Mortality after Fluid Bolus in African Children with Severe Infection (Maitland et al, 2011)

Background

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. Children who do not have an adequate response to fluid resuscitation require intensive care for inotropic and ventilatory support. Substantial improvements in the outcomes of pediatric septic shock have been attributed to this approach. Nevertheless, evidence regarding the criteria for intervention and the volume and type of fluid is lacking.

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, despite evidence of their cost-effectiveness. Malaria, sepsis, and other infectious conditions cause major health burdens for children in sub-Saharan Africa and are associated with high early mortality. Hypovolemic shock (a term incorporating all degrees of impaired perfusion) is common and increases mortality substantially. However, World Health Organization guidelines 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 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.

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 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)

Screening, Randomization, and Follow-up. 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 assignments. 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

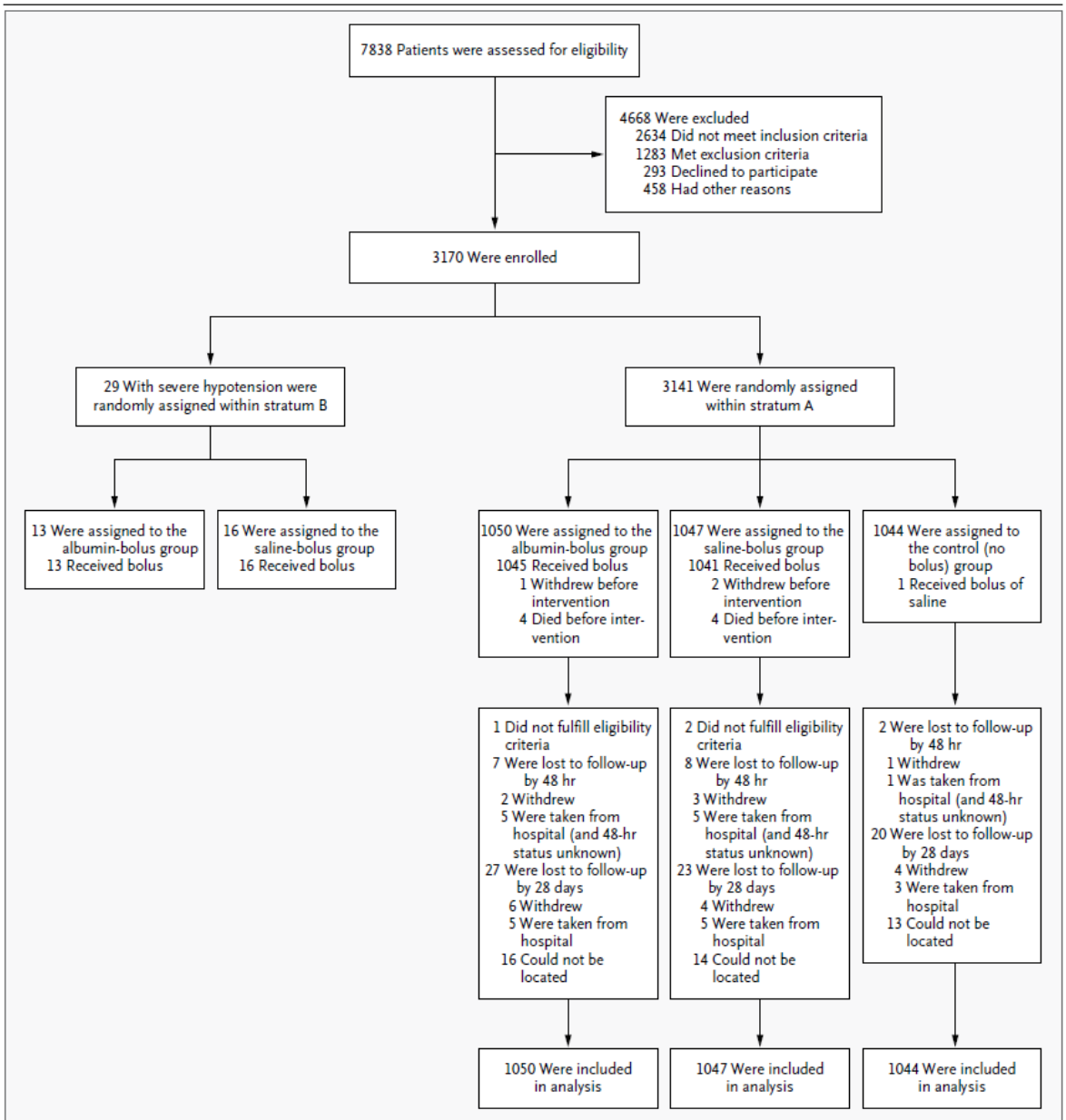


Figure 1. Screening, Randomization, and Follow-up.

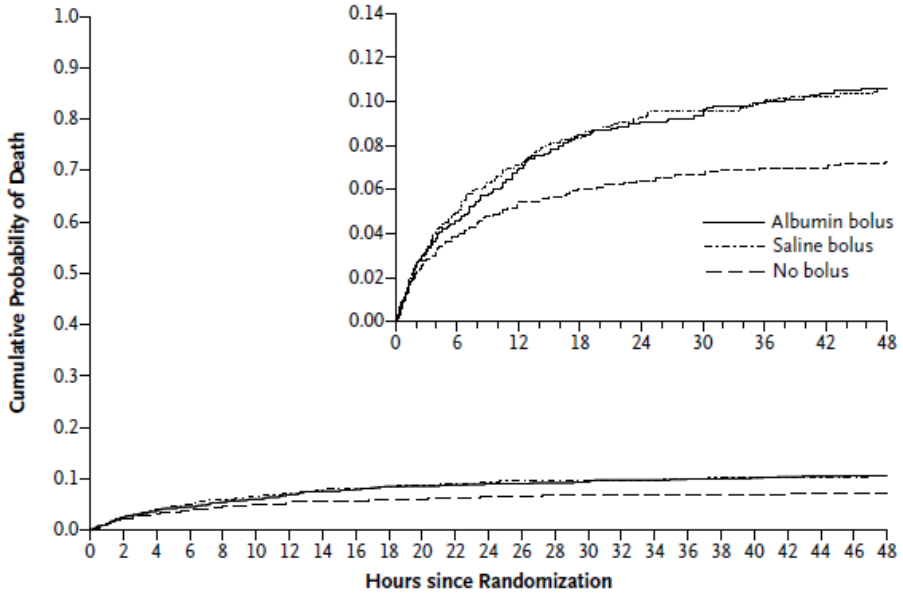
Of the 4668 children excluded after initial assessment for eligibility, 2634 with severe illness did not meet the inclusion criteria because they did not have at least one of the following: impaired perfusion, impaired consciousness, fever, or respiratory distress. A total of 1283 children met exclusion 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.

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

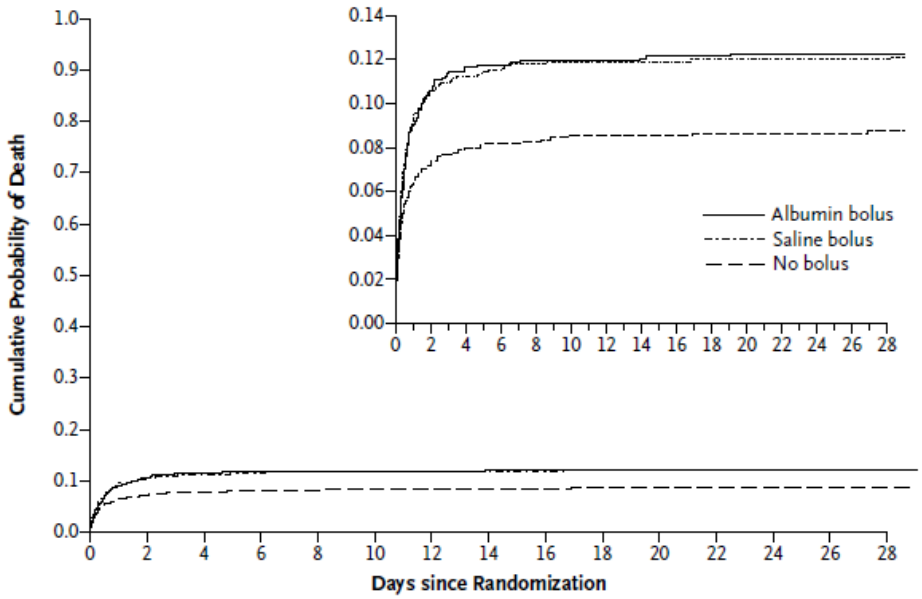
* Severe hypotension was defined as a systolic blood pressure of less than 50 mm Hg in children younger than 12 months of age, less than 60 mm Hg in children 1 to 5 years of age, and less than 70 mm Hg in children older than 5 years of age, plus one or more features of impaired perfusion.
† Four children — 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.

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

Questions:

1. Was the study ethical?
2. Was the design appropriate?
3. What were the key results?
4. What are the implications of the study?