sulfamethoxazole.

Ethics committees at Imperial College London, Makerere University (Kampala, Uganda), and the College of Medicine (Blantyre, Malawi) approved the protocol, which is available at NEJM.org. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol; all the authors contributed to the writing of the manuscript. There was no commercial support for the trial.

**SCREENING AND RANDOMIZATION**

Children with suspected severe anemia (severe pallor) had hemoglobin measured (with the use of a HemoCue system) and were clinically assessed for severity. Either oral assent with deferred written informed consent or written in-
formed consent from the children’s parents or guardians was obtained before randomization, which was stratified according to center and severity stratum. Details are provided in the accompanying article by Maitland et al.15 and in the Methods section in the Supplementary Appendix.

**TRIAL PROCEDURES**

General clinical management, timing of observation, and blinding are described in Maitland et al.15 Units of blood were weighed before and after transfusion and administered in burettes with volume markers to ensure an accurate volume.20 Whole-blood cells were transfused over a period of 3 to 4 hours, and packed or settled cells were transfused over a period of 2 to 3 hours. Blood was not specifically reserved for the trial; enrollment was temporarily suspended if blood became unavailable. Additional transfusions were permitted for new or persistent hemoglobin levels of less than 4 g per deciliter or severity features (see above) if the hemoglobin level remained below 6 g per deciliter. Second transfusions followed the initial randomized volume; children who continued to fulfill the trial criteria received further transfusions of 20 ml of whole-blood equivalent per kilogram.

**OUTCOMES**

The primary outcome was mortality at 28 days after randomization. Secondary outcomes were mortality at 48 hours, 90 days, and 180 days; the development of new profound anemia (hemoglobin level, <4 g per deciliter) during the primary hospitalization or development of severe anemia (<6 g per deciliter) after discharge; hospital readmission; the percentage of patients with anemia correction (>9 g per deciliter, on the basis of WHO guidelines); suspected transfusion reactions (febrile reactions and transfusion-related acute lung injury); serious adverse events; and cost and cost-effectiveness. Details are provided in the article by Maitland et al.15

**STATISTICAL ANALYSIS**

We determined that the randomization of 2977 children would provide the trial with 80% power to detect a 30% relative difference in 28-day mortality (13.7% in the group receiving 20 ml per kilogram and 9.6% in the group receiving 30 ml per kilogram), assuming that 6% of the children would be lost to follow-up by 6 months (allowing for different primary-outcome timing in other randomizations) and a two-sided alpha level of 0.013 (four comparisons across randomizations). (For details, see the Methods section in the Supplementary Appendix.) Randomized groups were compared on an intention-to-treat basis with the use of log-rank tests or competing-risks methods for time-to-event outcomes, Fisher’s exact test for binary outcomes, and generalized estimating equations for repeated measures. Confidence intervals and P values were not adjusted for multiple testing, except for unadjusted heterogeneity P values of less than 0.05 for subgroup analyses, which are reported as Sidak-adjusted values; 16 subgroup analyses were performed. For details regarding meetings of the data monitoring committee and further details of the statistical analysis, see Maitland et al.15 and the Methods section in the Supplementary Appendix.

**RESULTS**

**PARTICIPATING CHILDREN**

From September 2014 through May 2017, a total of 3199 children with hemoglobin levels of less than 6 g per deciliter were randomly assigned to receive 30 ml of whole-blood equivalent per kilogram or 20 ml of whole-blood equivalent per kilogram; consent was declined for 3 children after oral assent had been obtained, and they were excluded (Fig. 1). Of the 3196 included children, 2418 (75.7%) had a hemoglobin level of less than 4 g per deciliter or severity features; 1137 (35.6%) had two or more severity features. Baseline characteristics were balanced between the randomized groups (Table 1, and Table S1 in Figure 1 (facing page). Screening, Randomization, and Follow-up.

Severity features of anemia were a hemoglobin level of less than 4 g per deciliter, reduced consciousness, respiratory distress, acute hemoglobinuria, or disclosed sickle cell disease. Data regarding loss to follow-up are presented for 0 to 28 days and 0 to 180 days (i.e., data that were lost by 28 days are a subset of the data lost by 180 days). No screening took place on days when no blood was available for transfusion.
6171 Children were assessed for eligibility

2185 Were excluded
  1415 Did not have anemia
  329 Had parent or guardian who was unable or unwilling to give consent
  102 Had parent or guardian who was unable to commit to follow-up
  93 Did not have blood sample available
  54 Were not in age range
  50 Had terminal illness or renal, liver, or heart failure
  34 Were breast-feeding
  31 Had a severity feature, but enrollment to this part of the trial had closed
  19 Were admitted for surgery
  5 Died during eligibility screening
  53 Had unknown reason

787 Were assigned to control and were not part of this comparison

3199 Underwent randomization

1598 Were assigned to transfusion of 30 ml of whole-blood equivalent/kg of body weight

1601 Were assigned to transfusion of 20 ml of whole-blood equivalent/kg of body weight

3 Had parent or guardian who declined consent after oral assent

1598 Were included in the analysis

1592 Received transfusion
  5 Died before start of transfusion
  1 Had health form that was lost
  13 Were lost to follow-up by 28 days
  1 Was withdrawn
  5 Left center during primary hospitalization
  1 Had parent or guardian who lost interest in trial
  6 Could not be traced
  65 Were lost to follow-up by 180 days
  4 Were withdrawn
  3 Left center during primary hospitalization
  4 Had parent or guardian who lost interest in trial
  2 Had parent or guardian who became unable to bring child to the center because of social problems
  7 Moved away
  43 Could not be traced

1596 Received transfusion
  2 Died before start of transfusion
  12 Were lost to follow-up by 28 days
  3 Were withdrawn
  2 Left center during primary hospitalization
  1 Moved away
  6 Could not be traced
  65 Were lost to follow-up by 180 days
  4 Were withdrawn
  2 Left center during primary hospitalization
  3 Had parent or guardian who lost interest in trial
  9 Moved away
  47 Could not be traced

1598 Were included in the analysis
Table 1. Characteristics of the Children at Baseline.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Lower Volume:</th>
<th>Higher Volume:</th>
<th>Total:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20 ml/kg (N=1598)</td>
<td>30 ml/kg (N=1598)</td>
<td>N=3196</td>
</tr>
<tr>
<td>Median age (IQR) — mo</td>
<td>37 (18–64)</td>
<td>37 (18–63)</td>
<td>37 (18–64)</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>913 (57.1)</td>
<td>900 (56.3)</td>
<td>1813 (56.7)</td>
</tr>
<tr>
<td>Median hemoglobin (IQR) — g/dl</td>
<td>4.3 (3.4–5.2)</td>
<td>4.2 (3.3–5.2)</td>
<td>4.2 (3.4–5.2)</td>
</tr>
<tr>
<td>Median weight (IQR) — kg</td>
<td>12 (9–16)</td>
<td>12 (9.2–15.8)</td>
<td>12 (9.1–16.0)</td>
</tr>
<tr>
<td>Median heart rate (IQR) — beats/min</td>
<td>147 (131–162)</td>
<td>146 (131–161)</td>
<td>146 (131–161)</td>
</tr>
<tr>
<td>Median circumference of mid upper arm (IQR) — cm</td>
<td>14.5 (13.5–15.5)</td>
<td>14.5 (13.5–15.5)</td>
<td>14.5 (13.5–15.5)</td>
</tr>
<tr>
<td>History of fever in current illness — no. (%)</td>
<td>1540 (96.4)</td>
<td>1566 (98.0)</td>
<td>3106 (97.2)</td>
</tr>
<tr>
<td>Median axillary temperature at screening (IQR) — °C†</td>
<td>37.3 (36.7–38.0)</td>
<td>37.3 (36.7–38.0)</td>
<td>37.3 (36.7–38.0)</td>
</tr>
<tr>
<td>Fever — no. (%)</td>
<td>618 (38.7)</td>
<td>635 (39.7)</td>
<td>1253 (39.2)</td>
</tr>
<tr>
<td>Hypothermia — no. (%)</td>
<td>67 (4.2)</td>
<td>55 (3.4)</td>
<td>122 (3.8)</td>
</tr>
<tr>
<td>Median blood pressure (IQR) — mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>91 (84–98)</td>
<td>92 (83–99)</td>
<td>91 (83–99)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>54 (47–61)</td>
<td>54 (47–62)</td>
<td>54 (47–62)</td>
</tr>
<tr>
<td>Median oxygen saturation (IQR) — %</td>
<td>97 (95–99)</td>
<td>97 (95–99)</td>
<td>97 (95–99)</td>
</tr>
<tr>
<td>Median respiratory rate (IQR) — breaths/min</td>
<td>42 (33–51)</td>
<td>41 (34–52)</td>
<td>41 (34–52)</td>
</tr>
<tr>
<td>Shock — no. (%)‡</td>
<td>527 (33.0)</td>
<td>531 (33.2)</td>
<td>1058 (33.1)</td>
</tr>
<tr>
<td>Severe dehydration — no. (%)§</td>
<td>120 (7.5)</td>
<td>120 (7.5)</td>
<td>240 (7.5)</td>
</tr>
<tr>
<td>HIV positivity — no./total no. (%)</td>
<td>49/1526 (3.2)</td>
<td>49/1520 (3.2)</td>
<td>98/3046 (3.2)</td>
</tr>
<tr>
<td>Malaria slide or RDT positivity — no. (%)</td>
<td>1025 (64.1)</td>
<td>1025 (64.1)</td>
<td>2050 (64.1)</td>
</tr>
<tr>
<td>Positive blood culture — no./total no. (%)</td>
<td>54/1374 (3.9)</td>
<td>38/1377 (2.8)</td>
<td>92/2751 (3.3)</td>
</tr>
<tr>
<td>Median C-reactive protein (IQR) — mg/dl</td>
<td>61.2 (23.3–112.3)</td>
<td>62.4 (24.1–119.5)</td>
<td>61.6 (23.8–114.4)</td>
</tr>
<tr>
<td>Median lactate (IQR) — mmol/liter</td>
<td>3.0 (2–4.7)</td>
<td>2.8 (1.9–4.6)</td>
<td>2.9 (1.9–4.7)</td>
</tr>
<tr>
<td>Previous blood transfusion in current illness — no. (%)</td>
<td>32 (2.0)</td>
<td>32 (2.0)</td>
<td>64 (2.0)</td>
</tr>
<tr>
<td>Blood transfusion ever — no./total no. (%)</td>
<td>586/1583 (37.0)</td>
<td>573/1590 (36.0)</td>
<td>1159/3173 (36.5)</td>
</tr>
<tr>
<td>Severity features — no. (%)¶</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>1208 (75.6)</td>
<td>1210 (75.7)</td>
<td>2418 (75.7)</td>
</tr>
<tr>
<td>Impaired consciousness</td>
<td>373 (23.3)</td>
<td>385 (24.1)</td>
<td>758 (23.7)</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>436 (27.3)</td>
<td>424 (26.5)</td>
<td>860 (26.9)</td>
</tr>
<tr>
<td>Hemoglobinuria</td>
<td>300 (18.8)</td>
<td>290 (18.1)</td>
<td>590 (18.5)</td>
</tr>
<tr>
<td>Profound anemia</td>
<td>660 (41.3)</td>
<td>682 (42.7)</td>
<td>1342 (42.0)</td>
</tr>
<tr>
<td>Reported sickle cell disease</td>
<td>237 (14.8)</td>
<td>226 (14.1)</td>
<td>463 (14.5)</td>
</tr>
<tr>
<td>Sickle cell disease ascertained by genotyping — no./total no.</td>
<td></td>
<td>440/1579 (27.9)</td>
<td>446/1588 (28.1)</td>
</tr>
</tbody>
</table>

* There was no evidence of imbalances in baseline characteristics between the randomized groups (P≥0.06). 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 of more than 37.5°C. Hypothermia was defined as a temperature of less than 36.0°C.
‡ Shock was defined by any of the following: a capillary refill time of more than 2 seconds, temperature gradient, or weak pulse.
§ Severe dehydration was defined as decreased skin turgor, sunken eyes, or both.
¶ Profound anemia was defined as a hemoglobin level of less than 4 g per deciliter. Reported sickle cell disease was defined according to a parental statement at screening.
‖ Sickle cell disease was ascertained by the presence of hemoglobin SS in batch genotyping at Kilifi, Kenya. For detailed results, see Table S1 in the Supplementary Appendix.
but human immunodeficiency virus (HIV) in-}
 malaria was present in 2050 children (64.1%),
 lower-volume group (absolute difference, 6.4 per-
 volume group and in 300 of 1596 (18.8%) in the
 in 197 of 1592 children (12.4%) in the higher-
 talization, the mean (±SD) volume of whole-blood
 equivalent was 475±385 ml in the higher-volume
 lower-volume group. During the primary hospi-
 volume group and in 2024 of 2074 (97.6%) in the
 1841 of 1914 transfusions (96.2%) in the higher-
ard (interquartile range, 6 to 19) (Table S2 and Fig. S1
number of children with sickle cell disease increased from 463 (14.5%) (reported) to
 866 (27.7%) (actual) after batch genotyping.

**RANDOMIZED INTERVENTIONS**

A total of 1592 children (99.6%) who were as-
signed to receive 30 ml per kilogram and 1596
(99.9%) who were assigned to 20 ml per kilo-
gram started transfusion, both at a median of
1.2 hours (interquartile range, 0.9 to 1.7) after
randomization. First transfusions were within
3 ml per kilogram of the randomized volume in
1525 of 1592 children (95.8%) in the higher-
volume group and in 1551 of 1596 (97.2%) in the
lower-volume group. First transfusions were stopped for
reactions in 17 of 1592 children (1.1%) in the
higher-volume group and in 10 of 1596 (0.6%) in the
lower-volume group. First transfusions were whole blood in 700 of 1592 children (44.0%) in the
higher-volume group and in 703 of 1596 (44.0%) in the
lower-volume group; the median hemoglobin level of the donor unit was 16.4 g
per deciliter (interquartile range, 13.8 to 19.2),
and the median blood storage time was 12 days
(interquartile range, 6 to 19) (Table S2 and Fig. S1
in the Supplementary Appendix).

A further transfusion or transfusions occurred in
197 of 1592 children (12.4%) in the higher-
volume group and in 300 of 1596 (18.8%) in the
lower-volume group (absolute difference, 6.4 per-
centage points; 95% confidence interval [CI], 3.9
to 8.9) (Fig. S2 in the Supplementary Appendix);
the randomized volume strategy was followed in
1841 of 1914 transfusions (96.2%) in the higher-
volume group and in 2024 of 2074 (97.6%) in the
lower-volume group. During the primary hospi-
talization, the mean (±SD) volume of whole-blood
equivalent was 475±385 ml in the higher-volume
group and 353±348 ml in the lower-volume
group. Overall, similar numbers of units of blood
were used (mean units, 1.47±1.03 in the higher-
volume group and 1.46±1.12 in the lower-volume
group) (Table S3 in the Supplementary Appendix).

**HEMOGLOBIN RECOVERY**

The hemoglobin level increased more at 48 hours
among children receiving 30 ml per kilogram
than among those receiving 20 ml per kilogram
(mean difference, 0.99 g per deciliter; 95% CI,
0.80 to 1.18) (Fig. S3A in the Supplementary Appendix). Similarly, hemoglobin recovery to more
than 9 g per deciliter occurred faster with 30 ml
per kilogram, and a new hemoglobin level of less
than 4 g per deciliter occurred less frequently
(Table 2, and Fig. S3B through S3E in the Supple-
mental Appendix). However, from day 28
through day 180, there was no evidence of dif-
fers in hemoglobin level between the two
groups (Fig. S3A and S3B in the Supplementary
Appendix).

**MORTALITY**

Vital status at day 28 (primary outcome) was
unknown for 13 children (0.8%) assigned to
receive 30 ml per kilogram and 12 (0.8%) assigned
to receive 20 ml per kilogram and at day 180 for
65 children (4.1%) in each group. There was no
evidence of differences in mortality between the
two groups at day 28 — at which time 55 chil-
dren (3.4%) in the higher-volume group and 72
(4.5%) in the lower-volume group had died (haz-
ard ratio, 0.76; 95% CI, 0.54 to 1.08; P = 0.12 by
log-rank test) (Fig. 2A) — or at day 180 (Table 2).
There was no evidence of interaction with other
factorial randomizations to postdischarge micro-
nutrients (unadjusted P = 0.73) or trimethoprim–
sulfamethoxazole (P = 0.12) or with severity strata
(P = 0.09). No cause could be assigned in 145 of
288 deaths, primarily because these deaths oc-
curred outside the hospital or insufficient infor-
mation was available (Table S4 in the Supple-
mental Appendix). Specific infections were the
most commonly assigned primary cause of death
(in 51 children [17.7%]), followed by hematolo-
getic conditions (in 45 [15.6%]) and pneumonia
(in 22 [7.6%]).

Of the 10 subgroup analyses that were pre-
specified in the protocol and 6 additional analy-
theses that were prespecified in the statistical
analysis plan (available with the protocol at
**Table 2. Primary, Secondary, and Other Outcomes.**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Higher Volume: 30 ml/kg (N = 1598)</th>
<th>Lower Volume: 20 ml/kg (N = 1598)</th>
<th>Total (N = 3196)</th>
<th>Hazard Ratio (95% CI)†</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death — no. (%)</td>
<td>32 (2.0)</td>
<td>34 (2.1)</td>
<td>66 (2.1)</td>
<td>0.94 (0.58–1.52)</td>
<td></td>
</tr>
<tr>
<td>At 48 hr‡</td>
<td>32 (2.0)</td>
<td>34 (2.1)</td>
<td>66 (2.1)</td>
<td>0.94 (0.58–1.52)</td>
<td></td>
</tr>
<tr>
<td>At 28 days: primary outcome</td>
<td>55 (3.4)</td>
<td>72 (4.5)</td>
<td>127 (4.0)</td>
<td>0.76 (0.54–1.08)</td>
<td>0.12</td>
</tr>
<tr>
<td>At 90 days‡</td>
<td>93 (5.8)</td>
<td>114 (7.1)</td>
<td>207 (6.5)</td>
<td>0.81 (0.61–1.06)</td>
<td></td>
</tr>
<tr>
<td>At 180 days‡</td>
<td>134 (8.4)</td>
<td>154 (9.6)</td>
<td>288 (9.0)</td>
<td>0.86 (0.68–1.08)</td>
<td></td>
</tr>
<tr>
<td>Correction of anemia during the primary hospitalization — no. (%)‡</td>
<td>678 (42.4)</td>
<td>349 (21.8)</td>
<td>1027 (32.1)</td>
<td>2.13 (1.89–2.41)</td>
<td></td>
</tr>
<tr>
<td>Development of new profound anemia during the primary hospitalization — no. (%)‡</td>
<td>40 (2.5)</td>
<td>85 (5.3)</td>
<td>125 (3.9)</td>
<td>0.47 (0.32–0.68)</td>
<td></td>
</tr>
<tr>
<td>Development of severe anemia after discharge — no. (%)‡</td>
<td>338 (21.2)</td>
<td>303 (19.0)</td>
<td>641 (20.1)</td>
<td>1.10 (0.94–1.28)</td>
<td></td>
</tr>
<tr>
<td>Readmission to hospital — no. (%)‡</td>
<td>301 (18.8)</td>
<td>278 (17.4)</td>
<td>579 (18.1)</td>
<td>1.08 (0.92–1.27)</td>
<td></td>
</tr>
<tr>
<td>Serious adverse event — no. of patients (%)‡</td>
<td>431 (27.0)</td>
<td>416 (26.0)</td>
<td>847 (26.5)</td>
<td>1.03 (0.90–1.18)</td>
<td>0.63</td>
</tr>
<tr>
<td>Type of serious adverse event</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia¶</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least one event — no. of patients (%)‡</td>
<td>230 (14.4)</td>
<td>224 (14.0)</td>
<td>454 (14.2)</td>
<td>0.80</td>
<td></td>
</tr>
<tr>
<td>No. of events</td>
<td>323</td>
<td>292</td>
<td>615</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malaria</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least one event — no. of patients (%)</td>
<td>129 (8.1)</td>
<td>108 (6.8)</td>
<td>237 (7.4)</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>No. of events</td>
<td>149</td>
<td>119</td>
<td>268</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>At least one event — no. of patients (%)</td>
<td>67 (4.2)</td>
<td>78 (4.9)</td>
<td>145 (4.5)</td>
<td>0.40</td>
<td></td>
</tr>
<tr>
<td>No. of events</td>
<td>85</td>
<td>95</td>
<td>180</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobinuria</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least one event — no. of patients (%)</td>
<td>52 (3.3)</td>
<td>44 (2.8)</td>
<td>96 (3.0)</td>
<td>0.39</td>
<td></td>
</tr>
<tr>
<td>No. of events</td>
<td>64</td>
<td>51</td>
<td>115</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suspected allergic reaction — no. (%)‡**</td>
<td>25 (1.6)</td>
<td>20 (1.3)</td>
<td>45 (1.4)</td>
<td>0.55</td>
<td></td>
</tr>
<tr>
<td>Suspected transfusion-related lung injury — no. (%)‡**</td>
<td>2 (0.1)</td>
<td>3 (0.2)</td>
<td>5 (0.2)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Suspected raised intracranial pressure — no. (%)**</td>
<td>1 (0.1)</td>
<td>0 (0.0)</td>
<td>1 (&lt;0.1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Correction of anemia was defined as a hemoglobin level of more than 9 g per deciliter. 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. Suspected transfusion-related lung injury refers to suspected pulmonary overload, transfusion-related acute lung injury, or transfusion-related cardiac overload. CI denotes confidence interval.

† Hazard ratios are for the higher-volume group as compared with the lower-volume 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 from competing-risks subhazard regression.

¶ 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.

‖ This P value was calculated with Fisher’s exact test.

*** Grades of adverse events are shown in Table S9 in the Supplementary Appendix.
Figure 2. Mortality through 180 Days and at 28 Days.

The lower-volume group was assigned to receive 20 ml of whole-blood equivalent per kilogram, and the higher-volume group was assigned to receive 30 ml of whole-blood equivalent per kilogram. The window for the 180-day visit was defined as 120 to 240 days after randomization.
one (fever \(>35^\circ\text{C}\) vs. no fever at screening, prespecified in the protocol) showed substantial heterogeneity with respect to 28-day mortality (Sidak-adjusted \(P=0.001\); unadjusted \(P=0.08\) for other comparisons) (Fig. 2B, and Figs. S4 and S5 in the Supplementary Appendix). In 1943 children (60.8%) with a body temperature of 37.5°C or less at screening, 24 of 963 (2.5%) in the higher-volume group and 56 of 980 (5.7%) in the lower-volume group died by 28 days (hazard ratio, 0.43; 95% CI, 0.27 to 0.69). In contrast, in 1253 children (39.2%) with fever at screening, 31 of 635 (4.9%) in the higher-volume group and 16 of 618 (2.6%) in the lower-volume group died by 28 days (hazard ratio, 1.91; 95% CI, 1.04 to 3.49).

With respect to the actual temperature at screening (rather than the prespecified dichotomization at 37.5°C), the risk of death was high in both groups at very low and very high temperatures (Fig. 2C). However, in the higher-volume group, the risk of death dropped more quickly as the temperature increased to 37.5°C before rising substantially, which led to almost equal and opposite benefits and risks from the two strategies, depending on the temperature being above or no more than 37.5°C (Fig. 2D). As expected, there were some modest differences between children with fever and those without fever at screening in baseline characteristics (Table S5 in the Supplementary Appendix), but the receipt of other interventions was similar (Table S6 in the Supplementary Appendix). There was no evidence of heterogeneity in five additional exploratory subgroup analyses (unadjusted \(P>0.2\) for all comparisons) (Fig. S6 in the Supplementary Appendix), nor was there heterogeneity according to the temperature 30 minutes after transfusion, when other treatments (including antipyretics) were considered, higher temperatures at screening drove different treatment effects (Table S7 in the Supplementary Appendix). Heterogeneity according to the presence or absence of fever persisted even after adjustment for a weak interaction with C-reactive protein levels (see the Results section in the Supplementary Appendix).

Heterogeneity according to the presence or absence of fever was already evident in mortality at 48 hours (Sidak-adjusted \(P=0.05\)) and persisted through day 180 (Sidak-adjusted \(P=0.06\)), with no strong evidence implicating any specific cause (Fig. S7 in the Supplementary Appendix). Temperatures differed substantially between children with fever and those without fever at screening for 8 hours after randomization (Fig. S8 in the Supplementary Appendix). Recovery of hemoglobin level, heart rate, and respiratory rate occurred similarly in children with fever and those without fever (Fig. S9 in the Supplementary Appendix).

**SECONDARY CLINICAL OUTCOMES TO 180 DAYS**

Children spent a median of 4 days (interquartile range, 3 to 5) in the hospital in the two groups, but the time until discharge was shorter in the group receiving 30 ml per kilogram than in the group receiving 20 ml per kilogram (hazard ratio, 1.12; 95% CI, 1.04 to 1.20) (Fig. S10 in the Supplementary Appendix), with a mean length of stay of 4.7 days in the higher-volume group and 4.9 days in the lower-volume group. Readmission within 180 days occurred in 301 children (18.8%) in the higher-volume group and in 278 (17.4%) in the lower-volume group (hazard ratio, 1.08; 95% CI, 0.92 to 1.27) (Fig. S11 in the Supplementary Appendix), with no evidence of heterogeneity according to the presence or absence of fever at screening (unadjusted \(P=0.78\)) (Fig. S7 in the Supplementary Appendix).

One or more serious adverse events occurred in 431 children (27.0%) in the higher-volume group and in 416 (26.0%) in the lower-volume group (\(P=0.63\)) (Table 2, and Table S8 in the Supplementary Appendix), with no evidence of differences between the two groups in serious adverse events related to anemia, malaria, sepsis, or hemoglobinuria (\(P>0.15\) for all comparisons). Allergic reactions occurred in 25 children (1.6%) in the higher-volume group and in 20 (1.3%) in the lower-volume group (\(P=0.55\)); there were no fatal reactions (Table S9 in the Supplementary Appendix). Suspected pulmonary or cardiovascular serious adverse events occurred in 2 children (0.1%) in the higher-volume group and in 3 (0.2%) in the lower-volume group (\(P=1.00\)); there were 2 deaths from pulmonary or cardiovascular causes. A neurologic (grade 3) serious adverse event occurred in 1 child in the higher-volume group.

**COSTS AND COST-EFFECTIVENESS**

The main cost drivers were hospital length of stay (mean, $33.38 [U.S. dollars] in children re-
ceiving 30 ml per kilogram and $32.59 in children receiving 20 ml per kilogram), blood transfusions (mean, $25.18 and $27.26, respectively), and hemoglobin tests (mean, $8.53 and $8.46, respectively), resulting in total costs per child of $80.62 in the higher-volume group and $81.97 in the lower-volume group (Tables S10 through S12 in the Supplementary Appendix). Life-years gained over a period of 180 days were slightly higher in the group receiving 30 ml (0.473) than in the group receiving 20 ml per kilogram (0.466). Overall, a transfusion volume of 30 ml per kilogram appeared to offer additional benefits, at an increased cost of $87 per life-year gained through 180 days (adjusted model) (Table S13 in the Supplementary Appendix). However, for the subgroup without fever at screening, costs per life-year gained were reduced to $20 per life-year gained, whereas for the subgroup with fever at screening, a transfusion volume of 30 ml per kilogram was less costly but also less effective than a volume of 20 ml per kilogram. (Results of regression and sensitivity analyses are provided in the Results section in the Supplementary Appendix.)

28-DAY MORTALITY
Key predictors of death by 28 days were clinical severity features, including the Blantyre coma score and convulsions (Table 3). A lower oxygen saturation, a higher respiratory rate, and a higher lactate level were also associated with increased mortality. Malaria infection reduced the risk of death, whereas HIV infection and AB blood group increased the risk. There was no evidence of association between 28-day mortality and the characteristics of the blood used (the hemoglobin level of the donor unit, the type of blood unit transfused [hazard ratio for whole blood vs. packed or settled cells, 1.18; 95% CI, 0.78 to 1.78], or the duration of storage) or the presence of sickle cell disease. Results were broadly similar at 180 days (see the Results section and Table S14 in the Supplementary Appendix).

Table 3. Predictors of Death at 28 Days after Blood Transfusion in Children with a Hemoglobin Level of Less Than 6 g per Deciliter.

<table>
<thead>
<tr>
<th>Factor at Randomization</th>
<th>Hazard Ratio (95% CI) from Multivariable Model*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria</td>
<td>0.52 (0.34–0.78)</td>
</tr>
<tr>
<td>Higher oxygen saturation</td>
<td>0.91 (0.88–0.94)†</td>
</tr>
<tr>
<td>Higher respiratory rate</td>
<td>1.03 (1.01–1.04)‡</td>
</tr>
<tr>
<td>Higher lactate level</td>
<td>1.09 (1.04–1.15)§</td>
</tr>
<tr>
<td>HIV positivity</td>
<td>2.58 (1.32–5.05)</td>
</tr>
<tr>
<td>Convulsions in current illness</td>
<td>1.87 (1.05–3.33)</td>
</tr>
<tr>
<td>Blantyre coma score¶</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1.00</td>
</tr>
<tr>
<td>4</td>
<td>0.83 (0.31–2.17)</td>
</tr>
<tr>
<td>3</td>
<td>2.19 (0.97–4.95)</td>
</tr>
<tr>
<td>2</td>
<td>2.48 (1.22–5.05)</td>
</tr>
<tr>
<td>1</td>
<td>3.29 (0.97–12.5)</td>
</tr>
<tr>
<td>0</td>
<td>3.21 (1.04–9.89)</td>
</tr>
<tr>
<td>Blood type</td>
<td></td>
</tr>
<tr>
<td>O</td>
<td>1.00</td>
</tr>
<tr>
<td>A</td>
<td>1.03 (0.64–1.68)</td>
</tr>
<tr>
<td>B</td>
<td>0.74 (0.43–1.27)</td>
</tr>
<tr>
<td>AB</td>
<td>2.59 (1.41–4.78)</td>
</tr>
</tbody>
</table>

* Estimates were adjusted for randomized comparison, continuous variation in temperature, and the interaction between the two with the use of natural cubic splines (details in the Supplementary Appendix).
† Shown is the hazard ratio for each increment of 1% in oxygen saturation.
‡ Shown is the hazard ratio for each increment of 1 breath per minute in the respiratory rate.
§ Shown is the hazard ratio for each increment of 1 mmol per liter in the lactate level.
¶ The Blantyre coma scale is used to assess malarial coma in children. Scores range from 0 to 5, with lower scores indicating lower levels of consciousness.

Discussion
In this large, multicenter trial involving children with severe anemia, we observed no overall evidence of differences in mortality at 48 hours, 28 days, or 180 days between those receiving a transfusion volume approximately one third higher than recommended (30 ml per kilogram) and those receiving the recommended volume (20 ml per kilogram). By 48 hours, the higher-volume group had superior correction of anemia (to >9 g per deciliter), less development or redevelopment of profound anemia, and fewer additional transfusions. Nevertheless, by day 28, hemoglobin levels were similar in the two groups, and the two strategies used similar numbers of units of blood per child overall.

The overall results obscure an important and potentially unusually strong interaction with fever, which meets six of nine relevant criteria proposed to assess credibility of subgroup findings. Among the majority of children who did not have fever at admission, 28-day mortality with a transfusion volume of 30 ml per kilogram was less than half that with a transfusion volume...
of 20 ml per kilogram, a finding consistent with the hypothesis of the trial. This difference occurred soon after randomization and persisted, at a cost of $20 per life-year gained, falling well within recently published cost-effectiveness thresholds for Uganda and Malawi.22 Because 6 to 15% of children who are admitted to African hospitals have severe anemia,2,3 a transfusion strategy of 30 ml per kilogram may have substantial implications for improving outcome for the two thirds who are hospitalized with anemia but without documented fever.

Conversely, among the one third of children with fever (>37.5°C) at screening, 28-day mortality with a transfusion volume of 30 ml per kilogram was nearly twice as high as that with a transfusion volume of 20 ml per kilogram. In contrast, underlying disease (e.g., malaria and sickle cell disease) and physiological characteristics (e.g., shock, oxygen saturation, heart rate, and lactate level) did not affect differences between the two groups, nor did differences in these characteristics or in C-reactive protein levels explain the differential effect according to the presence or absence of fever. Although 97.2% of the children had a history of fever, children who were febrile at screening remained febrile through 8 hours, whereas nonfebrile children remained afebrile, which indicates that this measurement was not an isolated one.

One explanation for this finding could be the time course of intercurrent illness. Neither the length of illness nor referral from another health facility affected the response to the transfusion volume. However, in a post hoc analysis, effects of 30 ml per kilogram were strongest in children who received a transfusion within 2.5 hours after admission (Table S15 in the Supplementary Appendix). Alterations in the hemoglobin dissociation curve with fever could alter the balance between risks and benefits from 30 ml as compared with 20 ml per kilogram; however, the mechanism for harm with a higher transfusion volume in children with fever remains unclear. We are exploring several hypotheses related to infection, including altered iron metabolism. Further research is needed to understand how temperature might affect the risk–benefit ratio of transfusion volume. We observed few transfusion-related adverse events nor cases of pulmonary or cardiovascular overload with 30 ml per kilogram.

It is important that neither the use of whole blood (44% of units transfused) nor longer storage age of (non–leukocyte-reduced) donor blood adversely affected 28-day or 180-day mortality. Thus, component preparation, recently introduced to blood-transfusion services in sub-Saharan Africa at substantial cost, does not appear to be essential for safe transfusion practice.

Strengths of the trial include broad eligibility criteria, which enhance generalizability, and high adherence to the randomized strategy and follow-up (>95%). The enrollment of large subgroups of children with malaria and sickle cell disease should ensure relevance across Africa. An important limitation is that mortality was lower than anticipated, probably because of the consistent standard of care provided by trial staff and the pausing of recruitment when blood was unavailable. However, the trial retained high power to identify effects on hospital readmissions (18% by day 180). The trial was open-label, by necessity; although adherence to thresholds for retransfusion was high, we cannot rule out the possibility that knowledge of group assignment influenced retransfusion for some children. Substantial uncertainty exists regarding costs of units of blood (which vary according to country), unit size and type, and hemoglobin testing and monitoring during the hospitalization. The economic analysis does not capture longer-term mortality benefits, which could increase the cost-effectiveness (value for money) of 30 ml per kilogram in children without fever. Further implementation research is required to estimate cost savings from providing whole blood rather than packed or settled cells and to evaluate practical approaches to giving 30 ml per kilogram to children without fever and 20 ml per kilogram to children with fever in real-world settings.

In conclusion, overall mortality did not differ between the two transfusion strategies. Among afebrile children, a transfusion volume of 30 ml of whole-blood equivalent per kilogram resulted in lower mortality and lower rates of re-transfusion than current recommendations of 20 ml per kilogram. However, higher transfusion volume was associated with higher mortality among febrile children.

The views expressed are those of the authors and not necessarily those of the National Institute for Health Research or the Department of Health and Social Care.

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

We thank all the children and staff members from all the centers who participated in the trial.

APPENDIX


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