EDITORIAL

Fluid Resuscitation in Acute Illness — Time to Reappraise the Basics

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Fluid resuscitation is a fundamental intervention in the treatment of critically ill patients. However, there is little conclusive evidence to guide clinicians about the best type of resuscitation fluid; the appropriate timing, volume, and rate of fluid administration; and the optimal way to adequately monitor the efficacy and safety of fluid resuscitation in various clinical conditions.[1]

Although the complications associated with excessive volume of resuscitation fluid — such as pulmonary and interstitial edema — are well recognized, an emerging body of evidence suggests that the type of resuscitation fluid may adversely affect the outcomes in specific clinical conditions; for example, albumin is associated with increased mortality in patients with traumatic brain injury,[2] and high-molecular-weight preparations of hydroxyethyl starch are associated with acute kidney injury in patients with severe sepsis.[3]

Conversely, improved outcomes associated with the use of albumin for resuscitation have been shown in children with severe malaria[4] and in a subgroup of adults with severe sepsis in the Saline versus Albumin Fluid Evaluation study (SAFE; Current Controlled Trials number, ISRCTN76588266).[5,6] However, these reports were not sufficiently conclusive to justify the adoption of strong clinical recommendations.

The results of the Fluid Expansion as Supportive Therapy (FEAST) trial,[7] reported in this issue of the *Journal*, are an important contribution to the literature. This remarkable, pragmatic, randomized, controlled trial, conducted in six hospitals in Kenya, Tanzania, and Uganda, assessed the effects of bolus-fluid resuscitation with albumin or saline as compared with no bolus fluid in children with febrile medical illness and impaired perfusion. Children with severe hypotension, or decompensated shock, received boluses of either albumin or saline for resuscitation. The trial centers had no access to intensive care units, and the trial included a comprehensive education program aimed at optimizing early case recognition and by training in emergency pediatric life support. The primary outcome was 48-hour mortality — a relevant patient-centered outcome in regions in which the high prevalence of severe sepsis in children, often due to malaria, is associated with high early mortality.[8]

The trial was powered to determine a plausible absolute risk reduction in 48-hour mortality (as derived from power calculations described in the Methods section in the article) of 5 percentage points and was conducted with high standards of internal validity — excellent randomization procedures, a high rate of adherence to the protocol, concealment of the treatment assignments, a minimal loss to follow-up, the use of the intention-to-treat principle for the analyses, and performance of analyses according to prespecified subgroups. The sample size was appropriately increased from 2800 patients to 3600 patients after an interim analysis showed that the rate of death was lower than predicted in the intervention groups. However, the trial was stopped after the recruitment of 3141 patients when bolus-fluid resuscitation with albumin or saline was shown to increase the absolute risk of death at 48 hours by 3.3 percentage points and the risk of death, neurologic sequelae, or both at 4 weeks by 4 percentage points. No difference in mortality was observed in patients with decompensated shock, although these patients were few in number and had significantly higher mortality. The excess mortality associated with bolus-fluid resuscitation was consistent across all prespecified subgroups, which included subgroups according to age, lactate level, base deficit, presence or ab-

sence of severe anemia, and status with respect to coma and malaria.

These results will have an immediate effect on the way children presenting with febrile illness due to medical causes and with associated hypotension are treated in resource-poor settings. In conjunction with a program of education and training, discontinuation of the practice of bolus-fluid resuscitation in patients with febrile illness due to medical causes and impaired perfusion or compensated shock must be recommended. Given that 2 million children die from this condition each year in sub-Saharan Africa, the potential impact is enormous. Extrapolating these results to children with other hypotensive conditions, such as severe dehydration from gastroenteritis and malnutrition, burns, and surgery, is not justified on the basis of these data; further research would be required.

The results of the FEAST trial, as with those of other trials that generated results contrary to clinical opinion and practice,[9,10] make it imperative that we reappraise the fundamentals. Early identification of shock, basic life support, and early antimicrobial therapy remain at the forefront of the clinical care of young patients with severe infection and shock. It is highly probable that education, training, and participation in a high-quality, randomized, controlled trial itself had a substantive positive effect on the overall rate of death, although these factors were not directly assessed in this trial. However, the entrenched practice of fluid-bolus resuscitation in patients with compensated shock remains highly questionable.

We can only speculate about the mechanisms by which bolus-fluid resuscitation had adverse biologic effects in these patients. Potential mechanisms may include the interruption of genetically determined catecholamine-mediated host defense responses by the rapid increase in plasma volume, which might result in a reperfusion injury. Similarly, transient hypervolemia or hyperosmolality might exacerbate capillary leak in patients who are susceptible to intracranial hypertension[2] or pulmonary edema, with fatal consequences.

How should clinicians who work under circumstances different from those in this trial — that is, in high-income countries with access to intensive care units — or clinicians who care for adult patients interpret the results of this important trial? It seems clear that the results of this trial indicate that bolus-fluid resuscitation with either crystalloids or colloids in patients with compensated shock who do not have a clinical fluid deficit must be practiced with much greater caution than is now the case and with increased vigilance.

Fluid resuscitation is such a fundamental intervention in acute medicine that these results indicate that further high-quality research is urgently required to define appropriate practice for fluid resuscitation, including a study of the timing and rates of fluid administration and ways to monitor its effects. Similarly, a careful assessment of the safety, efficacy, and cost-effectiveness of various resuscitation fluids is mandatory before their incorporation into clinical practice.

The courage and dedication of the FEAST investigators and attending clinicians must be acknowledged, not only because of the quality of the research they conducted in this vitally important area of acute medicine, but also because they conducted a landmark trial in such challenging economic conditions in sub-Saharan Africa.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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ORIGINAL ARTICLE

Mortality after Fluid Bolus in African Children with Severe Infection

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ABSTRACT

BACKGROUND

The role of fluid resuscitation in the treatment of children with shock and life-threatening infections who live in resource-limited settings is not established.

METHODS

We randomly assigned children with severe febrile illness and impaired perfusion to receive boluses of 20 to 40 ml of 5% albumin solution (albumin-bolus group) or 0.9% saline solution (saline-bolus group) per kilogram of body weight or no bolus (control group) at the time of admission to a hospital in Uganda, Kenya, or Tanzania (stratum A); children with severe hypotension were randomly assigned to one of the bolus groups only (stratum B). Children with malnutrition or gastroenteritis were excluded. The primary end point was 48-hour mortality; secondary end points included pulmonary edema, increased intracranial pressure, and mortality or neurologic sequelae at 4 weeks.

RESULTS

The data and safety monitoring committee recommended halting recruitment after 3141 of the projected 3600 children in stratum A were enrolled. Malaria status (57% overall) and clinical severity were similar across groups. The 48-hour mortality was 10.6% (111 of 1050 children), 10.5% (110 of 1047 children), and 7.3% (76 of 1044 children) in the albumin-bolus, saline-bolus, and control groups, respectively (relative risk for saline bolus vs. control, 1.44; 95% confidence interval [CI], 1.09 to 1.90; P=0.01; relative risk for albumin bolus vs. saline bolus, 1.01; 95% CI, 0.78 to 1.29; P=0.96; and relative risk for any bolus vs. control, 1.45; 95% CI, 1.13 to 1.86; P=0.003). The 4-week mortality was 12.2%, 12.0%, and 8.7% in the three groups, respectively (P=0.004 for the comparison of bolus with control). Neurologic sequelae occurred in 2.2%, 1.9%, and 2.0% of the children in the respective groups (P=0.92), and pulmonary edema or increased intracranial pressure occurred in 2.6%, 2.2%, and 1.7% (P=0.17), respectively. In stratum B, 69% of the children (9 of 13) in the albumin-bolus group and 56% (9 of 16) in the saline-bolus group died (P=0.45). The results were consistent across centers and across subgroups according to the severity of shock and status with respect to malaria, coma, sepsis, acidosis, and severe anemia.

CONCLUSIONS

Fluid boluses significantly increased 48-hour mortality in critically ill children with impaired perfusion in these resource-limited settings in Africa. (Funded by the Medical Research Council, United Kingdom; FEAST Current Controlled Trials number, ISRCTN69856593.)

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Rapid, early fluid resuscitation in patients with shock, a therapy that is aimed at the correction of hemodynamic abnormalities, is one component of goal-driven emergency care guidelines. This approach is widely endorsed by pediatric life-support training programs, which recommend the administration of up to 60 ml of isotonic fluid per kilogram of body weight within 15 minutes after the diagnosis of shock.[1] Children who do not have an adequate response to fluid resuscitation require intensive care for inotropic and ventilatory support.[1] Substantial improvements in the outcomes of pediatric septic shock have been attributed to this approach.[2,3] Nevertheless, evidence regarding the criteria for intervention and the volume and type of fluid is lacking.[4,5]

In hospitals with poor resources in sub-Saharan Africa, in which intensive care facilities are rarely available, child-survival programs have largely ignored the role of triage and emergency care,[6] despite evidence of their cost-effectiveness.[7,8] Malaria, sepsis, and other infectious conditions cause major health burdens for children in sub-Saharan Africa[9,10] and are associated with high early mortality.[11] Hypovolemic shock (a term incorporating all degrees of impaired perfusion) is common and increases mortality substantially.[12-15] However, World Health Organization guidelines[16] recommend reserving the practice of fluid resuscitation for children with advanced shock (characterized by a delayed capillary refill time of more than 3 seconds, weak and fast pulse, and cold extremities); consequently, it is not widely practiced. Most children in hospitals in sub-Saharan Africa receive no specific fluid management apart from blood transfusion for severe anemia[17] or maintenance fluids.

The Fluid Expansion as Supportive Therapy (FEAST) study was designed to investigate the practice of early resuscitation with a saline bolus as compared with no bolus (control) and with an albumin bolus as compared with a saline bolus.

METHODS

DESIGN AND TREATMENT PROTOCOL

We conducted this two-stratum, multicenter, open, randomized, controlled study in six clinical centers in Kenya (one center), Tanzania (one center), and Uganda (four centers). In stratum A, we enrolled children without severe hypotension; children with severe hypotension (systolic blood pressure of <50 mm Hg in children younger than 12 months of age, <60 mm Hg in children 1 to 5 years of age, and <70 mm Hg in children older than 5 years of age) were enrolled in stratum B. In stratum A, eligible children were randomly assigned, in a 1:1:1 ratio, to rapid volume expansion over the course of 1 hour with 20 ml of intravenous 0.9% saline solution per kilogram (saline-bolus group), 20 ml of 5% human-albumin solution per kilogram (albumin-bolus group), or no bolus (control group). Children in stratum B were randomly assigned to receive 40 ml of albumin bolus or saline bolus per kilogram. In both strata, the saline-bolus and albumin-bolus groups, but not the control group, received an additional 20 ml of bolus solution per kilogram at 1 hour if impaired perfusion (see below) persisted. If severe hypotension developed, the child was treated with 40-ml boluses of study fluid per kilogram (saline in the case of the control group); no crossover between bolus groups was permitted. Bolus volumes and rates were conservative relative to U.S. and European guidelines[1] because we were concerned about the potential risk of pulmonary edema developing in children who were being treated in settings that lacked intensive care facilities. The initial boluses were increased to 40 ml per kilogram (60 ml per kilogram in stratum B) after a protocol amendment in June 2010. The study protocol and a detailed description of study methods are available with the full text of this article at NEJM.org.

STUDY OVERSIGHT

The ethics committees at Imperial College, London, Makerere University, Uganda, Medical Research Institute, Kenya, and National Medical Research Institute, Tanzania, approved the protocol. In cases in which prior written consent from parents or guardians could not be obtained, provision was made for oral assent from a legal surrogate, followed by delayed written informed consent as soon as practicable.

An independent data and safety monitoring committee reviewed the interim analyses from the study twice a year. The Haybittle–Peto criterion[18] was the statistical guide that the committee used in considering a recommendation to stop or modify the trial. At the fifth interim review

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of data on January 12, 2011, with data available from 2995 children, the independent data and safety monitoring committee recommended stopping enrollment owing to safety concerns in the saline-bolus and albumin-bolus groups and because it was very unlikely that superiority of the bolus strategy over the control strategy would be shown.

ROLE OF THE FUNDING SOURCES

The study was funded by the Medical Research Council, United Kingdom; Baxter Healthcare donated the 5% albumin and 0.9% saline solutions. Neither of those bodies, nor Imperial College, London, which held the legal responsibility for the trial, had any role in the design of the study, the collection, analysis, or interpretation of the data, or the writing of the manuscript. The corresponding author had full access to all trial data and assumes final responsibility for the decision to submit the manuscript for publication.

STUDY POPULATION

Children were eligible for inclusion in the study if they were between 60 days and 12 years of age and presented with a severe febrile illness complicated by impaired consciousness (prostration or coma), respiratory distress (increased work of breathing), or both, and with impaired perfusion, as evidenced by one or more of the following: a capillary refill time of 3 or more seconds, lower-limb temperature gradient,[19] weak radial-pulse volume, or severe tachycardia (>180 beats per minute in children younger than 12 months of age, >160 beats per minute in children 1 to 5 years of age, or >140 beats per minute in children older than 5 years of age) (Fig. 1). Exclusion criteria were severe malnutrition, gastroenteritis, noninfectious causes of shock (e.g., trauma, surgery, or burns), and conditions for which volume expansion is contraindicated.

END POINTS

The primary end point was mortality at 48 hours after randomization. Secondary end points were mortality at 4 weeks, neurologic sequelae at 4 and 24 weeks, episodes of hypotensive shock within 48 hours after randomization, and adverse events potentially related to fluid resuscitation (pulmonary edema, increased intracranial pressure, and severe allergic reaction). An end-point review committee, whose members were unaware of the treatment assignments, reviewed all deaths, neurologic sequelae, and adverse events.

RANDOMIZATION

Randomization was performed in permuted blocks of random sizes and was stratified according to clinical center. The trial statistician at the Medical Research Council Clinical Trials Unit, London, generated and kept all the randomization schedules. The schedule for each center contained a list of trial numbers and the randomly assigned intervention. Trial numbers were kept inside opaque, sealed envelopes, which were numbered consecutively and opened in numerical order by a study clinician.

STUDY PROCEDURES

Children were treated on general pediatric wards; assisted ventilation other than short-term bag-and-mask support was unavailable. Training in triage and emergency pediatric life support was given to participating providers throughout the trial to optimize case recognition, supportive management, and adherence to the protocol. Basic infrastructural support was provided for emergency care and for the monitoring of patients' oxygen saturation and blood pressure, which was measured with the use of an automated blood-pressure monitor. Children received intravenous maintenance fluids (2.5 to 4.0 ml per kilogram per hour); antibiotics; antimalarial, antipyretic, and anticonvulsant drugs; treatment for hypoglycemia (if the blood glucose was <2.5 mmol per liter [45 mg per deciliter]); and transfusion with 20 ml of whole blood per kilogram over the course of 4 hours if the hemoglobin level was less than 5 g per deciliter, according to national guidelines.

A structured clinical case-report form was completed at admission and at 1, 4, 8, 24, and 48 hours. Hypovolemia, neurologic and cardiorespiratory status, and adverse events — particularly suspected pulmonary edema, increased intracranial pressure, and allergic reaction — were recorded. Adverse events were reported to the Clinical Trials Facility in Kilifi, Kenya, within 2 days and were verified against source documents by visiting monitors. At 4 weeks, assessments of neurologic sequelae were performed, and these were reviewed by an independent clinician, who was unaware of the treatment as-

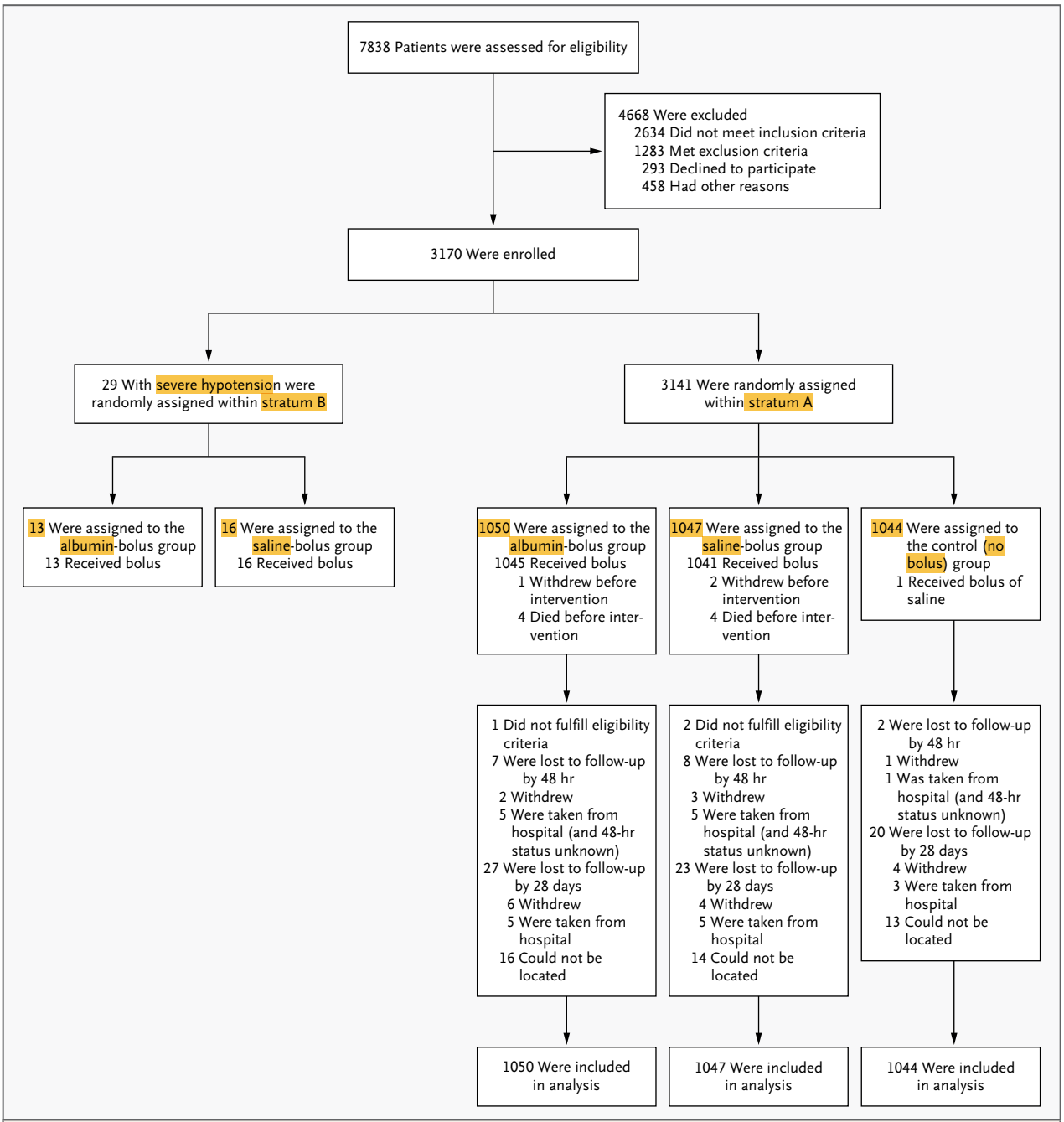

Figure 1. Screening, Randomization, and Follow-up.

Of the 4668 children excluded after initial assessment for eligibility, 2634 with severe illness did not meet the inclusion criteria because they did not have at least one of the following: impaired perfusion, impaired consciousness, fever, or respiratory distress. A total of 1283 children met exclusion criteria because they had evidence of severe acute malnutrition, defined as visible severe wasting or kwashiorkor (254 children); gastroenteritis (792); chronic renal failure, pulmonary edema, or other conditions in which volume expansion is contraindicated (90); or noninfectious causes of severe illness (68); or because they had already received isotonic volume resuscitation (79). In addition, 458 children were not enrolled in the trial because they were unable to return for follow-up assessments (111 children), were enrolled in a different study (65), had been previously enrolled in the FEAST trial (17), or died before enrollment (11); because no fluid or blood or trial packs were available (47); or because of other reasons (181). The reason for noneligibility was missing in the case of 26 children. During the intervention period, among children in stratum A, 1 child in the albumin-bolus group did not fulfill the eligibility criteria because the child had no fever or history of fever, and 2 children in the saline-bolus group did not fulfill the eligibility criteria, one because the child had severe hypotension and the other because the child did not have impaired perfusion.

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signments. Children with neurologic sequelae at 4 weeks were reassessed at 24 weeks.

STATISTICAL ANALYSIS

The protocol specified two primary comparisons (saline bolus vs. control, and albumin bolus vs. saline bolus) with respect to the risk of death from any cause by 48 hours. In stratum A, the initial sample size of 2800 assumed a risk of death of 15% in the control group[12]; however, through a protocol amendment in June 2010, the sample size was increased to 3600 because the risk of death in the combined groups was lower than anticipated. We estimated that with a sample size of 3600 children, the study would have 80% power to detect a 33% relative reduction in mortality with a saline bolus as compared with the control group and a 40% reduction with an albumin bolus as compared with a saline bolus, assuming a risk of death of 11% in the control group, at a two-sided alpha level of 0.05, adjusted for two comparisons with the use of a nominal alpha of 0.025.

All the analyses were performed according to the intention-to-treat principle, and all the statistical tests were two-sided. The three treatment groups were compared with respect to the primary end point (48-hour mortality) with the use of the chi-square test, and the relative difference among the groups was estimated by a calculation of the relative risk (the ratio of the proportion of children who died by 48 hours), adjusted for stratification according to clinical center and randomization date (before or after the protocol amendment) with the use of a Mantel–Haenszel type of adjustment.[20] Kaplan–Meier plots show the time to death according to treatment group during the first 48 hours. The few children whose vital status was unknown (because of withdrawal of consent or loss to follow-up) were assumed to be alive at the end of the study. The same methods were used for the prespecified secondary comparisons, including pairwise comparisons of the risk of death or neurologic sequelae by 4 weeks and comparisons of bolus therapy (combined albumin bolus and saline bolus) with control (no bolus) with respect to the risk of death at 48 hours and the risk of neurologic sequelae or death by 4 weeks. Comparisons among the three groups with respect to the primary end point were also summarized for predefined subgroups according to coma status, positive or negative status for malaria, presence or absence of severe anemia (hemoglobin level <5 g per deciliter vs. ≥5 g per deciliter), age, sex, base deficit (≥8 mmol per liter vs. <8 mmol per liter), lactate level (≥5 mmol per liter vs. <5 mmol per liter), and date of randomization (before or after the protocol amendment).

RESULTS

STUDY PATIENTS

In stratum A, 3141 children were randomly assigned from January 13, 2009, through January 13, 2011 — 1050 to the albumin-bolus group, 1047 to the saline-bolus group, and 1044 to the control group. Three children who did not meet the eligibility criteria were included in all the analyses (Fig. 1). The baseline characteristics of the children were similar across the groups (Table 1). The median age was 24 months (interquartile range, 13 to 38); 62% had prostration, 15% were comatose, and 83% had respiratory distress. The majority of children (52%) had more than one feature of impaired perfusion, most commonly severe tachycardia and cold extremities. Moderate-to-severe acidosis was present in 51% of the children (1070 of 2079) and severe lactic acidosis (lactate ≥5 mmol per liter) in 39% (1159 of 2981). The mean (±SD) hemoglobin level was 7.1±3.2 g per deciliter, and the glucose was 6.9±3.9 mmol per liter (124±70 mg per deciliter). Malaria was confirmed in 57% of the children (1793 of 3123), and 4% (106 of 2483) were positive for human immunodeficiency virus infection. Only 17 children (0.5%) were lost to follow-up for the primary end point — 7 in the albumin-bolus group, 8 in the saline-bolus group, and 2 in the control group. Vital status at 4 weeks was ascertained in 97% (1023 of 1050), 98% (1024 of 1047), and 98% (1024 of 1044) of the children in the three groups, respectively. A total of 29 children were enrolled in stratum B. The median systolic blood pressure was 57 mm Hg (interquartile range, 51 to 59) (Table 1 in the Supplementary Appendix, available at NEJM.org); no children in stratum B were lost to follow-up. In both strata, working diagnoses were reported by a clinician at 48 hours (Table 2 in the Supplementary Appendix).

ADMINISTERED FLUIDS

A total of 99.5% of the children in the albumin-bolus group (1045 of 1050 children) and 99.4% of the children in the saline-bolus group (1041 of 1047) received the treatment to which they had been randomly assigned (Fig. 1). One child in the

control group received a saline bolus in the first hour (owing to hypotension). The median volumes of all fluids (including blood) received during the first and second hours were 20.0 ml per kilogram (interquartile range, 20.0 to 20.0) and 4.5 ml per kilogram (interquartile range, 1.7 to 16.2), respectively, in the albumin-bolus group; 20.0 ml per kilogram (interquartile range, 20.0 to 20.0) and 5.0 ml per kilogram (interquartile range, 1.7 to 16.0), respectively, in the saline-bolus group; and 1.2 ml per kilogram (interquartile range, 0 to 2.5) and 2.9 ml per kilogram (interquartile range, 0.2 to 4.2), respectively, in the control group. Over the course of 8 hours, the median cumulative volume of fluid received was 40.0 ml per kilogram (interquartile range, 30.0 to 50.0) in the albumin-bolus group, 40.0 ml per kilogram (interquartile range, 30.4 to 50.0) in the saline-bolus group, and 10.1 ml per kilogram (interquartile range, 10.0 to 25.9) in the control group. A total of 1408 children received blood transfusions — 472 (45%) in the albumin-bolus

Table 1. Baseline Characteristics of the Children.*

Variable	Albumin Bolus (N=1050)	Saline Bolus (N=1047)	No Bolus (N=1044)	Total (N=3141)
Demographic and anthropometric characteristics				
Age — mo				
Median	23	23	25	24
Interquartile range	14–37	13–37	14–40	13–38
Female sex — no. (%)	474 (45)	480 (46)	498 (48)	1452 (46)
Mid-upper-arm circumference ≤11.5 cm — no./total no. (%)	21/982 (2)	24/974 (2)	25/1003 (2)	70/2959 (2)
Findings at presentation				
Axillary temperature >39°C — no. (%)	243 (23)	236 (23)	264 (25)	743 (24)
Hypothermia (temperature <36°C) — no. (%)	59 (6)	64 (6)	66 (6)	189 (6)
Respiratory distress — no./total no. (%)	874/1048 (83)	854/1045 (82)	857/1037 (83)	2585/3130 (83)
Respiratory rate — breaths/min	58±15	58±15	57±15	58±15
Oxygen saturation <90% — no. (%)†	249/1015 (25)	253/1008 (25)	257/1015 (25)	759/3038 (25)
Bradycardia (<80 beats/min) — no. (%)	13 (1)	7 (1)	10 (1)	30 (1)
Severe tachycardia — no. (%)	736 (70)	721 (69)	738 (71)	2195 (70)
Weak radial pulse — no. (%)	210 (20)	238 (23)	206 (20)	654 (21)
Capillary refill time — no. (%)				
≥2 sec	712 (68)	720 (69)	673 (64)	2105 (67)
≥3 sec	263 (25)	299 (29)	257 (25)	819 (26)
Positive temperature gradient — no. (%)‡	620 (59)	629 (60)	610 (58)	1859 (59)
Systolic blood pressure — mm Hg				
Median	92	93	92	93
Interquartile range	85–101	85–101	86–101	85–101
Moderate hypotension — no./total no. (%)§	66/1030 (6)	69/1036 (7)	57/1034 (6)	192/3100 (6)
Dehydration — no. (%)¶	78 (7)	95 (9)	58 (6)	231 (7)
Severe pallor manifested in lips, gums, or inner eyelids — no. (%)	523 (50)	546 (52)	520 (50)	1589 (51)
Prostration — no./total no. (%)‖	655/1048 (62)	667/1046 (64)	619/1044 (59)	1941/3138 (62)
Coma — no. (%)**	156 (15)	161 (15)	140 (13)	457 (15)
Convulsions during this illness — no./total no. (%)	414/1047 (40)	387/1045 (37)	371/1039 (36)	1172/3131 (37)
Hemoglobinuria (dark urine) — no. (%)	122 (12)	123 (12)	144 (14)	389 (12)
Jaundice visible to clinician — no. (%)	336 (32)	336 (32)	330 (32)	1002 (32)

Table 1. (Continued.)

Variable	Albumin Bolus (N=1050)	Saline Bolus (N=1047)	No Bolus (N=1044)	Total (N=3141)
Laboratory assessments††				
Positive for malaria parasitemia — no./total no. (%)‡‡	590/1044 (57)	612/1042 (59)	591/1037 (57)	1793/3123 (57)
Hemoglobin — no./total no. (%)				
<5 g/dl	323/1024 (32)	332/1015 (33)	332/1015 (33)	987/3054 (32)
>10 g/dl	231/1024 (23)	230/1015 (23)	244/1015 (24)	705/3054 (23)
Glucose — no./total no. (%)				
<2.5 mmol/liter (45 mg/dl)	43/990 (4)	46/991 (5)	42/989 (4)	131/2970 (4)
<3.0 mmol/liter (54 mg/dl)	67/990 (7)	61/991 (6)	59/989 (6)	187/2970 (6)
Lactate ≥5 mmol/liter — no./total no. (%)	357/1000 (36)	407/989 (41)	395/992 (40)	1159/2981(39)
Base deficit ≥8 mmol/liter — no./total no. (%)	380/710 (54)	360/689 (52)	330/680 (49)	1070/2079 (51)
Severe acidemia (pH <7.2) — no./total no. (%)	71/712 (10)	73/694 (11)	65/685 (9)	209/2091 (10)
Hyperkalemia (potassium >6.5 mmol/liter) — no./total no. (%)	67/686 (10)	68/687 (10)	65/670 (10)	200/2043 (10)
Positive for HIV antibody — no./total no. (%)	37/817 (5)	28/827 (3)	41/839 (5)	106/2483 (4)
Positive blood culture — no. of positive cultures/total no. of cultures (%)	38/347 (11)	52/360 (14)	36/363 (10)	126/1070 (12)
Positive cerebrospinal fluid culture — no. of positive cultures/total no. of cultures (%)	2/94 (2)	4/102 (4)	4/96 (4)	10/292 (3)

* Plus–minus values are mean ±SD. HIV denotes human immunodeficiency virus.
† Oxygen saturation and pulse rate were recorded by a pulse oximeter.
‡ The temperature gradient was assessed by running the back of hand from the toe to the knee; a positive temperature gradient was defined as a notable temperature change from cold (dorsum of foot) to warm (knee).
§ Moderate hypotension was defined as a systolic blood pressure of 50 to 75 mm Hg in children younger than 12 months of age, 60 to 75 mm Hg in children 12 months to 5 years of age, and 70 to 85 mm Hg in children older than 5 years of age, as measured with the use of an automated blood-pressure monitor.
¶ Dehydration was identified by the presence of sunken eyes or decreased skin turgor.
‖ Prostration was defined as the inability of a child older than 8 months of age to sit upright or the inability of a child 8 months of age or younger to breast-feed.
** Coma was defined as the inability to localize a painful stimulus.
†† Venous blood samples were obtained at admission for immediate analyses of pH level and potassium level with the use of a handheld blood analyzer (i-STAT, Abbott Laboratories); measurement of hemoglobin (HemoCue), blood glucose, and lactate levels; and HIV antibody testing. Denominators vary because data for some children were not available. Blood smears to test for malaria parasites were prepared for immediate reading and subsequent quality control. Blood cultures at admission were obtained at certain centers only.
‡‡ The parasite that was identified was *Plasmodium falciparum* in every case except four: three in which *P. vivax* was identified and one in which *P. ovale* was identified.

group, 487 (47%) in the saline-bolus group, and 449 (43%) in the control group. Transfusion was initiated marginally earlier in the control group, but by 2 hours the proportion of children who received transfusions and the volumes of blood received were similar across all groups (Fig. 1 and Table 3 in the Supplementary Appendix).

END POINTS

By 48 hours, 111 of the children in the albumin-bolus group (10.6%), 110 children in the saline-bolus group (10.5%), and 76 children in the control group (7.3%) had died. The relative risk of death with a saline bolus versus no bolus was 1.44 (95% confidence interval [CI], 1.09 to 1.90; P=0.01); the relative risk of death with an albumin bolus versus a saline bolus was 1.00 (95% CI, 0.78 to 1.29; P=0.96); and the relative risk of death with bolus therapy (combined albumin bolus and saline bolus) versus no bolus was 1.45 (95% CI, 1.13 to 1.86; P=0.003) (Table 2); the absolute difference in risk was 3.3 percentage points (95% CI, 1.2 to 5.3). There was no evidence of heterogeneity according to center (Fig. 2 in the Supplementary Appendix) or date of randomization before or after the protocol amendment (Fig. 2). In stratum B, 9 of 13 children in the albumin-bolus group (69%) and 9 of 16 in the saline-bolus group (56%) died (relative risk with albumin bolus, 1.23; 95% CI, 0.70 to 2.16; P=0.45).

Table 2. Death and Other Adverse Event End Points at 48 Hours and 4 Weeks.

End Point	Albumin Bolus (N=1050)	Saline Bolus (N=1047)	No Bolus (N=1044)	Saline Bolus vs. No Bolus		Albumin Bolus vs. No Bolus		Albumin Bolus vs. Saline Bolus		Albumin and Saline Boluses vs. No Bolus	
				Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
		no. (%)									
48 Hours											
Death — no. (%)	111 (10.6)	110 (10.5)	76 (7.3)	1.44 (1.09–1.90)	0.01	1.45 (1.10–1.92)	0.008	1.00 (0.78–1.29)	0.96	1.45 (1.13–1.86)	0.003
Pulmonary edema — no. (%)	14 (1.3)	6 (0.6)	6 (0.6)								
Increased intracranial pressure — no. (%)	16 (1.5)	18 (1.7)	11 (1.1)								
Severe hypotension — no. (%)*	1 (0.1)	2 (0.2)	3 (0.3)								
Allergic reaction — no. (%)	3 (0.3)	4 (0.4)	2 (0.2)								
Pulmonary edema, increased intracranial pressure, or both — no. (%)†	27 (2.6)	23 (2.2)	17 (1.6)	1.34 (0.72–2.51)	0.34	1.57 (0.87–2.88)	0.10	1.17 (0.68–2.03)	0.49	1.46 (0.85–2.53)	0.17
4 Weeks											
Death — no. (%)	128 (12.2)	126 (12.0)	91 (8.7)	1.38 (1.07–1.78)	0.01	1.40 (1.08–1.80)	0.01	1.01 (0.80–1.28)	0.91	1.39 (1.11–1.74)	0.004
Neurologic sequelae — no./total no. (%)‡	22/990 (2.2)	19/996 (1.9)	20/997 (2.0)	0.95 (0.51–1.77)	0.87	1.10 (0.61–2.01)	0.74	1.16 (0.63–2.14)	0.62	1.03 (0.61–1.75)	0.92
Neurologic sequelae or death — no./total no. (%)‡	150/990 (15.2)	145/996 (14.6)	111/997 (11.1)	1.31 (1.04–1.65)	0.02	1.36 (1.08–1.71)	0.008	1.04 (0.84–1.28)	0.71	1.33 (1.09–1.64)	0.005

* Severe hypotension was defined as a systolic blood pressure of less than 50 mm Hg in children younger than 12 months of age, less than 60 mm Hg in children 1 to 5 years of age, and less than 70 mm Hg in children older than 5 years of age, plus one or more features of impaired perfusion.
† Four children — three in the albumin-bolus group and one in the saline-bolus group — had both increased intracranial pressure and pulmonary edema.
‡ A total of 60 children in the albumin-bolus group, 51 in the saline-bolus group, and 47 in the control group did not have a neurologic assessment at 4 weeks.

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The risk of death 1 hour after randomization was similar in the three groups (1.2% in the albumin-bolus group, 1.1% in the saline-bolus group, and 1.3% in the control group). Beyond 1 hour, there was a persistent trend to higher mortality in the bolus groups as compared with the control group (Fig. 2A). Most deaths occurred before 24 hours (259 deaths, 87%). Only a small number of deaths occurred after 48 hours, and there was no evidence that children in the control group had excess delayed mortality (Fig. 2B). The excess mortality associated with the bolus groups as compared with the control group was consistent across all prespecified subgroups (Fig. 3), and there was no evidence supporting a benefit from bolus fluid infusion in any subgroup. At 4 weeks, neurologic sequelae were noted in 22 children (2.2%) in the albumin-bolus group, 19 (1.9%) in the saline-bolus group, and 20 (2.0%) in the control group ($P=0.92$ for bolus vs. control) (Table 2). The 24-week follow-up assessment is ongoing.

Suspected pulmonary edema occurred in 26 children (14 in the albumin-bolus group, 6 in the saline-bolus group, and 6 in the control group) and increased intracranial pressure in 45 children (16 in the albumin-bolus group, 18 in the saline-bolus group, and 11 in the control group) ($P=0.17$ for the comparison of bolus with control with respect to combined pulmonary edema and increased intracranial pressure) (Table 2). Details of the review of deaths and targeted adverse events by the end-point review committee are provided in Tables 4A and 4B in the Supplementary Appendix.

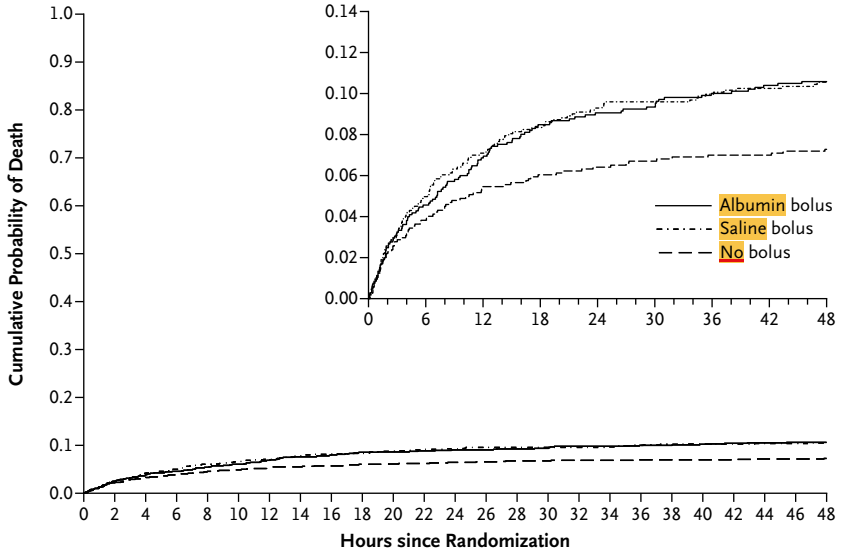
DISCUSSION

We evaluated the effect of resuscitation with bolus fluids in children who presented to the hospital with severe febrile illness and impaired perfusion, in order to generate practical data for resource-poor settings in sub-Saharan Africa in which malaria is endemic. Bolus-fluid resuscitation with either albumin or saline, as compared with control, increased the absolute risk of death at 48 hours by 3.3 percentage points and the risk of death, neurologic sequelae, or both at 4 weeks by nearly 4 percentage points. There was no evidence of a difference in either primary or secondary end points between the albumin-bolus and saline-bolus groups. Most deaths (87%) occurred before 24 hours; however, the predicted severe adverse effects of fluid overload (pulmonary edema or increased intracranial pressure) developed in few children. Our findings appear to be robust owing to the large number of children enrolled, the multinational nature of the sample, the small loss to follow-up, the concealment of treatment assignments, and the high rate of adherence to the assigned treatment. The results do not support the routine use of bolus resuscitation in severely ill febrile children with impaired perfusion in African hospitals and also raise questions about its use in other settings.

Our large, controlled trial of fluid resuscitation applied an international standard of practice (bolus-fluid resuscitation) and compared it with the local standard of care (no bolus-fluid resuscitation). It was conducted in typical African hospitals, which have no intensive care facilities. The inclusion criteria were broad, but children with gastroenteritis, severe malnutrition, or noninfectious causes of shock were excluded, so results cannot be extrapolated to those groups. Few children were recruited to stratum B, which was reserved for children with severe hypotension, in whom randomization to a control group was considered to be unethical, and mortality was high in both bolus groups in that stratum.

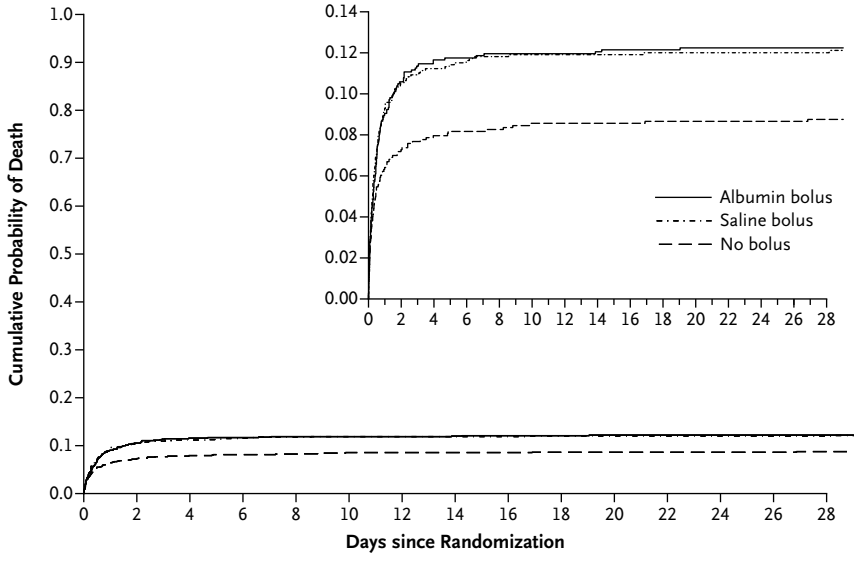
Clinical differentiation of major causes of severe illness in sub-Saharan Africa — in particular, severe malaria, sepsis, pneumonia, and meningitis — is not possible at the time of admission to the hospital.[21,22] However, recommendations regarding fluid resuscitation differ substantially among these conditions,[16] and the practice of fluid resuscitation remains highly controversial in children with severe malaria.[23-25] By including in our study children with these critical illnesses, our trial offered an efficient means of providing practical information for hospitals that have few diagnostic facilities. Mortality was lower than expected and than previously reported.[12,14,22] Consistent with other studies,[22,26] mortality was lower in children with severe malaria than in the subgroup without malaria, but there was no evidence that the increase in 48-hour mortality associated with boluses differed between the two subgroups. Although fluid boluses adversely affected the outcome, important survival gains, across all the groups, may have resulted from training and implementation of triage, basic life-support measures, and regular observation.

A Mortality at 48 Hours



	Hr 1			Hr 2			Hr 3			Hr 4			Hr 5–8			Hr 9–24			Hr 24–48		
	Albumin bolus	Saline bolus	No bolus	Albumin bolus	Saline bolus	No bolus	Albumin bolus	Saline bolus	No bolus	Albumin bolus	Saline bolus	No bolus	Albumin bolus	Saline bolus	No bolus	Albumin bolus	Saline bolus	No bolus	Albumin bolus	Saline bolus	No bolus
No. at Risk	1050	1047	1044	1037	1033	1030	1024	1018	1021	1016	1010	1015	1010	1001	1011	992	980	996	954	945	975
Died	13	12	14	13	15	9	8	7	6	6	9	4	17	20	14	38	34	20	16	13	9
%	1.2	1.1	1.3	1.3	1.5	0.9	0.8	0.7	0.6	0.6	0.9	0.4	1.7	2.0	1.4	3.8	3.5	2.0	1.7	1.4	0.9

B Mortality at 4 Weeks



	Day 1			Day 2			Day 3–7			Day 8–14			Day 15–21			Day 21–28		
	Albumin bolus	Saline bolus	No bolus	Albumin bolus	Saline bolus	No bolus	Albumin bolus	Saline bolus	No bolus	Albumin bolus	Saline bolus	No bolus	Albumin bolus	Saline bolus	No bolus	Albumin bolus	Saline bolus	No bolus
No. at Risk	1050	1047	1044	954	945	975	914	917	947	901	909	940	899	902	933	897	901	934
Died	95	97	67	16	13	9	11	7	7	2	6	2	2	1	4	2	1	1
%	9.0	9.3	6.4	1.7	1.4	0.9	1.2	0.8	0.7	0.2	0.7	0.2	0.2	0.1	0.4	0.2	0.1	0.2

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Figure 2. Kaplan–Meier Curves for Mortality.
Kaplan–Meier curves show the rate of death in the three study groups over the course of 48 hours from randomization (Panel A) and over the course of 4 weeks from randomization (Panel B).

We could not identify any subgroup in which fluid resuscitation was beneficial; this is remarkable given that many of the baseline characteristics of the children in this study are considered to be important criteria for bolus-fluid therapy, including moderate hypotension and severe metabolic acidosis.[27] All the children received maintenance fluids and the standard of care recommended by national guidelines. The receipt, and the timing of the receipt, of blood, quinine, and antibiotics were similar across groups; only bolus-fluid resuscitation differed between the intervention and control groups. The apparent lack of effect on early mortality (<1 hour), followed by an increasing negative effect over time, without amelioration of neurologic events, suggests a consistent adverse effect of bolus resuscitation with both saline and albumin. It has been thought that albumin has physiological benefits over saline, a hypothesis that was supported by the results of small trials involving children with severe malaria[28-30] and a recent analysis of the sepsis subgroup[31,32] of the adult Saline versus Albumin Fluid Evaluation trial (SAFE; Current Controlled Trials number, ISRCTN76588266). However, we observed no detectable differences between the bolus groups, providing evidence against a beneficial effect of albumin over saline. The excess mortality with fluid resuscitation was consistent across all subgroups, irrespective of physiological derangement or underlying microbial pathogen, also raising fundamental questions about our understanding of the pathophysiology of critical illness.

We had predicted that complications of fluid

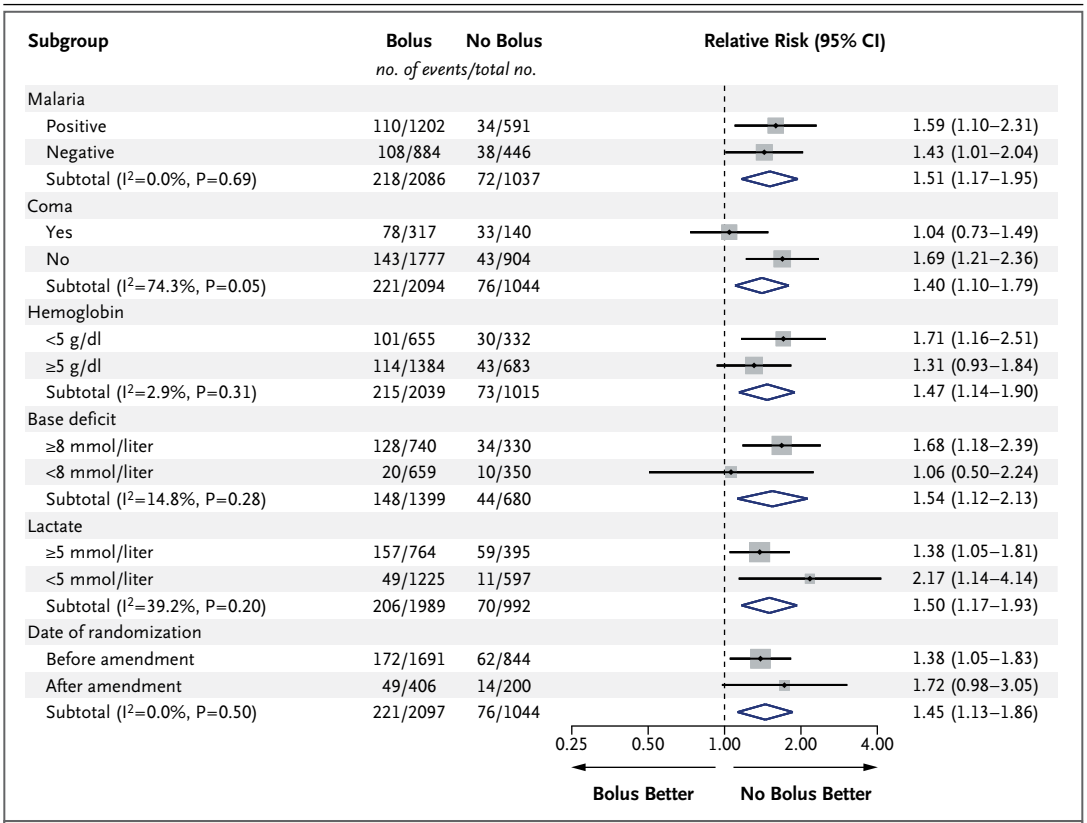

Figure 3. Mortality at 48 hours in Prespecified Subgroups.
The sizes of the boxes are proportional to the Mantel–Haenszel weights. The I^2 statistic indicates the percentage of total variation that was due to heterogeneity.

overload would develop in some children and incorporated mandatory clinical reviews to monitor for pulmonary edema and increased intracranial pressure. All reported adverse events were reviewed by the end-point review committee, whose members were unaware of the treatment assignments; in addition the committee reviewed the records of all deaths for evidence of the presence of pulmonary edema or increased intracranial pressure. Few events were identified by this process, and there was no evidence of differences among the groups; most deaths appeared to be attributable to the severity of the underlying condition. The question therefore arises as to the reasons for the excess mortality among children receiving boluses. Our a priori hypothesis was that the benefit of bolus interventions would be greatest for the group that was at the highest risk, which included the children with the most severe hemodynamic and metabolic derangement. However, although the degree of shock has been shown to be prognostic for an adverse outcome,[12,14] our results suggest that it may not be a surrogate on the causal pathway for the effect of bolus resuscitation on survival. One could speculate that the vasoconstrictor response in shock confers protection by reducing perfusion to nonvital tissues and that rapid reversal with fluid resuscitation is deleterious. Alternatively, the adverse consequences of fluid boluses (even at low volumes) might act through other mechanisms such as reperfusion injury, subclinical effects on pulmonary compliance, myocardial function, or intracranial pressure.[33]

In conclusion, the results of this study challenge the importance of bolus resuscitation as a lifesaving intervention in resource-limited settings for children with shock who do not have hypotension and raise questions regarding fluid-resuscitation guidelines in other settings as well.

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CORRESPONDENCE

Mortality after Fluid Bolus in African Children with Sepsis

TO THE EDITOR: The Fluid Expansion as Supportive Therapy (FEAST; Current Controlled Trials number, ISRCTN69856593) Trial Group (June 30 issue)[1] performed a meticulous study of fluid resuscitation in children with sepsis. We note that the excess mortality in the intervention group was most pronounced among severely anemic children but not statistically significant among children with a hemoglobin level of 5 g per deciliter or more (Fig. 3 of the article).

This finding suggests that acute hemodilution in children with preexisting anemia may have caused the increased mortality in the resuscitation group. Assuming a circulating blood volume of 80 ml per kilogram of body weight, a child with a hemoglobin level of 5 g per deciliter on admission would undergo hemodilution to 4 g per deciliter. The most comprehensive pediatric literature on anemia in children with sepsis and in pediatric intensive care unit (ICU) populations has studied a transfusion threshold hemoglobin level of 7.0 g per deciliter.[2,3] Below this level, evidence is anecdotal.[4] The physiological effect of severe dilutional anemia is predictable and detrimental: impaired oxygen delivery leading to organ failure.

This is not a criticism of the trial per se, but it is a possible mechanism for the apparent harm of fluid resuscitation with an agent other than blood in children with anemia and sepsis seen in this study.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: Maitland et al. report increased 48-hour mortality among African children with severe febrile illness without hypotension after fluid resuscitation as compared with no resuscitation. Although the authors report the exclusion of children with severe malnutrition and gastroenteritis, among other clinical conditions, it is not clear what criteria were used to determine nutritional status and the relevance of moderate undernutrition among the groups. We deem that these criteria are relevant, given the different car-

THIS WEEK'S LETTERS

diovascular and inflammatory responses that are adaptive manifestations of the nutritional status of an ill child.[1] Second, the authors describe malaria as the cause of febrile illness in 57% of the children, but they do not describe the causes of the other cases of febrile illness. We believe it is important to discriminate among the three groups other causes known to alter host vascular permeability, such as dengue, and the differences in the inflammatory response triggered by different types of pathogens.[2] The results presented are innovative, but in some aspects in conflict with the higher volume of fluids recommended by current guidelines, which are based on studies that have shown lower mortality among children mainly in developing countries.[2-4]

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TO THE EDITOR: Maitland et al. expand our deficient knowledge on fluid resuscitation, since they established that fluid boluses containing albumin and saline might increase mortality among African children with severe infection. Physicians struggle worldwide with the optimal fluid-resuscitation strategy. In one study involving 391 ICUs across 25 countries, colloid was administered to more patients than crystalloid,[1] despite the association with adverse effects.[1,2] The attempt to find a truly physiological crystalloid preparation has been going on for 175 years, and the results have inevitably been a compromise.[3] In the meantime, we infuse billions of liters of 0.9% saline worldwide, although this fluid is neither "normal," nor "physiological," because it differs markedly from plasma.[3,4] Chloride-rich solutions such as 0.9% saline or albumin, when used in large volumes, can potentiate metabolic acidosis, but trading part of the chloride content with ions such as lactate (Ringer's lactate) may be at the expense of other side effects (e.g., metabolic alkalosis).[4] Without international studies, we may never be able to make rational choices about fluid resuscitation.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: As members of UNC (University of North Carolina) Project–Uganda who provide education and pediatric emergency care in that resource-limited country, we dispute the conclusion that bolus crystalloid resuscitation is harmful in the treatment of shock.

The importance of rapid fluid resuscitation in shock is supported by the World Health Organization (WHO) emergency triage, assessment, and treatment (ETAT)[1] and the pediatric advanced life support (PALS)[2] guidelines. In this study, 43% of all patients had severe anemia. In the "no bolus" control group, 20% of the patients received whole-blood transfusion within 1 hour. In contrast, only 2% of patients in the albumin-bolus group and 4% of patients in the saline-bolus group received this definitive therapy for severe anemia because they were receiving bolus fluid; this could have resulted in the observed 3.3 percentage-point increase in the absolute risk of death.[3] Our firsthand experience has shown that rapid infusion of bolus crystalloid fluids followed by reassess-

ment in severe shock is highly beneficial in patients without severe anemia. This study also shows that improvements in mortality can be obtained by creating a rapid triage and treatment delivery system for children — something that is lacking in most of Africa.

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TO THE EDITOR: In 2005, the *Journal* published an article that said that fluid boluses were associated with nearly 100% survival among patients with previously fatal hypovolemic dengue shock syndrome in Southeast Asia.[1] The accompanying editorial called for an evaluation of the use of fluid boluses in the sub-Saharan population because blood — not fluid boluses — is recommended in populations with isovolumic, high-output, anemic shock.[2] The FEAST Trial Group found fluid boluses harmful as compared with maintenance fluids. Patients with hypovolemic dehydration were excluded, and fluid boluses were given for hypotension, a surrogate for hypovolemia. Patients with a hemoglobin level of less than 5 g per deciliter received transfusions of 20 ml of whole blood per kilogram over 4 hours. Blood transfusion was delayed in the "fluid-bolus" groups as compared with the "no-fluid-bolus" group (3% vs. 20% of children began to receive fluid in the first hour). Fluid boluses were most harmful in subgroups of patients who had signs that were consistent with severe anemic shock (hemoglobin level <5 g per deciliter and base deficit >8 mmol per liter, without coma). These findings provide support for two therapeutic approaches — first, use a fluid bolus in patients with hypovolemic shock who have dengue shock syndrome but no severe anemia; second, patients with severe anemic shock without hypotension should undergo transfusion with blood (do not administer a fluid bolus).

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Drs. Kissoon and Carcillo report being cochairs of the Global Sepsis Initiative of the World Federation of Pediatric Intensive and Critical Care Societies. No other potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: The examination by Maitland et al. of resuscitation with fluids shows the rarity of early hypotension in pediatric febrile illness. Their inclusion criteria were consistent with pediatric sepsis guidelines recommending diagnosis through physical examination findings, but these are unproved in a normotensive population.[1] Of recommended physical findings, only mental status predicted organ dysfunction in children with sepsis in U.S. emergency departments.[2] Diagnostic criteria were adapted differently in recent studies involving children with sepsis in emergency departments, resulting in dissimilar populations.[3-5]

In the study reported by Maitland et al., interpretation rests on whether the patients were in shock. The increased mortality among patients in the bolus groups may indicate that fluids harm ill patients who are not in shock. Alternatively, boluses may produce harm in patients with shock. Most likely, low-volume fluid resuscitation without critical care is insufficient for patients in shock and excessive for the remainder of this population.

Until diagnostic strategies in early sepsis in

children are refined and consensus is achieved, evaluation of therapies in the most proximal phase of illness will be limited.

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THE AUTHORS REPLY: The correspondence regarding the FEAST trial raises three important issues: first, the definition of shock used in the FEAST trial; second, the effect of anemia and transfusions on results; and third, the effect of nutritional status. We address these points and include new analyses of our data.

In our trial, we compared bolus with no bolus in subgroups of children fulfilling different definitions of shock with respect to 48-hour mortality[1-3] (Table 1). The FEAST criteria most closely resembled the American College of Critical Care Medicine definition of "cold shock," which was present in 2127 participants (68%). The WHO ETAT shock criteria identified only 65 children (2%); however, even in this small subgroup, there was a significant excess risk associated with boluses, with an absolute difference in risk of 28 percentage points (95% confidence interval [CI], 3.4 to 52.5). We acknowledge problems with interobserver variation and specificity of the bedside assessment of shock that are inherent in current definitions of pediatric shock. However, objective measures such as moderate hypotension were also associated with higher mortality in the bolus groups as compared with the no-bolus group (absolute difference in risk; 9.4 percentage points; 95% CI, –2.6 to 21.4). Despite some ambiguity in interpretation of different definitions of shock, the findings are remarkably consistent and all point to the same conclusion.

The suggestion that anemia is a reason for the increased mortality among bolus-treated children is not supported in our analyses; excess mortality in the bolus groups was as apparent among children without severe anemia (hemoglobin level, ≥5 g per deciliter) as among children with severe anemia (hemoglobin level, <5 g per deciliter) (Fig. 3 of our article and Table 5 in the Supplementary Appendix, available with the full text of our article at NEJM.org). Similar results were also apparent in children with a hemoglobin level of 10 g per deciliter or more or less than 10 g per deciliter. Questions about earlier initiation of blood transfusion in the control group were also raised; however, the volume of blood received in all groups was small in the first hour (the mean [±SD]) volume by 1 hour in the bolus vs. no-bolus groups was 0.05±0.7 ml per kilogram vs. 0.6±1.6 ml per kilogram) (Table 3a in the Supplementary Appendix).

Children with acute severe malnutrition (according to clinical judgment) were excluded. However, 70 children (2%) had a mid-upper-arm circumference of 11.5 cm or less (Table 1 of our article). The effect of bolus fluids was not significantly different in children with a mid-upper-arm circumference of more than 11.5 cm (absolute difference in risk, 1.2 percentage points; 95% CI, –0.5 to 3.0) or 11.5 cm or less (absolute difference in risk, 3.5 percentage points; 95% CI, –13.0 to 20.1; P=0.96 for heterogeneity).

There was little clinical evidence of dengue infection or its life-threatening complications where our trial took place. Severe dengue in-

Table 1. Risk of Death Among Participants, According to Various Definitions of Shock in Children.*

Definition of Shock	Application of Criteria to FEAST Admission Data	Mortality			Percentage-Point Difference (95% CI)†
		Overall (All Groups)	Bolus (Saline or Albumin)	No Bolus (Control Group)	
		no. of patients/total no. (%)			
FEAST inclusion criteria					
History of fever or axillary temperature >37.4°C or <36°C and impaired consciousness (prostration or coma), respiratory distress, or both; plus ≥1 of: capillary refill time >2 sec, lower-limb temperature gradient, weak pulse, tachycardia (heart rate >180 beats/min in children <12 mo; >160 beats/min in children 12 mo–5 yr; >140 beats/min in children >5 yr)	—	297/3141 (9.5)	221/2097 (10.5)	76/1044 (7.3)	3.3 (1.2 to 5.3)
ACCM					
Cold shock (with one sign)					
Pyrexia or hypothermia; plus clinical signs of inadequate tissue perfusion including any of the following: decreased or altered mental status, capillary refill time >2 sec, diminished pulses, mottled cool extremities	Axillary temperature >37.4°C or <36°C; plus ≥1 of: prostration or coma or Blantyre coma score‡ <5, capillary refill time >2 sec, weak pulse, increased temperature gradient	194/2127 (9.1)	150/1452 (10.3)	44/675 (6.5)	3.8 (1.4 to 6.2)
Cold shock (with two signs)					
Pyrexia or hypothermia; plus clinical signs (which could be interpreted as ≥2) of inadequate tissue perfusion including any of the following: decreased or altered mental status, capillary refill time >2 sec, diminished pulses, mottled cool extremities	Axillary temperature >37.4°C or <36°C; plus ≥2 of: prostration or coma or Blantyre coma score <5, capillary refill time >2 sec, weak pulse, increased temperature gradient	189/1733 (10.9)	147/1196 (12.3)	42/537 (7.8)	4.5 (1.5 to 7.4)
PALS					
Compensated shock					
Typical signs include: tachycardia, cool and pale distal extremities, capillary refill time >2 sec despite warm ambient temperature, weak peripheral pulses as compared with central pulses, normal systolic blood pressure	Two of the following: tachycardia (see FEAST above), increased temperature gradient, capillary refill time >2 sec, or weak pulse	218/1650 (13.2)	161/1113 (14.5)	57/537 (10.6)	3.9 (0.5 to 7.2)

Decompensated shock					
Signs and symptoms consistent with inadequate delivery of oxygen to tissues (one of the following signs: pallor, peripheral cyanosis, tachypnea, mottling of skin, decreased urine output, metabolic acidosis, depressed mental status); also weak or absent peripheral pulses, weak central pulses, or hypotension (systolic blood pressure <70 mm Hg in children 1–12 mo; <70 mm Hg plus twice child's yr of age) in children 1–10 yr; <90 mm Hg in children ≥10 yr)	One of the following: pallor; tachypnea (respiratory rate >50 breaths/min in children <12 mo; >40 breaths/min in children 1–4 yr; >30 breaths/min in children >5 yr); metabolic acidosis (base deficit >8 or lactate >5 mmol/liter); coma or prostration or Blantyre coma score <5; plus weak pulse or hypotension	157/755 (20.8)	115/513 (22.4)	42/242 (17.4)	5.1 (−0.9 to 11.0)
WHO ETAT					
Cold hands or feet with both capillary refill time >3 sec and weak and fast pulse	Cold hands or feet with both capillary refill time >3 sec and weak and fast pulse	27/65 (41.5)	24/50 (48.0)	3/15 (20.0)	28.0 (3.4 to 52.5)

* ACCM denotes American College of Critical Care Medicine, FEAST Fluid Expansion as Supportive Therapy, PALS pediatric advanced life support, and WHO ETAT World Health Organization emergency triage, assessment, and treatment.
† Percentage-point differences are for the absolute risk of death in the bolus groups versus no-bolus groups.
‡ The Blantyre coma score is rated on a scale of 0 to 5, with 0 indicating the complete absence of any response to a painful stimulus and 5 indicating full consciousness.

cludes hypovolemic shock with or without hemorrhagic manifestations. Its pathogenesis includes severe vascular leakage leading to hypovolemia, with vomiting, abdominal pain, increasingly tender hepatomegaly, narrow pulse pressure, and hemoconcentration. Management of severe dengue has been informed by several trials, including the trial described by Kissoon and Carcillo that showed almost 100% survival. The results of FEAST do not conflict with the conclusions of that trial and treatment guidelines for dengue.

The FEAST trial team, like many experts in the field of fluids and infection, did not expect a result documenting harm from the rapid infusion of fluids in African children with shock. That the effect appeared to be strongest in children with the most severe shock was especially surprising. However, we have scrutinized the trial results over many months, and we have found consistency over all sites and subgroups. In the current context, the results clearly show that the use of bolus fluids in children with impaired perfusion, irrespective of the definition of shock and the presence or absence of anemia or undernutrition, was associated with an increased risk of death. The trial provides important evidence for the care of severely ill children in Africa and raises questions about rapid early administration of fluid boluses in other places.

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Since publication of their article, the authors report no further potential conflict of interest.

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