ORIGINAL ARTICLE

Intravenous Rehydration for Severe Acute Malnutrition with Gastroenteritis

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ABSTRACT

BACKGROUND

International recommendations advise against the use of intravenous rehydration therapy in children with severe acute malnutrition because of the concern about fluid overload, but evidence to support this concern is lacking. Given the high mortality associated with the current recommendations, the adoption of intravenous rehydration strategies might improve outcomes.

METHODS

We conducted a factorial, open-label superiority trial in four countries in Africa. Children 6 months to 12 years of age with severe acute malnutrition with gastroenteritis and dehydration underwent randomization in a 2:1:1 ratio to one of three rehydration strategies: oral rehydration, plus intravenous boluses for shock; a rapid intravenous strategy that consisted of lactated Ringer's solution (100 ml per kilogram of body weight) administered over a period of 3 to 6 hours, with boluses for shock; or a slow intravenous strategy that consisted of the same solution administered over a period of 8 hours, with no boluses. The primary end point was death at 96 hours.

RESULTS

A total of 272 children underwent randomization; 138 were assigned to the oral strategy, 67 to the rapid intravenous strategy, and 67 to the slow intravenous strategy. Participants were followed for 28 days. A nasogastric tube was used for oral rehydration in 126 of 135 participants (93%) in the oral group and in 82 of 126 (65%) in the intravenous groups. Intravenous boluses were administered at admission in 12 participants (9%) in the oral group, 7 (10%) in the rapid intravenous group, and none in the slow intravenous group. At 96 hours, 11 participants (8%) in the oral group and 9 (7%) in the intravenous groups (5 in the rapid group and 4 in the slow group) had died (risk ratio, 1.02; 95% confidence interval [CI], 0.41 to 2.52; P=0.69). At 28 days, 17 participants (12%) in the oral group and 14 (10%) in the intravenous groups had died (hazard ratio, 0.85; 95% CI, 0.41 to 1.78). Serious adverse events occurred in 32 participants (23%) in the oral group, 14 (21%) in the rapid intravenous group, and 10 (15%) in the slow intravenous group. No evidence of pulmonary edema, heart failure, or fluid overload was noted.

CONCLUSIONS

Among children with severe acute malnutrition and gastroenteritis, no evidence of a difference in mortality at 96 hours was noted between oral and intravenous rehydration strategies. (Funded by the Joint Global Health Trials scheme and others; GASTROSAM Current Controlled Trials number, ISRCTN76149273.)

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*A list of the members in the GASTROSAM Trial Group is provided in the Supplementary Appendix, available at NEJM.org.

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In 2016, the World Health Organization (WHO), United Nations Children's Fund, and World Bank Group Interagency estimated that 17 million children younger than 5 years of age were severely undernourished.[1] Severe acute malnutrition, the most extreme form of undernourishment, is a leading cause of hospital admissions among children in Africa.[2,3] Many children with severe malnutrition have additional complications such as severe dehydration due to diarrhea,[4] which is associated with high in-hospital mortality (27 to 41%).[4-6] Current recommendations for rehydration in children with severe acute malnutrition differ from those for children without malnutrition.[7] Intravenous rehydration is not recommended in severe acute malnutrition because malnourished children are at high risk for compromised cardiac function and sodium overload.[8,9] Low-sodium oral rehydration solutions are not recommended for similar reasons. Although such guidance documents have been in place for more than two decades, no previous[10] or subsequent evidence[11,12] has supported these recommendations. Therefore, oral rehydration is the recommended option, with intravenous boluses provided only in the event of shock. This approach often necessitates the use of a nasogastric tube to administer oral rehydration, since most children with severe acute malnutrition are unable to take or retain oral fluids. In addition, most children receive care in busy, overcrowded pediatric units or in dedicated nutrition units with limited nursing staff available to ensure safe implementation of oral nasogastric rehydration and to monitor for signs of shock. Shock is a complication in approximately 25% of children with severe dehydration,[13] and in-hospital mortality among children with shock is high (>40%).[13-15]

Physiological studies have supported the safety of intravenous fluids in the treatment of severe malnutrition, with no evidence of compromised cardiac function.[16,17] A cohort study that matched hospitalized children with severe acute malnutrition to children who were not malnourished according to complications at presentation also showed no evidence that children with severe acute malnutrition were more likely than others to have cardiac dysfunction or arrhythmias.[16] Another study showed fluid responsiveness on the basis of Frank–Starling curves among children who received boluses or rehydration only.[15] Given the results of such studies, randomized, controlled trials are needed to provide more evidence.[11]

The intravenous rehydration strategy recommended by the WHO for children with gastroenteritis and severe dehydration (defined by an estimated fluid loss of 10%, or approximately 100 ml per kilogram of body weight) who are not malnourished is called plan C.[7] The plan includes two phases of intravenous rehydration therapy (an initial fast component, followed by a slower phase that is performed over a period of 4 to 6 hours), with the rate of administration differing for infants and for children older than 1 year of age, plus fluid boluses (20 ml per kilogram) in the event of hypovolemic shock. Because the Fluid Expansion as Supportive Therapy (FEAST) trial showed harm from fluid boluses in African children with nonhypovolemic shock,[18] we were concerned that such harm might also occur with aggressive rehydration for severe dehydration. In a randomized, controlled trial[19] that enrolled children in Uganda and Kenya who were not malnourished and had severe dehydration due to gastroenteritis, we compared the use of plan C (rapid strategy) with an intravenous strategy that used an equivalent volume of solution (100 ml per kilogram) administered slowly over a period of 8 hours (without boluses for shock). Outcomes with the slow strategy were similar to those with plan C, and the slow strategy was simpler to implement, requiring less oversight by staff.[20] In the current trial, we assessed whether intravenous rehydration (administered either rapidly or slowly) would result in lower mortality than the standard oral rehydration strategy among hospitalized children with severe acute malnutrition with gastroenteritis.[21]

METHODS

TRIAL DESIGN AND OVERSIGHT

We conducted an investigator-initiated, multicenter, factorial, open-label, randomized superiority trial at six hospitals: two in Uganda, two in Kenya, one in Niger, and one in Nigeria (details are provided in the Supplementary Methods section in the Supplementary Appendix, available with the full text of this article at NEJM.org). Of note, participants in Niger and Nigeria made up more than 90% of the trial population. The protocol[21] (available at NEJM.org) was approved by local ethics committees. Two of the authors, including the

last author, vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The director of the Kenya Medical Research Institute gave permission for the manuscript to be submitted for publication.

TRIAL POPULATION

Children were eligible if they were 6 months to 12 years of age and were hospitalized with severe acute malnutrition (defined by a weight-for-height z score ≤3, mid-upper-arm circumference <11.5 cm, or presentation with edematous malnutrition [kwashiorkor] with edema in both feet or more generalized edema[7]) with gastroenteritis (with more than three loose stools per day) and signs of severe dehydration. Signs of severe dehydration, according to WHO criteria, included two or more of the following: altered level of consciousness, sunken eyes, reduced skin turgor (slow abdominal skin pinch return [>2 seconds]), or inability to take or retain oral fluids. The level of consciousness was assessed on the basis of the four-component AVPU scale, with "Alert" indicating that the patient is aware and can respond independently, "Verbal" indicating that the patient responds only to verbal stimuli, "Pain" indicating that the patient responds only to the application of painful stimuli, and "Unresponsive" indicating that the patient does not respond to verbal or painful stimuli. Altered level of consciousness was considered to be a status of Verbal, Pain, or Unresponsive. Children with known congenital or rheumatic heart disease or with diarrhea lasting longer than 14 days were excluded.

SCREENING AND RANDOMIZATION

All children with severe acute malnutrition with gastroenteritis who were admitted to the trial-site hospitals were screened for inclusion by trial staff. In Niger and Nigeria, participants were transferred to an intensive care unit (although assisted ventilation was not available) where they were treated by a dedicated trial team. In Uganda and Kenya, participants were treated in general pediatric units. When prior written consent from parents or legal guardians could not be obtained, verbal assent was obtained, with deferred written informed consent obtained as soon as practical, as approved by the ethics committees.[22] Otherwise, written informed consent was obtained from parents or guardians before randomization. The statistician in London generated the sequential randomization list, which was computer-generated with the use of variably sized permuted blocks. Trial-group assignments were sealed in sequentially numbered, opaque envelopes and were opened in numerical order at trial sites.

Participants were randomly assigned in a 2:1:1 ratio to one of three rehydration strategies: oral rehydration (the control), a rapid intravenous strategy, or a slow intravenous strategy (Fig. S1 in the Supplementary Appendix). Participants in the oral group received (in accordance with WHO guidelines for children with severe acute malnutrition) oral rehydration solution (5 ml per kilogram), which was administered every 30 minutes for the first 2 hours, followed by 5 to 10 ml per kilogram every hour for the next 4 to 10 hours, alternating hourly with F-75 milk formula, with boluses of lactated Ringer's solution (15 ml per kilogram) for those with shock or those in whom shock developed (Table S4). Participants in the rapid intravenous group received (in accordance with WHO treatment plan C) lactated Ringer's solution (100 ml per kilogram), which was administered over a period of 3 to 6 hours (according to age), with boluses (20 ml per kilogram) for those with shock (Table S2). Participants in the slow intravenous group received lactated Ringer's solution (100 ml per kilogram), administered over a period of 8 hours, with no boluses (Table S3). Details regarding the rehydration solutions are provided in Table S5. Shock was defined by the presence of all of the following: cold hands or feet, a weak and fast pulse (rate not specified), and a capillary refill time of longer than 3 seconds.[15]

All the participants were simultaneously randomly assigned in a factorial manner, in a 1:1 ratio, to receive one of two WHO-recommended oral rehydration solutions: rehydration solution for malnutrition (ReSoMal) or oral rehydration solution for children without severe acute malnutrition. Details are provided in the Supplementary Methods section. The results of the comparison of the two strategies are not reported here.

TRIAL PROCEDURES AND FOLLOW-UP

Basic infrastructural support was provided for emergency care, patient monitoring, and point-of-care bedside assessment of hemoglobin, glucose, and lactate levels. Bedside observations were performed at admission and every 30 minutes

for the first 2 hours, every hour until 8 hours after admission, and at 12, 24, 36, and 48 hours after randomization. Biochemical assessments were performed at randomization and at 8 and 24 hours after randomization. Blood cultures were performed where facilities permitted. Participants who could not take oral fluids had a nasogastric tube placed for administration of oral rehydration fluids and nutritional milk; the positioning of the tube was checked at each administration to ensure that it was placed correctly. Participants were actively monitored for serious adverse events, particularly suspected cardiac or pulmonary overload, at each clinical assessment. Participants underwent clinical assessment at 7 days and 28 days (the end of follow-up) after randomization. Trial staff were aware of the trial-group assignments throughout the trial. Laboratory testing was performed in a blinded manner.

END POINTS

The primary end point was death at 96 hours. Secondary efficacy end points were death at 28 days, the change in weight at 3 days and 7 days, the change in mid-upper-arm circumference at 3 days and 7 days, and urine output at 8 hours. Safety end points were evidence of pulmonary edema or heart failure, the change in the sodium level from 8 hours to 24 hours, and correction of electrolyte abnormalities (severe hyponatremia [sodium level <125 mmol per liter] or severe hypokalemia [potassium level <2.5 mmol per liter]).

STATISTICAL ANALYSIS

We calculated that the enrollment of 272 children with severe dehydration would provide 80% power to detect a 30% lower mortality at 96 hours in the pooled intravenous groups than in the oral group (assuming that 58% of the participants in the oral group and 41% of those in the intravenous groups would die and that there would be no loss to follow-up at 96 hours), at a two-sided alpha level of 0.05 (see the Supplementary Methods section). An independent data monitoring committee reviewed the interim data at four meetings. We report here the prespecified primary comparison of the pooled intravenous groups with the oral group (as the control). The two intravenous groups were also compared separately with the oral group. The analyses were performed on an intention-to-treat basis. We used Mantel–Haenszel methods to calculate a risk ratio for death at 96 hours (the primary end point), with adjustment for the prespecified covariate of trial site (hospital). Cox regression was used to calculate death at 28 days (secondary end point). Continuous end points were compared with the use of linear regression to estimate the mean between-group difference and confidence intervals at each time point. Proportions were compared with the use of chi-square tests (prespecified according to the statistical analysis plan, which is available with the protocol) and are reported with odds ratios and confidence intervals derived with the use of logistic regression. Time-to-event analyses with competing-risks regression were used to assess correction of hyponatremia and hypokalemia, with death as a competing risk. The confidence intervals were not adjusted for multiplicity and may not be used in place of hypothesis testing. Complete case analyses were used to assess the primary and secondary end points (in accordance with the statistical analysis plan) under a missing-completely-at-random assumption, given that missingness was evenly distributed between groups and was below the prespecified threshold of 10%. However, for the secondary end points for which missingness was close to the threshold, multiple imputation was performed under the missing-at-random assumption (Supplementary Methods section). Analyses were performed with the use of Stata software, version 18 (StataCorp).

RESULTS

PARTICIPANTS

From September 2, 2019, to October 27, 2024, a total of 272 participants underwent randomization: 138 were assigned to the oral rehydration group, and 134 to the intravenous rehydration groups (67 to the rapid group and 67 to the slow group). The median age was 13 months. Four participants (1%) were lost to follow-up. All the participants were included in all the analyses (Fig. S2). Recruitment was halted from March 2020 through November 2021 because of the coronavirus disease 2019 pandemic (Fig. S3). The characteristics of the participants at baseline were well balanced among the groups, and the differences were fewer than would be expected by chance (Table 1). Most of the participants had three or more signs of dehydration: 267 (98%) had sunken eyes, 242 (89%) had decreased skin

turgor, 215 (79%) were unable to take or retain oral fluids, and 76 of 261 (29%) had moderate hypotension. Previously identified risk factors for death[4,5] were highly prevalent, including altered level of consciousness (104 participants [38%]), bacteremia (largely gram-negative) (12 of 98 participants [12%]), severe hyponatremia (137 of 262 participants [52%]), and severe hypokalemia (115 of 258 participants [45%]). Few of the participants (11 [4%]) had kwashiorkor or known human immunodeficiency virus infection (2 [1%]). The representativeness of the trial population is shown in Table S1.

ADHERENCE TO ASSIGNED REHYDRATION STRATEGY AND CLINICAL MANAGEMENT

A total of 31 participants (22%) in the oral group received intravenous fluids within 24 hours, starting at a median of 123 minutes (interquartile range, 13 to 470) after randomization; 12 participants (9%) in the oral group who had shock received boluses immediately, and 14 (10%) later received boluses after shock had developed or another serious adverse event had occurred (Table 2 and Table S6). A total of 66 participants (99%) in the rapid intravenous group received intravenous fluids starting at a median of 16 minutes (interquartile range, 10 to 28) after randomization; 7 of 8 participants (88%) in the rapid intravenous group who had shock received a bolus immediately (1 participant died before administration of the bolus). All 67 participants in the slow intravenous group received intravenous fluids without boluses (5 had shock at the time of randomization) starting at a median of 12 minutes (interquartile range, 8 to 22) after randomization. Oral rehydration was started in 135 participants (98%) in the oral rehydration group (2 died before oral rehydration was initiated and 1 had missing data) at a median of 0.3 hours (interquartile range, 0.2 to 0.5). A nasogastric tube was used in 126 of 135 participants (93%) in the oral rehydration group and in 82 of 126 (65%) in the intravenous groups. Oral rehydration solution was administered after intravenous rehydration in 64 participants in the rapid intravenous group (1 died before oral rehydration solution was administered and 1 had unknown status) at a median of 5.3 hours (interquartile range, 4.0 to 7.0) (a nasogastric tube was used in 43 [67%]), and in 62 participants in the slow intravenous group (2 had unknown status) at a median of 8.7 hours (interquartile range, 8.4 to 9.2) (a nasogastric tube was used in 39 [63%]). The incidence of vomiting and use of a nasogastric tube to administer oral rehydration was higher in the oral group than in the intravenous groups (Table 2).

DEATH

Vital status was known for 271 participants (100%) at 96 hours and for 267 (98%) at 28 days. At 96 hours, 11 participants (8%) in the oral group and 9 (7%) in the intravenous groups (5 [7%] in the rapid group and 4 [6%] in the slow group) had died (adjusted risk ratio, 1.02; 95% confidence interval [CI], 0.41 to 2.52; P=0.69) (Fig. 1 and Table 3). At 28 days, 17 participants (12%) in the oral group and 14 (10%) in the intravenous groups (8 [12%] in the rapid group and 6 [9%] in the slow group) had died (hazard ratio, 0.85; 95% CI, 0.41 to 1.78). The adjusted risk ratio for death at 96 hours in the rapid intravenous group as compared with the oral group was 1.16 (95% CI, 0.40 to 3.40), and for the slow intravenous group as compared with the oral group was 0.89 (95% CI, 0.28 to 2.80) (Table S8). Findings for the primary end point were consistent across four prespecified subgroups defined according to the oral rehydration solution received, age (<1 or ≥1 year), level of consciousness, and respiratory distress at randomization (Table S9).

SAFETY AND OTHER END POINTS

Neither pulmonary edema nor signs consistent with heart failure were observed in participants in the trial. There was no evidence of a difference among groups in the incidence of serious adverse events (Table 3 and Tables S10 and S11). Deterioration in the level of consciousness or seizures occurred in 18 of 138 participants (13%) in the oral group and in 10 of 133 (8%) in the intravenous groups (odds ratio, 0.54; 95% CI, 0.24 to 1.23). Shock developed in 11 of 126 participants (9%) in the oral group and in 6 of 121 (5%) in the intravenous groups (odds ratio, 0.55; 95% CI, 0.19 to 1.53). Severe hyponatremia occurred in more participants in the oral group than in the intravenous groups at 8 hours (in 58 of 129 [45%] vs. 20 of 128 [16%]; odds ratio, 0.23; 95% CI, 0.13 to 0.41) and at 24 hours (in 35 of 129 [27%] vs. 21 of 127 [17%]; odds ratio, 0.53; 95% CI, 0.29 to 0.98) (Table 3). The time to the correction of hyponatremia was faster in the intra-

Table 1. Characteristics of the Participants at Baseline.*

Characteristic	Oral Rehydration	Intravenous Rehydration		
	(N=138)	Pooled (N=134)	Rapid (N=67)	Slow (N=67)
Male sex — no. (%)	62 (45)	64 (48)	28 (42)	36 (54)
Median age (IQR) — mo	12 (9 to 22)	14 (9 to 23)	16 (9 to 24)	14 (9 to 22)
Median weight (IQR) — kg	5.3 (4.5 to 6.1)	5.2 (4.6 to 6.1)	5.0 (4.5 to 6.1)	5.3 (4.7 to 6.1)
Median weight-for-height z score (IQR)	−4.7 (−5.5 to −4.2)	−4.9 (−5.8 to −4.2)	−5.0 (−5.8 to −4.3)	−4.9 (−5.7 to −4.2)
Median mid-upper-arm circumference (IQR) — cm	10.5 (9.6 to 11.0)	10.1 (9.5 to 11.0)	10.0 (9.5 to 10.8)	10.4 (9.6 to 11.0)
Kwashiorkor — no. (%)†	5 (4)	6 (4)	4 (6)	2 (3)
Altered level of consciousness — no. (%)‡	50 (36)	54 (40)	29 (43)	25 (37)
Restlessness — no. (%)	44 (32)	42 (31)	22 (33)	20 (30)
Sunken eyes — no. (%)	136 (99)	131 (98)	65 (97)	66 (99)
Skin pinch return 1–2 sec — no. (%)	15 (11)	12 (9)	6 (9)	6 (9)
Skin pinch return >2 sec — no. (%)	120 (87)	122 (91)	61 (91)	61 (91)
Unable to take or retain oral fluids — no. (%)	111 (80)	104 (78)	53 (79)	51 (76)
Fever — no./total no. (%)	49/137 (36)	45/134 (34)	16/67 (24)	29/67 (43)
Tachypnea — no. (%)	34 (25)	35 (26)	21 (31)	14 (21)
Median oxygen saturation (IQR) — %	100 (99 to 100)	100 (98 to 100)	100 (98 to 100)	100 (98 to 100)
Median heart rate (IQR) — beats/min	139 (118 to 155)	136 (118 to 153)	132 (114 to 156)	140 (120 to 152)
Tachycardia — no. (%)§	12 (9)	14 (10)	9 (13)	5 (7)
Capillary refill time >3 sec — no. (%)	18 (13)	22 (16)	14 (21)	8 (12)
Weak pulse — no. (%)	23 (17)	28 (21)	17 (25)	11 (16)
Cold hands or feet — no./total no. (%)	18/138 (13)	23/133 (17)	12/66 (18)	11/67 (16)
Moderate hypotension — no./total no. (%)¶	42/134 (31)	34/127 (27)	18/62 (29)	16/65 (25)
Shock — no. (%)‖	12 (9)	13 (10)	8 (12)	5 (7)
Intercostal retraction — no./total no. (%)	12/138 (9)	17/132 (13)	11/66 (17)	6/66 (9)
Deep breathing — no./total no. (%)	15/138 (11)	11/132 (8)	6/66 (9)	5/66 (8)
Lung crackles — no./total no. (%)	14/134 (10)	19/129 (15)	10/65 (15)	9/64 (14)
Bloody diarrhea — no./total no. (%)	30/136 (22)	24/133 (18)	14/66 (21)	10/67 (15)
History of vomiting — no./total no. (%)	113/137 (82)	102/133 (77)	48/66 (73)	54/67 (81)
Median appetite score (IQR)**	3 (2 to 5)	3 (2 to 4)	3 (2 to 4)	3 (2 to 5)

Breastfeeding — no./total no. (%)	76/135 (56)	62/132 (47)	29/65 (45)	33/67 (49)
Receiving nutritional therapy — no./total no. (%)	9/135 (7)	19/128 (15)	10/63 (16)	9/65 (14)
Received oral rehydration solution during current illness — no./total no. (%)	76/138 (55)	83/133 (62)	42/66 (64)	41/67 (61)
Admitted to another facility during current illness — no./total no. (%)	67/136 (49)	74/128 (58)	36/63 (57)	38/65 (58)
Diarrhea in previous 6 mo — no./total no. (%)	73/137 (53)	72/132 (55)	36/65 (55)	36/67 (54)
Previous admission for malnutrition — no./total no. (%)	29/136 (21)	50/127 (39)	21/62 (34)	29/65 (45)
Laboratory measures				
Hypoglycemia — no./total no. (%)	12/135 (9)	13/131 (10)	10/64 (16)	3/67 (4)
Median sodium level (IQR) — mmol/liter	124 (118 to 129)	124 (119 to 130)	123 (117 to 130)	125 (120 to 129)
Severe hyponatremia — no./total no. (%)	70/131 (53)	67/131 (51)	35/66 (53)	32/65 (49)
Median potassium level (IQR) — mmol/liter	2.8 (2.0 to 3.4)	2.5 (2.0 to 3.2)	2.4 (2.0 to 3.3)	2.5 (2.0 to 3.2)
Severe hypokalemia — no./total no. (%)	52/129 (40)	63/129 (49)	33/65 (51)	30/64 (47)
Median chloride level (IQR) — mmol/liter	98 (92 to 103)	98 (93 to 106)	98 (92 to 105)	99 (93 to 106)
Median bicarbonate level (IQR) — mmol/liter	16 (11 to 19)	13 (10 to 17)	12 (8 to 14)	15 (13 to 20)
Positive for human immunodeficiency virus — no. (%)	0	2 (1)	1 (1)	1 (1)
Positive rapid test for malaria — no. (%)††	25 (18)	20 (15)	9 (13)	11 (16)
Median hemoglobin level (IQR) — g/dl	11.4 (9.7 to 12.6)	11.5 (9.6 to 12.9)	11.6 (9.9 to 12.8)	11.2 (9.5 to 12.9)
Severe anemia — no./total no. (%)	0/131 (0)	0/127 (0)	0/64 (0)	0/63 (0)
Bacteremia — no./total no. (%)	4/45 (9)	8/53 (15)	3/27 (11)	5/26 (19)

* Data for some of the characteristics listed vary from the N values shown in the column heads, as follows: mid-upper-arm circumference and oxygen saturation, 137 in the oral group; appetite score, 65 in the rapid group; sodium level, 131 in the oral group, 66 in the rapid group, and 65 in the slow group; potassium level, 129 in the oral group, 65 in the rapid group, and 64 in the slow group; chloride level, 129 in the oral group, 66 in the rapid group, and 64 in the slow group; bicarbonate level, 55 in the oral group, 29 in the rapid group, and 29 in the slow group; and hemoglobin level, 131 in the oral group, 64 in the rapid group, and 63 in the slow group. Fever was defined by a temperature of higher than 37.5°C, tachypnea by a respiratory rate of more than 40 breaths per minute, hypoglycemia by a glucose level of less than 3 mmol per liter, severe hyponatremia by a sodium level of less than 125 mmol per liter, severe hypokalemia by a potassium level of less than 2.5 mmol per liter, and severe anemia by a hemoglobin level of less than 5 g per deciliter. IQR denotes interquartile range.

† Participants with kwashiorkor had pitting edema in both feet or more generalized edema.

‡ Among the participants with an altered level of consciousness, 78 (29%) responded only to vocal stimuli, 24 (9%) responded only to painful stimuli, and 2 (1%) were unresponsive.

§ Tachycardia was defined by a heart rate of more than 160 beats per minute in children younger than 12 months of age or more than 120 beats per minute in children 12 months of age or older.

¶ Moderate hypotension was defined by a systolic blood pressure of 50 to 75 in children younger than 12 months of age, 60 to 75 in children 1 to 5 years of age, or 70 to 85 in children older than 5 years of age.

‖ Shock was defined according to World Health Organization guidelines as the presence of all the following: cold hands or feet, weak and fast pulse (rate not specified), and a capillary refill time of more than 3 seconds.

** Appetite was reported by the parents or guardians and was classified on an analogue scale from 0 (very poor) to 10 (very good).

†† A positive test was considered to be a point-of-care test result that indicated the presence of malaria parasites or malaria infection within the previous 10 to 14 days.

Table 2. Clinical Management and Characteristics during the First 24 Hours after Admission.

Variable	Oral Rehydration	Intravenous Rehydration			Odds Ratio (95% CI)*
	(N=138)	Pooled (N=134)	Rapid (N=67)	Slow (N=67)	
Intravenous fluids initiated within 24 hr after randomization — no. (%)	31 (22)†	133 (99)	66 (99)	67 (100)	
Median time to initiation of intravenous fluids (IQR) — min‡	123 (13–470)	14 (9–24)	16 (10–28)	12 (8–22)	
Shock at randomization — no. (%)	12 (9)	13 (10)	8 (12)	5 (7)	
Initial bolus administered for shock — no./total no. (%)	12/12 (100)	7/13 (54)	7/8 (88)	0/5 (0)	
Treatment for correction of glucose levels during first 24 hr after admission — no./total no. (%)	10/138 (7)	9/133 (7)	4/66 (6)	5/67 (7)	0.93 (0.36–2.37)
Nasogastric tube inserted during first 24 hr after randomization — no./total no. (%)	126/135 (93)	82/126 (65)	43/64 (67)	39/62 (63)	0.13 (0.06–0.30)
Vomiting during first 24 hr after admission — no./total no. (%)	96/136 (71)	69/133 (52)	33/66 (50)	36/67 (54)	0.44 (0.27–0.75)

* The odds ratios are for the pooled intravenous groups as compared with the oral group and were estimated with the use of Mantel–Haenszel methods. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used in place of hypothesis testing.

† Shock or another serious adverse event developed in 14 participants in the oral group within 24 hours and was treated with intravenous fluids. One participant received a small amount of fluid with thiamine. Three participants received small amounts of 10% dextrose solution. One participant received a 5% dextrose solution 20 hours after randomization.

‡ Data are shown for 31 participants in the oral group, 66 in the rapid group, and 67 in the slow group.

venous groups than in the oral group (subhazard ratio, 1.55; 95% CI, 1.14 to 2.09). At 8 hours and 24 hours, the potassium level had increased more slowly in the intravenous groups than in the oral group (mean difference at 8 hours, −0.3 mmol per liter; 95% CI, −0.5 to −0.2; mean difference at 24 hours, −0.4 mmol per liter; 95% CI, −0.6 to −0.2), but there was no evidence of a difference in the time to correction of severe hypokalemia (subhazard ratio, 0.82; 95% CI, 0.57 to 1.19). At 3 days, the increase in weight was greater with intravenous rehydration (0.5 kg; 95% CI, 0.4 to 0.5) than with oral rehydration (0.4 kg; 95% CI, 0.3 to 0.4) (mean difference, 0.1 kg; 95% CI, 0.1 to 0.2), but no difference was noted at 7 days (Table 3). Similar findings were observed in other anthropometric measures (Tables S7 and S8). Results from complete case analyses were not sensitive to the missing-completely-at-random assumption (Table S12).

DISCUSSION

This multicenter trial conducted in resource-poor conditions did not show a difference in mortality between a standard oral rehydration strategy and intravenous rehydration strategies among children with severe acute malnutrition. The liberal intravenous rehydration strategies were not associated with cardiac or pulmonary complications and resulted in the use of fewer fluid boluses for shock and less use of nasogastric tubes than the oral strategy.

The key limitation of our trial was the much lower overall mortality (11%) than we predicted on the basis of two small studies, in which mortality at hospital discharge or at 28 days was reported to be 68 to 82%,[14,15] which is at the high end of the range shown with observational data. Therefore, the power to detect a benefit with respect to mortality with intravenous rehydration as compared with oral rehydration was reduced. A key reason for the low mortality in our trial may be that most children were treated in high-dependency units (or step-down, intermediate care units) by dedicated clinical trial teams, with very close and frequent monitoring to identify and treat complications (specifically fluid overload, shock, or hypoglycemia) and to ensure protocol adherence. These measures were put in place to address

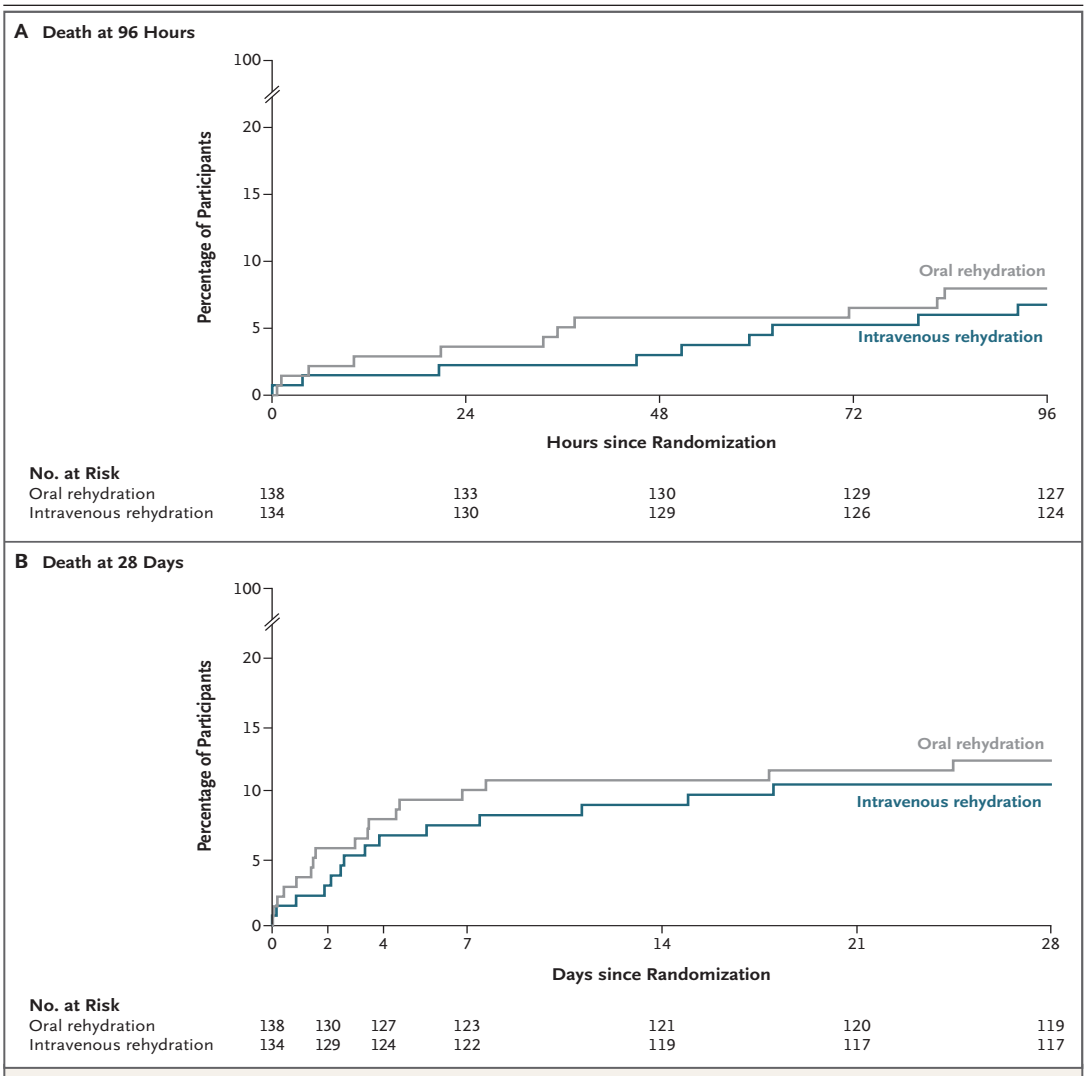

Figure 1. Death at 96 Hours and at 28 Days.

Participants were assigned to an oral rehydration strategy in accordance with the World Health Organization guidelines for children with severe acute malnutrition or to one of two intravenous strategies (a rapid strategy or a slow strategy). The primary end point was death at 96 hours (Panel A). Death at 28 days was a secondary end point (Panel B). Data shown are for the comparison of the oral rehydration group with the pooled intravenous rehydration groups.

concerns by ethics committees about the balance of risk to benefit for children participating in the trial, but the measures may reduce the generalizability of the findings. The concerns resulted from longstanding national and international guidance recommending against intravenous rehydration in children with severe acute malnutrition because of the perceived risk of incipient heart failure.[7] In routine practice in low-resourced, overcrowded pediatric units in Africa, the close clinical monitoring afforded by our trial is not possible, as evidenced by the poor outcomes reported among patients with severe acute malnutrition and severe dehydration who are under routine surveillance.[4-6] These factors underscore the need for simplified protocols for the management of dehydration. For example, at admission, 79% of the children in our trial were unable to take oral rehydration, which resulted in 93% of the participants in the oral group receiving a nasogastric tube for the administration of oral rehydration solution. The placement of a naso-

Table 3. End Points.*

End Point	Oral Rehydration	Intravenous Rehydration		Estimated Treatment Effect, Intravenous vs. Oral (95% CI)
	(N=138)	Pooled (N=134)	Rapid (N=67)	Slow (N=67)	
Primary end point					
Death at 96 hours — no. (%)	11 (8)	9 (7)	5 (7)	4 (6)	1.02 (0.41 to 2.52)†
Secondary end points					
Death at 28 days — no. (%)	17 (12)	14 (10)	8 (12)	6 (9)	0.85 (0.41 to 1.78)‡
Change in weight at 3 days — kg	0.4±0.2	0.5±0.3	0.5±0.2	0.5±0.3	0.1 (0.1 to 0.2)§
Change in mid-upper-arm circumference at 3 days — cm	0.2±0.3	0.3±0.4	0.3±0.5	0.3±0.4	0.1 (0.0 to 0.2)§
Change in weight at 7 days — kg	0.6±0.3	0.6±0.4	0.6±0.4	0.7±0.4	0.0 (0.0 to 0.1)§
Change in mid-upper-arm circumference at 7 days — cm	0.6±0.6	0.6±0.6	0.6±0.7	0.6±0.6	0.0 (−0.1 to 0.1)§
Urine output at 8 hr — ml	86±127	144±172	112±109	194±244	82 (−27 to 191)§
Safety end points					
Suspected pulmonary edema — no. (%)	0	0	0	0	
Signs consistent with heart failure — no. (%)	0	0	0	0	
Correction of severe hyponatremia					1.55 (1.14 to 2.09)¶
Correction of severe hypokalemia					0.82 (0.57 to 1.19)¶
Severe hyponatremia at 8 hr — no./total no. (%)	58/129 (45)	20/128 (16)	13/64 (20)	7/64 (11)	0.23 (0.13 to 0.41)‖
Severe hypokalemia at 8 hr — no./total no. (%)	40/128 (31)	57/127 (45)	27/63 (43)	30/64 (47)	1.79 (1.07 to 3.01)‖
Change in sodium level from 8 hr to 24 hr — mmol/liter	2.7±6.5	0.7±6.0	0.4±6.3	1.0±5.8	0.1 (−1.4 to 1.6)§
Other end points					
Serious adverse event — no. of participants (%)	32 (23)	24 (18)	14 (21)	10 (15)	0.73 (0.40 to 1.32)**
Development of shock — no./total no. (%)††	11/126 (9)	6/121 (5)	3/59 (5)	3/62 (5)	0.55 (0.19 to 1.53)**
Neurologic serious adverse event — no. (%)	0	1 (1)	0	1 (1)	
Change in sodium level at 8 hr — mmol/liter	1.9±6.0	7.5±5.0	7.4±5.3	7.5±4.7	5.7 (4.5 to 7.0)§
Hypernatremia at 8 hr — no./total no. (%)	2/129 (2)	2/128 (2)	0/64 (0)	2/64 (3)	1.01 (0.14 to 7.29)‖
Change in potassium level at 8 hr — mmol/liter	0.2±0.8	−0.1±0.9	−0.1±1.0	−0.1±0.8	−0.3 (−0.5 to −0.2)§
Change in sodium level at 24 hr — mmol/liter	4.4±7.4	8.2±7.2	7.8±7.8	8.6±6.6	4.1 (2.6 to 5.7)§
Severe hyponatremia at 24 hr — no./total no. (%)	35/129 (27)	21/127 (17)	13/64 (20)	8/63 (13)	0.53 (0.29 to 0.98)‖

Hypernatremia at 24 hr — no./total no. (%)	3/129 (2)	6/127 (5)	3/64 (5)	3/63 (5)	2.08 (0.51 to 8.51)‖
Severe hypokalemia at 24 hr — no./total no. (%)	26/128 (20)	36/125 (29)	17/62 (27)	19/63 (30)	1.59 (0.89 to 2.83)‖
Change in potassium level at 24 hr — mmol/liter	0.6±1.0	0.2±0.9	0.3±0.9	0.1±0.8	−0.4 (−0.6 to −0.2)§§

* Plus–minus values are means ±SD. Data for some of the end points listed vary from the N values shown in the column heads, as follows: change in weight and change in mid-upper-arm circumference at 3 days, 124 in the oral group, 62 in the rapid group, and 61 in the slow group; change in weight and change in mid-upper-arm circumference at 7 days, 124 in the oral group, 60 in the rapid group, and 62 in the slow group; urine output at 8 hours, 18 in the oral group, 11 in the rapid group, and 7 in the slow group; change in sodium level at 24 hours, 126 in the oral group, 64 in the rapid group, and 64 in the slow group; change in sodium level and potassium level at 8 hours, 126 in the oral group, 64 in the rapid group, and 64 in the slow group; change in sodium level and potassium level at 24 hours, 126 in the oral group, 64 in the rapid group, and 63 in the slow group. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used in place of hypothesis testing.

† The value is the risk ratio, estimated with the use of Mantel–Haenszel methods and adjusted for trial site ($P=0.69$).

‡ The value is the hazard ratio, estimated with the use of Cox regression. A test of the proportional-hazards assumption yielded a global P value of 0.89, with $P>0.22$ for all covariates.

§ The value is the difference in means.

¶ The value is the subhazard ratio, with death as a competing risk.

‖ The value is the odds ratio, estimated with the use of logistic regression.

** The value is the odds ratio.

†† This category does not include the participants who had shock at the time of randomization.

gastric tube is not a trivial, low-risk procedure, especially in children with impaired consciousness and high purging rates. The current recommendations have resulted in additional demands on limited personnel because oral rehydration solution cannot be administered by the child's caregiver (as noted in guidance documents). In contrast, slow intravenous rehydration, even compared with rapid rehydration, was simpler to implement in that it required no calculation of volumes for boluses or adjustment for the rapid and slower rehydration phases according to age.

Another limitation was the low number of participants with kwashiorkor, a key group that is expected to be at high risk for heart failure. However, our research group has previously shown that myocardial function is preserved in children with severe acute malnutrition, with no difference in fractional shortening (a global measure of myocardial function) between children with marasmus (severe wasting) and those with kwashiorkor.[16] Therefore, the results are most likely generalizable to this subgroup.

A study that is relevant to the broader population of hospitalized children with acute diarrhea with severe dehydration (fluid loss amounting to approximately 10% of body weight) showed that approximately 20% of the children in the study temporarily met the anthropometric criterion for severe acute malnutrition (mid-upper-arm circumference <11.5 cm) but were "reclassified" as undernourished after rehydration.[23] Thus, through "slippage," the current recommendations may have wider implications because potentially 20% of children without severe acute malnutrition could be inappropriately diagnosed as "malnourished" and "rehydrated." This factor may have contributed to the poor outcomes observed in the Global Enteric Multicenter Study (GEMS).[24]

Currently, at the bedside, clinicians need to consider nutritional status, age, and the presence of shock to determine which rehydration strategy to follow. Given the findings of this trial, in the absence of other data, we would suggest that current guidance be reviewed to consider simplifying rehydration protocols and removing the distinction in treatment between children with severe acute malnutrition and those who are not malnourished, which would be more pragmatic in the under-resourced settings where most children are treated.

Although there was no evidence of a differ-

ence in mortality at 96 hours between the rehydration strategies we assessed, the power to detect modest differences was low. Specifically, there was no apparent signal of harm with the use of the liberal intravenous rehydration strategies, including no evidence of fluid overload or sodium overload, as compared with the oral rehydration strategy currently recommended by the WHO.

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