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Reduction of unnecessary transfusion and intravenous fluids in severely malnourished children is not enough to reduce mortality

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Abstract

Aim: To test whether standardising the use of blood transfusions and intravenous (IV) infusions could reduce fatality in severely malnourished children admitted to Mulago Hospital, Kampala.

Methods: Improved adherence to the WHO protocol for blood transfusion and IV fluids was effected in patients with severe malnutrition by continuous medical education. A 'before and after' design was used to study 450 severely malnourished children (weight-for-height <-3 *Z*-score or presence of oedema) under 60 months of age. A total of 220 pre- and 230 post-'improved practice' patients were enrolled consecutively during the periods September to November 2003 and September to December 2004, respectively. Patients were followed up until discharge or death. The Kaplan–Meier survival curve and the Cox regression hazard model were used for univariate and multivariate analyses, respectively.

Results: Overall case fatality was 23.6% (52/220) in the pre-period and 24.8% (57/230) in the post-period ($p=0.78$). Most of the deaths occurred in the 1st week of admission (73%, 38/52 in the pre-period and 61%, 35/57 in the post-period) and were of children who had received blood transfusion or IV infusion or both in the pre-period. Mortality in children transfused and/or infused was significantly reduced in the post-period (82%, 31/38 in the pre-period *vs* 23%, 8/35 in the post-period, $p=0.008$). In the post-period, there was a significant reduction in the number of inappropriate blood transfusions (18%, 34/194 *vs* 3.5%, 8/230, $p=0.01$) and IV fluid infusions (27%, 52/194 *vs* 9%, 20/230, $p<0.001$). Survival improved in children who received blood transfusions in the post-period [hazards ratio (HR) 0.22, 95% CI 0.30–1.67 *vs* HR 4.80, 95% CI 1.71–13.51], as did that of children who received IV infusions (HR 2.10, 95% CI 0.84–5.23 *vs* HR 3.91, 95% CI 1.10–14.04).

Conclusion: Management according to the WHO protocol for severe malnutrition can reduce the need for blood and IV infusions. However, further studies are required to verify whether full implementation of the WHO protocol reduces the high case fatality in sub-Saharan hospitals.

Introduction

Hospital case-fatality rates for severe malnutrition remain high.[1–4] Poor-quality care, especially faulty case management, is considered to be the main cause.[3,5,6] WHO management guidelines include adequate and prompt triage, assessment and treatment.[7–9] Unfortunately, the financial and human resources required to implement the full WHO protocol and simultaneously address all aspects of management are unavailable in many low-resource settings.

Recently, we reported blood transfusions (BT) and intravenous (IV) fluid infusions to be major risk factors for mortality in severely malnourished children in Mulago Hospital.[10] This study was designed to

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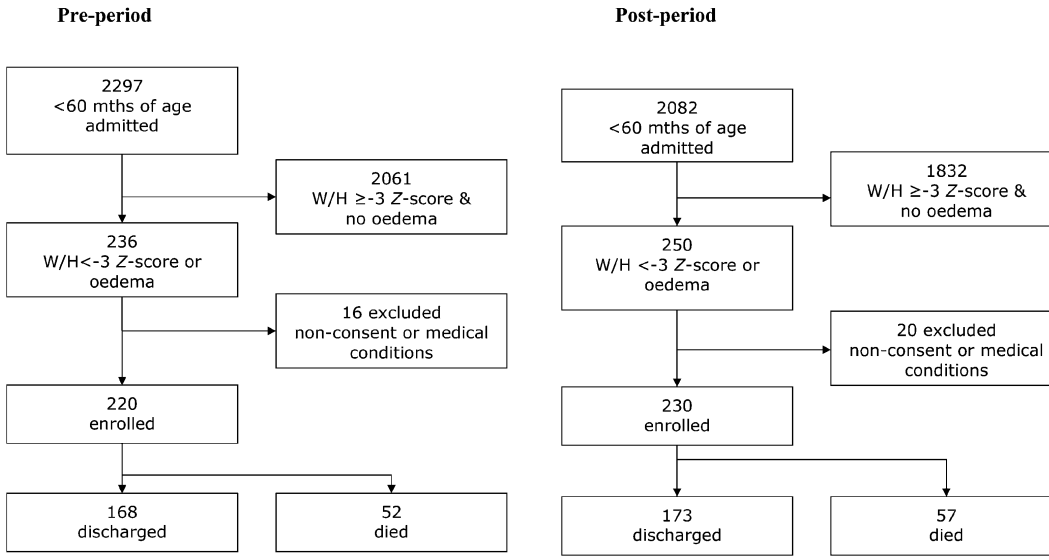

FIG. 1. Profile of the 450 severely malnourished children enrolled in the pre- and post-periods.

restrict the use of BT in children with very severe anaemia and to give IV infusions only to children with severe dehydration and shock with the aim of reducing mortality.

Subjects and Methods

The 'before and after' design[11] was used to study children <60 months of age admitted to Mulago Hospital, Kampala whose weight-for-height was <-3 *Z*-score of the United States National Center for Health Statistics median or who had bilateral pitting pedal oedema. The pre-period included children admitted to the paediatric wards between September and December 2003 before the introduction of the practice and the post-period included children admitted to the same paediatric wards between September and December 2004, 10 months after introduction of the improved practice (Fig. 1).

Improved practice to reduce unnecessary BT and IV infusions was in accordance with the WHO guidelines and included (i) BT for patients with haemoglobin (Hb) <4 g/dL or in septic shock with whole blood (not exceeding 10 ml/kg bodyweight and frusemide 1 mg/kg at the start of transfusion), (ii) patients with diarrhoea were given ReSoMal solution instead of standard WHO ORS, 5–10 ml/kg bodyweight every half hour for 2 hours then after every loose stool for up to 10 hours, alternating with F75 feeds; children who could not take oral feeds were given the solution by nasogastric tube (amount per kg bodyweight and frequency displayed on wall charts), (iii) restriction of IV fluids only to patients in shock (lethargic, unconscious with weak, fast pulse and cold hands) using either Ringers lactate (Na^+ 130 mmol/L, K^+ 5.4 mmol/L) or half-strength Darrow's (Na^+ 61 mmol/L, K^+ 17 mmol/L) plus 5% dextrose given at 15 ml/kg/h for 1 hour, then continued as for the regimen for treating dehydration. Doctors and nurses working in the paediatric wards and the nutrition unit received continuous medical education (CME) on the management of malnutrition. Supervision by the senior doctors and nurses was also strengthened.

F75 and F100 sachets were provided throughout the study period and given at 100 kcal/kg/day; feeds were given 3-hourly in phase 1 and the transition phase. Very sick children were fed 2-hourly by nasogastric

tube. These sachets replaced the high-energy milk used in the pre-period. Children with oedema received 100 kcal/kg/day and those with severe wasting were given 150 kcal/kg/day.

Other aspects of treatment remained the same. Systematic antibiotics were given parenterally for 7 days (ampicillin and gentamicin). Folic acid 5 mg daily and vitamin A were given as recommended by the national supplementation programme. Critical signs were recorded on each child's clinical monitoring form and included respiratory and pulse rates and temperature reading twice and weight once daily.

Children on BT or IV fluids were closely monitored in a side room where their respiratory and pulse rates were recorded every 30 minutes and clinical signs of fluid overload monitored (re-appearance or worsening of oedema and engorged jugular veins). For seriously ill children, serial weights were not taken because of the difficulty of using the hanging Salter scales. An increase in both respiratory and pulse rates, engorgement of the jugular veins or increasing oedema were a sign to stop IV fluids and re-assess the child for fluid overload.

Large feeding and rehydration charts were posted on the walls of the paediatric wards to aid correct selection of type, amount, route and period of administration of IV fluids. Copies of the guidelines were also distributed to all doctors and nurses and laboratory results were made available promptly to assist patient management.

Data collection

Details of the data collection have been published elsewhere.[10]

Ethical considerations

The study was approved by Makerere University Medical School, Mulago Hospital, the Uganda National Council for Science and Technology and the institutional review boards in Norway (REK VEST).

Statistical analysis

SPSS version 13 and STATA version 9 were used. Characteristics and health on admission were compared using the χ^2 test. Continuous parameters for cut-off points for normal levels were glucose <3 mmol/L, potassium <3.5 mmol/L, sodium <135 mmol/L, Hb <5 g/dL for severe anaemia, serum albumin <3.5 mg/dL and serum protein <5.5 mg/dL.

Kaplan–Meier curves were used to determine survival functions. Associations within and between groups were measured by univariate analysis using the log rank test. Cox's proportional hazards model was used to compare survival in the 1st week after BT or IV infusion with and without transfusion or with and without infusion adjusted for independent variables that were significant in univariate analysis in one of the two study periods and co-variates (sex and type of severe malnutrition). The median time from admission to first transfusion or infusion was 1 day [interquartile range (IQR) 0–3]. In children not receiving any transfusion or infusion, this median time of 1 day after admission was used as a starting point for the time variable in the regression. Failure was the death of a child. For both univariate and multivariate analyses, interactions between variables were not significant; we therefore present the models without these terms. A total of 98 and 184 cases with complete data were considered in the multivariate analysis in the pre- and post-periods, respectively.

Results

A total of 450 severely malnourished children <60 months of age were included in the study, 220 and 230 in the pre- and post-periods, respectively. The average median age of the children in the pre-period was

Annals of Tropical Paediatrics ATP8104.3d 7/1/08 22:01:36
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TABLE 1. *Characteristics of patients with severe malnutrition admitted in the pre- and post-periods.*

	Pre-period *n*/total (%)	Post-period *n*/total (%)
Male	131/220 (59)	150/230 (65)
Age ⩽24 mths	182/220 (83)	175/230 (76)
Oedema⋆	108/220 (49)	144/230 (63)
Diarrhoea	88/220 (40)	96/230 (42)
Severe dehydration†	12/220 (6)	32/230 (14)
Hypothermia[a]	5/174 (3)	19/225 (8)
Respiratory tract infection[b]	132/166 (79)	144/206 (70)
Bacteraemia	31/217 (14)	45/228 (20)
HIV-1-positive†	64/213 (30)	86/199 (43)
Malaria[c]	18/214 (8)	18/230 (8)
Hypoglycaemia[d†]	18/195 (9)	5/213 (2)
Hypokalaemia[e†]	75/212 (35)	103/218 (45)
Hyponatraemia[f⋆]	106/212 (64)	149/217 (50)
Severe anaemia[g]	14/217 (6)	19/230 (8)
Hypoproteinaemia[h]	133/212 (63)	147/218 (63)
Hypo-albuminaemia[i]	170/212 (80)	199/218 (86)

[a] Hypothermia, axillary temperature <35°C; [b] respiratory infection, diagnosed by chest radiograph; [c] malaria, blood slide positive for malaria parasites; [d] hypoglycaemia, blood glucose <3 mmol/L; [e] hypokalaemia, K^+ <3.5 mmol/L; [f] hyponatraemia, Na^+ <135 mmol/L; [g] severe anaemia, Hb <5 mg/dL); [h] hypoproteinaemia, serum protein <5.5 g/dL; [i] hypo-albuminaemia, serum albumin <3.5 g/dL. Significant difference: ⋆ $p<0.001$, † $p<0.05$.

16 months (IQR 12–24) and 18 months (IQR 13–24) in the post-period. Distribution by age and gender was similar in both periods. There were six children <6 months of age in each period. There were significantly more cases of oedematous malnutrition, severe dehydration, hypothermia, HIV infection and hypokalaemia and fewer of hypoglycaemia in the post-period than in the pre-period (Table 1). The median (IQR) duration of admission until death was similar in both periods [4 (2–9) and 5 (3–13) days] and also the duration of admission until self-discharge [8 (5–13) and 8 (3–17) days]. However, the duration of admission until formal discharge was significantly longer in the post-period [13 days (5–23)] than in the pre-period [8 days (4–19), $p=0.004$].

Case fatality

Overall case fatality was 23.6% (52/220) in the pre-period and 24.8% (57/230) in the post-period ($p=0.78$). Over 70% (38/52) of deaths in the pre-period and 61% (35/57) in the post-period occurred in the 1st week of admission (Table 2). Most early deaths in the pre-period were children who had received either BT or IV infusions or both (82%, 31/38) but significantly fewer deaths were associated with this in the post-period (23%, 8/35, $p=0.008$).

TABLE 2. *Number of patients who died in the 1st week of admission by BT and IV infusion status.*

Died in 1st week	Pre-period *n* (%)	Post-period *n* (%)	Total *n* (%)
Transfusion	12/38 (31.6)	5/35 (14.3)	17/73 (23.3)
Infusion	12/38 (31.6)	3/35 (8.6)	15/73 (20.5)
Both	7/38 (18.4)	0/35 (0)	7/73 (9.6)
Neither⋆	7/38 (18.4)	27/35 (77.1)	34/73 (73.0)
Total	38/38 (100)	35/35 (100)	73/73 (100)

⋆ Neither transfused nor infused

Blood transfusion and anaemia

The proportion of children who received IV fluids (BT and IV infusion) fell from 27% (52/194) to 9% (20/230) ($p<0.001$) and the number of children who received BT in the 1st week of admission also fell, from 18% (34/194) in the pre-period to 3.5% (8/230) in the post-period ($p=0.01$).

Patients were compared with regard to requirement for BT and outcome in the 1st week of admission in the two periods. The majority (44/51) of those who received BT in the pre-period did not have severe anaemia (Hb ⩾5 g/dL) and 39% of them died. As this practice declined, so did the associated mortality (Table 3). However, the likelihood of receiving transfusion also decreased in the group with very severe anaemia. In spite of this, mortality in this group also declined (Fig. 2).

By both univariate and multivariate analysis of the pre-period, BT was associated with significantly poorer survival (HR 3.20, 95% CI 1.74–5.86 and HR 4.80, 95% CI 1.71–13.51, respectively). In the post-period, however, BT was associated with improved survival (HR 0.83, 95% CI 0.26–2.69 and HR 0.22, 95% CI 0.30–1.67) (Tables 4 & 5).

IV fluid infusion and dehydration

The proportion of children who received IV infusions in the pre-period was 32% (62/193) and was significantly less in the post-period (15%, 35/230, $p<0.001$). However, >50% of the IV infusions were administered in the 1st week of admission in both periods, 60% (37/62) and 51% (18/35), respectively.

Twenty-eight per cent (53/184) of the children who were not severely dehydrated in the 1st week of admission received IV infusion in the pre period, irrespective of dehydration status, and 30% (16/53) died. As this practice decreased (27/214), so did the associated mortality (1/27) in the post-period (Table 6). However, the number of severely dehydrated children who were not infused increased slightly and their survival also declined. In addition, survival of those who received IV fluids in the 1st week did not improve much (Fig. 3).

IV infusions contributed significantly to lower survival in both univariate (HR 2.54, 95% CI 1.39–4.66) and multivariate analysis (HR 3.91, 95% CI 1.10–14.04). In the post-period, the contribution of IV infusion to poorer survival was not significant by either univariate (HR 21.54, 95% CI 0.71–3.32) or multivariate analysis (HR 2.10, 95% CI 0.84–5.23).

HIV/AIDS infection

Thirty per cent (64/213) of the children were infected with the HIV-1 virus in the pre-period and 43% (89/199) in the

TABLE 3. *Number of patients who died in the 1st week of admission by anaemia and BT status.*

	Pre-period *n*/total (%)	Post-period *n*/total (%)
Very severe anaemia (Hb <4 g/dL)		
Transfused	0/4 (0)	0/1 (0)
Not transfused	1/2 (50)	0/7 (0)
Severe anaemia (Hb 4–<5 g/dL)		
Transfused	1/3 (33)	0
Not transfused	1/2 (50)	3/11 (27)
No severe anaemia (Hb ⩾5 g/dL)		
Transfused	17/44 (39)	3/19 (16)
Not transfused	16/136 (12)	28/188 (15)
Total	36/191 (19)	34/226 (15)

All the numbers in the table are of patients with known haemoglobin and transfusion status.

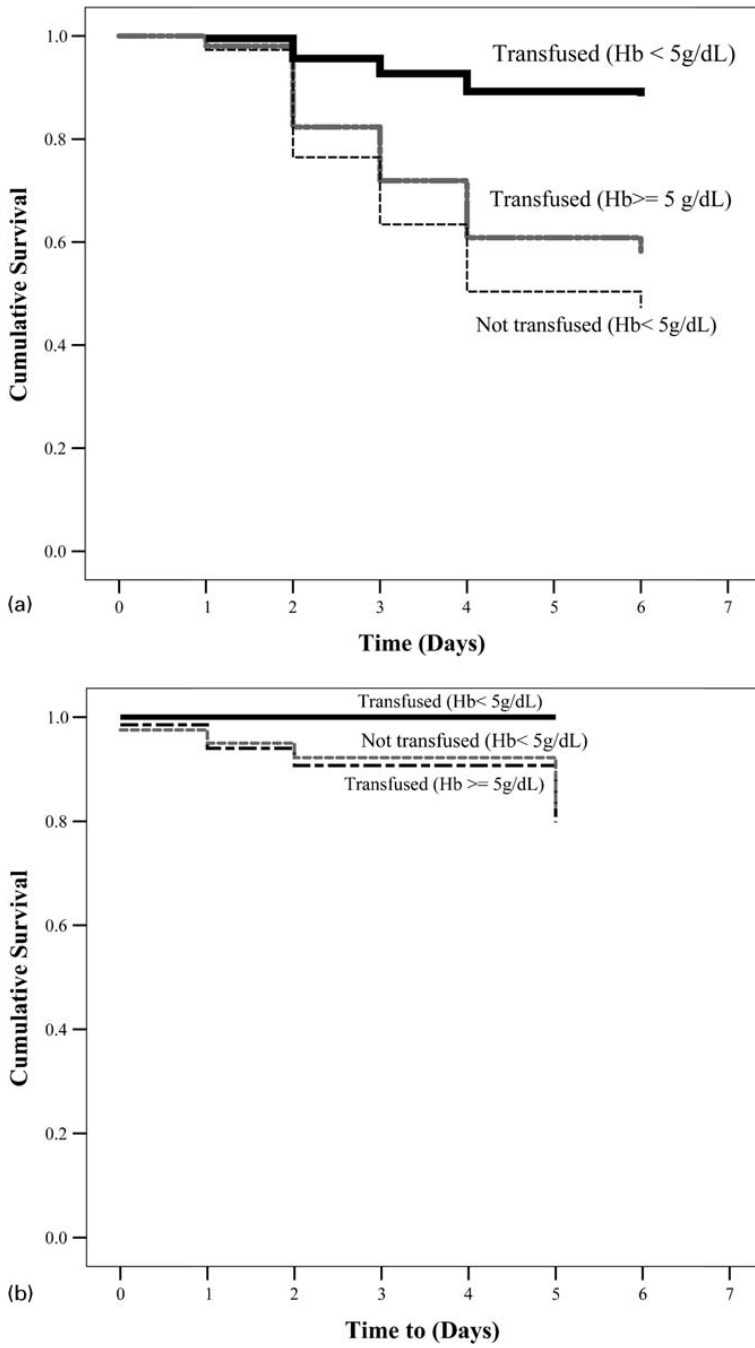

FIG. 2. Cox proportional survival regression curves showing unadjusted cumulative survival of patients 1 week after BT or IV infusion by transfusion status in the pre- (2a) and post-periods (2b).

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TABLE 4. *Univariate Cox regression analysis of selected factors, fluid management and death 1 week after transfusion or infusion**.

	Pre-period		Post-period	
	Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value
Male	0.84 (0.45–1.55)	0.575	0.63 (0.34–1.15)	0.132
Oedema	1.29 (0.70–2.38)	0.410	0.95 (0.51–1.78)	0.879
Diarrhoea	1.41 (0.77–2.59)	0.264	1.67 (0.92–3.04)	0.094
Respiratory infection	0.39 (0.17–0.88)	**0.023**	1.34 (0.66–2.73)	0.410
Bacteraemia	1.76 (0.84–3.69)	0.134	1.30 (0.64–2.64)	0.474
Bacteriuria	1.77 (0.80–3.90)	0.156	0.76 (0.30–1.94)	0.563
HIV-1 status	1.63 (0.87–3.07)	0.129	1.32 (0.71–2.44)	0.372
Hypothermia	2.67 (0.82–8.70)	0.103	1.09 (0.38–3.02)	0.884
Hypoglycaemia	2.57 (1.12–5.90)	0.025	3.98 (1.22–12.97)	0.022
Hypokalaemia	1.54 (0.83–2.88)	0.172	0.77 (0.42–1.43)	0.416
Hyponatraemia	1.35 (0.72–2.53)	0.343	0.94 (0.50–1.77)	0.861
Severe anaemia	1.79 (0.64–5.04)	0.269	1.21 (0.43–3.8)	0.721
Blood transfusion	3.20 (1.74–5.86)	**<0.001**	0.83 (0.26–2.69)	0.752
IV fluid infusion	2.54 (1.39–4.66)	**0.003**	1.54 (0.71–3.32)	0.271

* Starting point for the time variable was 1 day after admission.

TABLE 5. *Multivariate Cox regression analysis of selected factors, fluid management and death 1 week after transfusion or infusion**.

	Pre-period		Post-period	
	Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value
Male	0.86 (0.29–2.55)	0.79	0.60 (0.30–1.19)	0.15
Oedema	1.98 (0.58–6.78)	0.28	0.93 (0.41–2.01)	0.86
Diarrhoea	0.57 (0.17–1.85)	0.35	1.54 (0.78–3.03)	0.21
Hypothermia	2.18 (0.41–11.41)	0.36	0.94 (0.28–3.14)	0.93
Respiratory infection	0.37 (0.19–1.19)	0.10	1.26 (0.55–2.87)	0.58
Bacteraemia	3.1 (0.93–10.26)	0.07	1.69 (0.77–3.71)	0.19
Hypoglycaemia	0.53 (0.08–3.33)	0.52	5.35 (1.32–21.60)	0.02
Hypokalaemia	1.73 (0.64–4.70)	0.28	0.57 (0.27–1.20)	0.14
HIV-1-positive	1.31 (0.43–3.95)	0.63	0.89 (0.44–1.82)	0.76
Blood transfusion	4.80 (1.71–13.51)	**0.003**	0.22 (0.03–1.67)	0.14
IV fluid infusion	3.91 (1.10–14.04)	**0.04**	2.10 (0.84–5.23)	0.11

* Starting point for the time variable was 1 day after admission.

TABLE 6. *Number who died in the 1st week of admission by dehydration status.*

	Pre-period *n*/total (%)	Post-period *n*/total (%)
Severe dehydration		
IV-infused	3/9 (33)	1/8 (12)
Not IV-infused	0/1 (0)	4/8 (50)
No severe dehydration		
IV-infused	16/53 (30)	1/27 (4)
Not IV-infused	19/131 (14)	26/187 (14)
Total	38/194 (20)	32/230 (14)

Includes only children with known dehydration and IV infusion status.

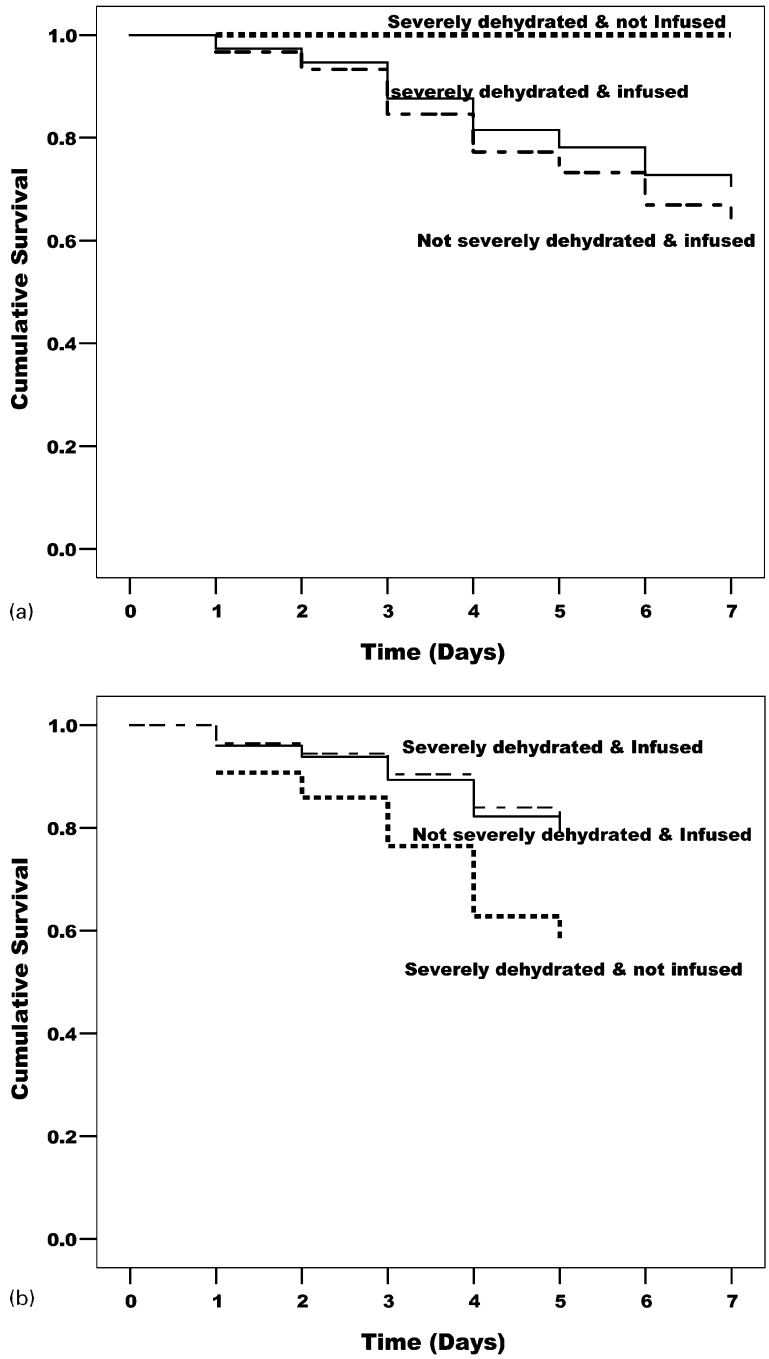

FIG. 3. Cox proportional survival regression curves showing unadjusted cumulative survival of patients 1 week after BT or IV fluids by intravenous fluid infusion status in the pre- (3a) and post-periods (3b).

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post-period. In both periods. however, HIV-1 infection was not a significant factor in mortality in the 1st week of admission by univariate and multivariate analysis (Tables 4 and 5).

Discussion

This and the previous study demonstrate that BT and IV infusions are important contributors to mortality in severely malnourished children.[10] They also demonstrate that severely malnourished children need extremely precise protocol management. There was a significant decrease in the number who received BT and IV infusions in children admitted in the post-period and the deaths associated with this mode of care declined significantly in the 1st week of admission. However, overall case fatality did not decrease (23.6% *vs* 24.8%), in contrast with a similar study in Bangladesh where the case fatality decreased from 47% to <5%.[12] Although such low fatality rates have been achieved/reported elsewhere,[12–15] they have not yet been reported in hospital settings in the sub-Saharan region.[5,16,17]

The reasons for the lack of an overall decline in case fatality despite improvement in practices for BT and IV infusions need to be explored. There were some differences between the pre- and post-period groups. Patients in the post-period had more severe dehydration, hypoglycaemia, hyponatraemia and hypokalaemia and a higher prevalence of oedema (Table 1). However, these differences between the groups are probably not sufficiently large to entirely explain the non-effect of the improved practice.

One particular factor that differed between the two periods was the number of patients with HIV infections (30% *vs* 43% in the pre- and post-periods, respectively). HIV-1 infection has increased the burden of disease in children[18,19] and led to an increase in paediatric admissions in sub-Saharan Africa along with the associated high mortality.[20–24] In Malawi, HIV-1 infection is a major contributor to mortality in severely malnourished children.[25] In this study, the proportion of severely malnourished, HIV-1-infected children and their mortality rate were similar to reports from elsewhere in the region.[21,25–27] The increase in children admitted with HIV infection probably reflects improved care in the community, including better accessibility to admission. This might be partly owing to the new paediatric infectious disease clinic in Mulago Hospital which identifies a greater number of HIV-infected children and refers them for admission when seriously ill. In our analysis, however, the increased prevalence of HIV in the study children did not seem to have contributed significantly to case fatality in the 1st week.

Another possible explanation is the role of infection and metabolic derangement. Infections are reported to be the main contributor to the continuously high case fatality rates in severely malnourished children in sub-Saharan Africa. A study in Tanzania demonstrated a high incidence of nosocomial bacterial infections in hospitalised, severely malnourished children and suggested that this could be the main cause of mortality.[28] However, most deaths in both study periods occurred in the 1st week of admission, limiting the influence of nosocomial bacterial infections. Late care-seeking is another factor. In Uganda, although awareness of childhood illnesses is high, care-seeking remains low. Less than 20% of mothers contact health facilities as the first care option.[29] Children present late, often in a critical condition.[30] If late arrival is coupled with inadequate triage on admission, the survival of severely malnourished children can be jeopardised, in spite of somewhat improved management. In this study, the children in the post-period were more sick and more immunocompromised than those in the pre-period on admission and presented with more complications

Annals of Tropical Paediatrics ATP8104.3d 7/1/08 22:01:51
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such as severe dehydration, hypothermia and hypokalaemia.

Improved practice regarding BT and IV infusions in the management of severe malnutrition was effective in reducing deaths associated with transfusion and infusion. However, it did not reduce overall case fatality. Perhaps, in this setting, the potential causes of mortality are so many that controlling only one merely shifts the mortality to other causes. Full implementation of the WHO protocol or locally adapted similar protocols with adequate financial and human resources might have a greater impact on overall case fatality.

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Annals of Tropical Paediatrics ATP8104.3d 7/1/08 22:01:51
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