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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). All children received appropriate antimicrobial treatment, intravenous maintenance fluids, and supportive care, according to guidelines. 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 guidelines¹⁶ 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 anemia¹⁷ 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 guidelines¹ 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 criterion¹⁸ was the statistical guide that the committee used in considering a recommendation to stop or modify the trial. At the fifth interim review

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, non-infectious 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-

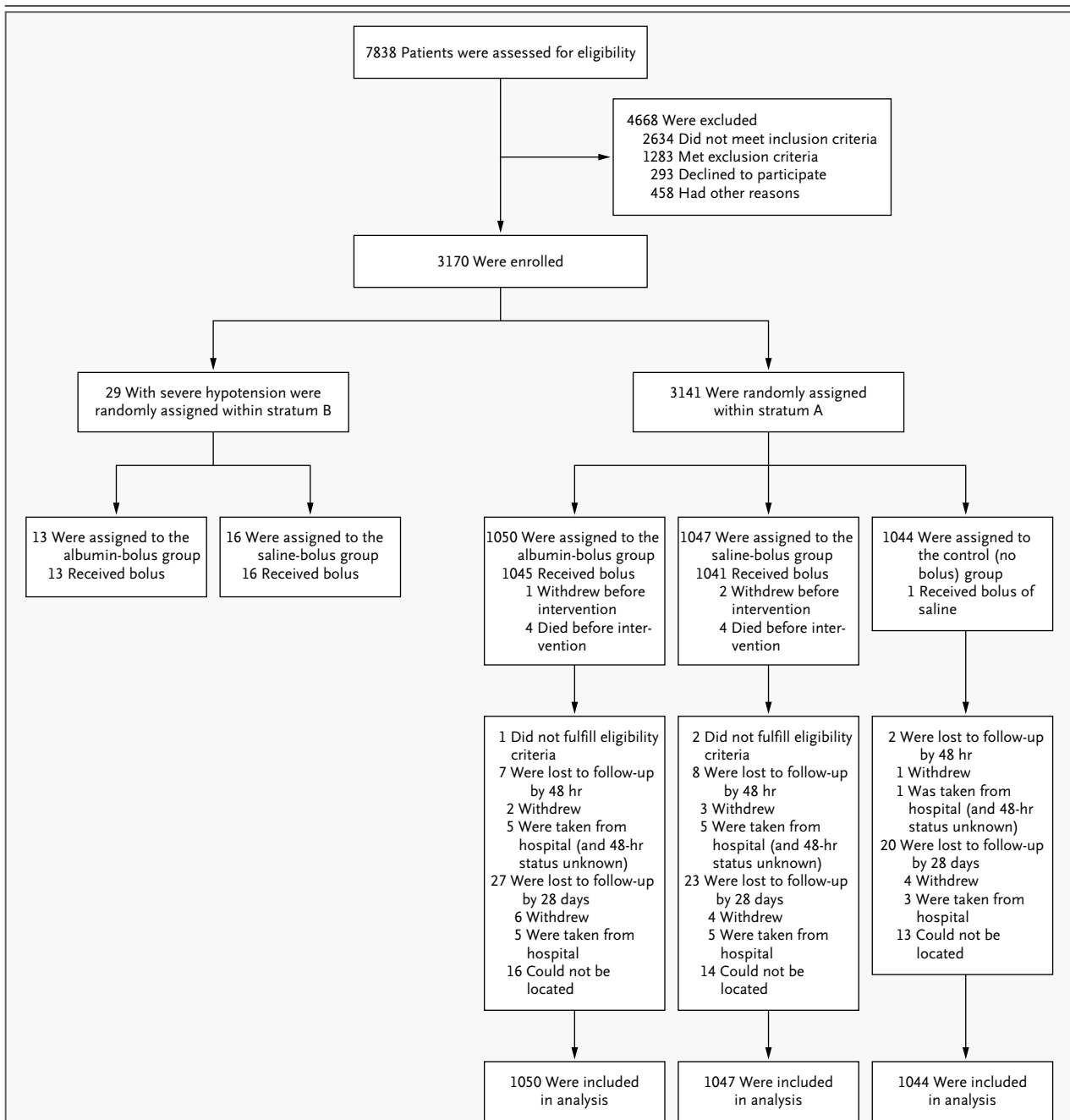


Figure 1. Screening, Randomization, and Follow-up.

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.

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 group¹²; 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 (hemo-

globin 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 (\pm 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 \leq 11.5 cm — no./total no. (%)	21/982 (2)	24/974 (2)	25/1003 (2)	70/2959 (2)
Findings at presentation				
Axillary temperature $>39^{\circ}\text{C}$ — no. (%)	243 (23)	236 (23)	264 (25)	743 (24)
Hypothermia (temperature $<36^{\circ}\text{C}$) — 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 \pm 15	58 \pm 15	57 \pm 15	58 \pm 15
Oxygen saturation $<90\%$ — no. (%) \dagger	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. (%) \ddagger	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. (%) \S	66/1030 (6)	69/1036 (7)	57/1034 (6)	192/3100 (6)
Dehydration — no. (%) \P	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
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.

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 non-infectious 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.

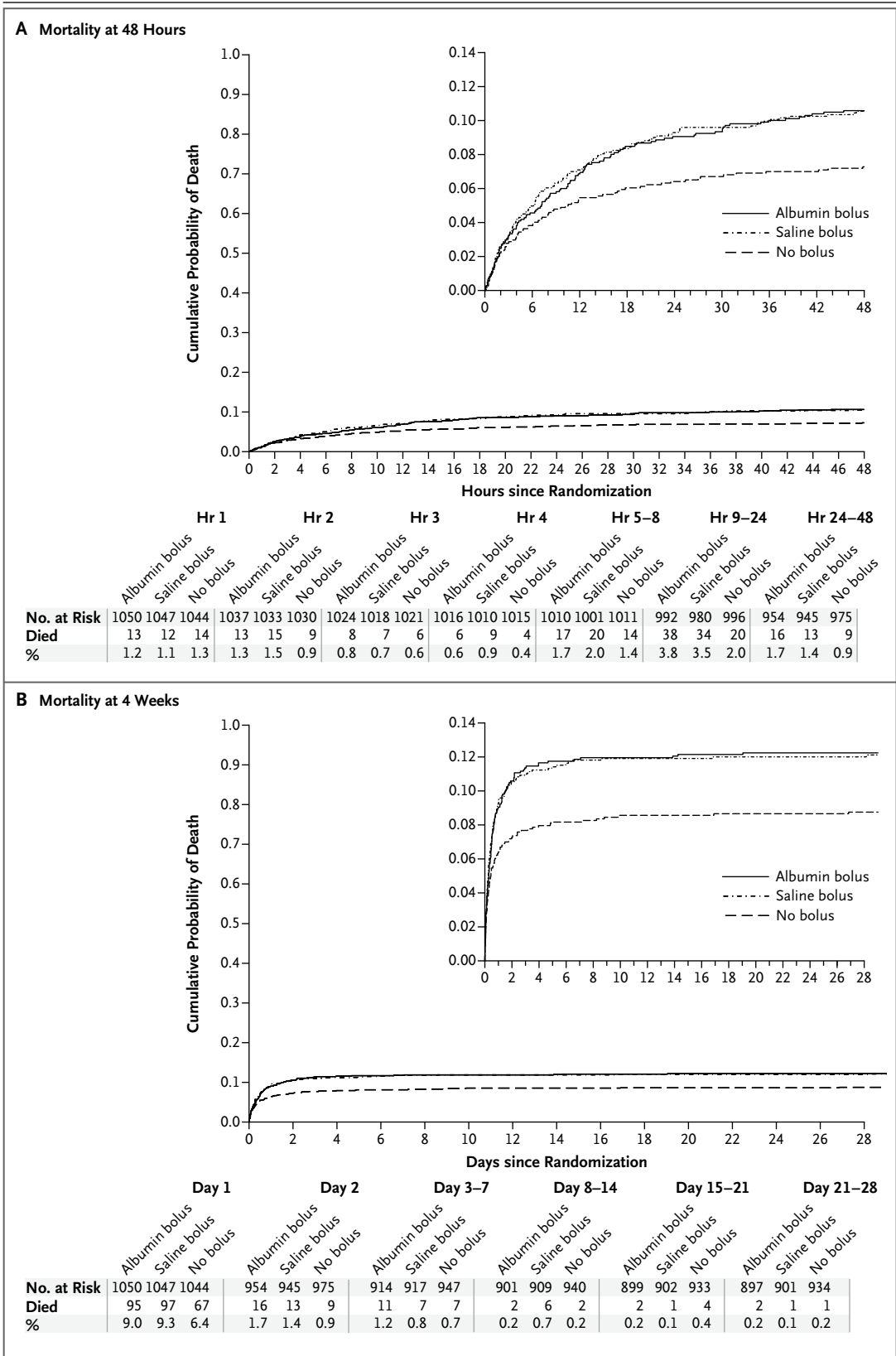


Figure 2. Kaplan–Meier Curves for Mortality.

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

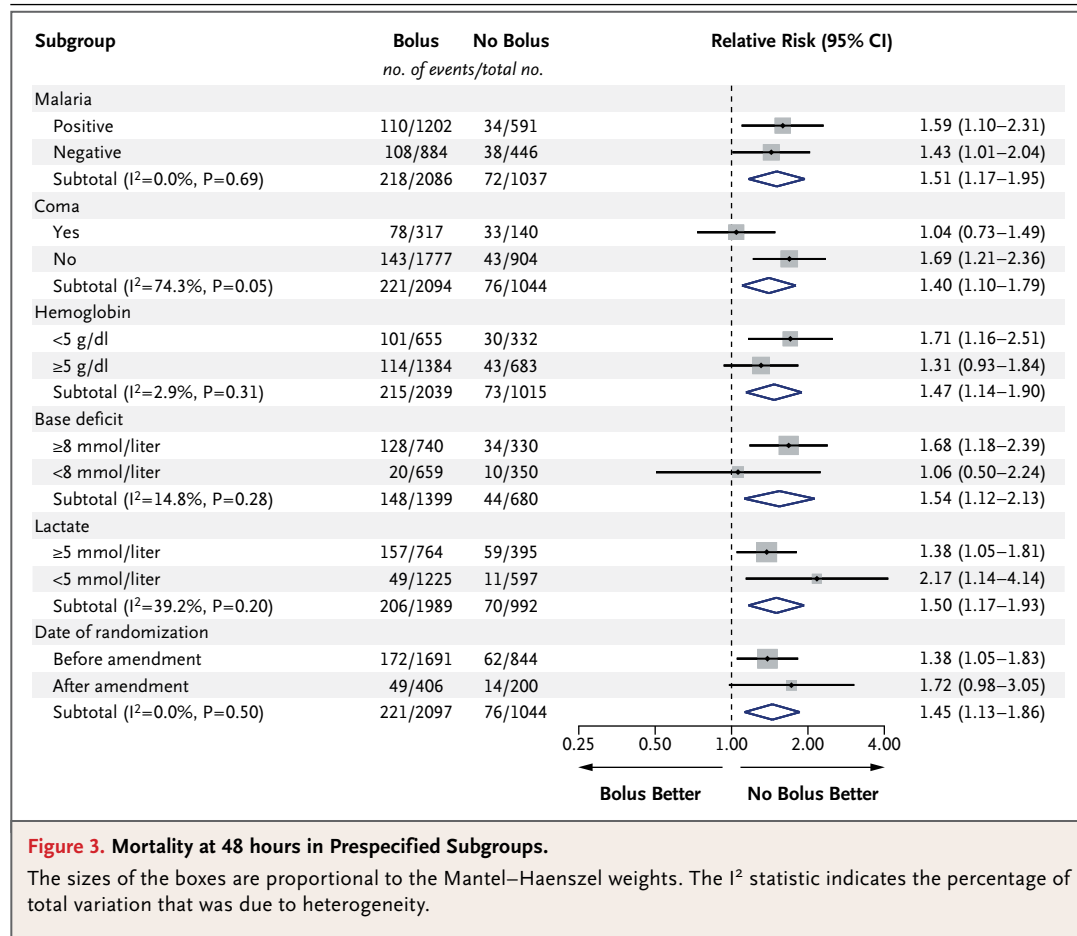


Figure 3. Mortality at 48 hours in Prespecified Subgroups.

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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