Systematic review of the role of fluid infusions and blood transfusions in the care of hospitalized children with severe acute malnutrition

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Abbreviations

CI	confidence interval
F-75	therapeutic milk used in stabilization phase of the treatment of SAM
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
Hb	Hemoglobin
HIV	human immunodeficiency virus
HR	hazard ratio
IQR	interquartile range
IV	intravenous
NCHS	National Center for Health Statistics
OR	odds ratio
ORS	oral rehydration salts
PICO	Population, Intervention, Comparator and Outcomes
RCT	randomized controlled trial
ReSoMal	rehydration solution for malnutrition
RUTF	ready-to-use therapeutic foods
SAM	severe acute malnutrition
WHZ	weight-for-height z-score
WHO	World Health Organization

Measurements

g	gram
dL	decilitre
kg	kilogram
ml	millilitre

Background

Undernutrition remains an underlying factor in more than one third of the deaths in children under 5 years of age worldwide (*1*). Children with severe acute malnutrition (SAM) – kwashiorkor (oedematous malnutrition), marasmus (severe wasting), or both (*2*) – continue to represent a large proportion of this disease burden as a common final pathway to mortality. While the majority of these children can be cared for in the outpatient setting with ready-to-use therapeutic food (RUTF) (*3*), the most severe cases of SAM continue to require inpatient hospital management for a variety of complications. In addition to a variety of superimposed infections and other complications often associated with or exacerbated by HIV, dehydration and anaemia are two of the most challenging and frequently encountered complications among hospitalized malnourished children.

Dehydration (usually due to profuse diarrhoea) is often difficult to diagnose in malnourished children as the clinical signs usually relied upon to diagnose it often overlap with those seen in severe wasting. Current international guidelines for the management of children hospitalized with SAM (*4–6*) all address the treatment of dehydration with appropriate caution, given the risk for overhydration and the induction of pulmonary and interstitial oedema, cerebral oedema and heart failure in malnourished children. These adverse effects of overhydration are particularly relevant in developing world settings without easy and rapid access to radiography, diuretics, inotropic support and other components of intensive care available in well-resourced settings. These concerns have recently gained even more attention due to the controversy (*7*) generated by the recent multicentre FEAST trial results (*8*) that showed an increased mortality among hospitalized children in Africa who received fluid boluses – even though children with severe malnutrition and gastroenteritis were specifically excluded from the study. Nevertheless, dehydrating diarrhoea remains a frequent problem complicating the care of malnourished children: sometimes as the triggers for SAM; sometimes as a consequence of poor intestinal absorption of high osmolar nutritional therapy. Thus, in order to balance these conflicting concerns, emphasis generally has been placed on the use of oral rehydration salts (ORS) such as ReSoMal for the treatment of dehydration in malnourished children, with intravenous (IV) therapy reserved for children with severe shock (*4–6*).

Another frequently encountered complication among children hospitalized for SAM is severe anaemia, often associated with bacteraemia, frequent bouts of malaria, hookworm infection, HIV infection and micronutrient deficiency (*9,10*). There are conflicting demands that must be balanced when caring for severely malnourished patients with anaemia – the conservation of limited blood products in resource-poor settings, the risk of transmission of HIV, hepatitis B, hepatitis C and other bloodborne pathogens

(*11*) and the risk of fluid overload (as with IV fluid infusions for dehydration) on the one hand, and the physiological damage and mortality that results from decreased oxygen perfusion to metabolically active tissues on the other hand. The most recent guidelines for hospitalized children with SAM and anaemia (*5,6*) recommend blood transfusion for children with hemoglobin (Hb) levels less than 4 g/dL or for a Hb of 4–6 g/dL with respiratory distress. It is recommended that the transfusions be given more slowly and at smaller volumes compared to what is given to well-nourished children, specifically either 10 ml/kg of whole blood over three hours preceded by furosemide 1 mg/kg IV at the start of transfusion. If there are signs of heart failure, the recommendation is to give 10 ml/kg of packed red blood cells instead of whole blood. Close monitoring of cardiac and respiratory rates also are recommended to monitor for fluid overload. A minimum duration of four days between transfusions also is advised. For children with SAM, deficient by their very nature in both the micronutrients and macronutrients necessary for hematopoiesis and often suffering from one or more infectious processes, the safety and efficacy of these transfusion recommendations remain an open question at the same time as blood transfusion is increasingly recognized as an important and effective component of hospital care for patients in the developing world (*11*).

Given the uncertainties in the management of hospitalized children with SAM with regard to fluid infusions for dehydrating diarrhoea and blood transfusions for anaemia, a systematic review of the available literature on the subject is reported here. The specific Population, Intervention, Comparator and Outcomes (PICO) question was:

> For children with SAM with severe dehydration or shock, do blood and/or plasma transfusions reduce mortality, time to recovery or the incidence of cardiac failure when compared to, or in combination with, crystalloid infusions or treatment without any intravenous fluids?

Methodology

A search of Medline and Google Scholar for all studies from 1985 to 2011 was carried out. Observational and randomized studies published in any language were included. Initial key words for searches included “malnutrition”, “severe malnutrition”, “kwashiorkor”, “marasmus”, “transfusion” and “infusion”. Outcome measures of interest included mortality and time to recovery as well as adverse events such as cardiac failure and fluid overload. Relevant studies were identified, reviewed and selected for inclusion by one scientific reviewer initially, with a second and third review by two other scientific reviewers. Reference lists, review articles, opinion pieces and personal literature

collections also were evaluated to identify other relevant articles that might have been missed in the initial searches.

An evidence-based Grading of Recommendations, Assessment, Development and Evaluation (GRADE) (*12*) review table was created for the PICO question of interest. GRADE provides a systematic evaluation of the quality of evidence in order to generate an indication of the confidence that an estimate of effect is correct. In the GRADE approach, randomized controlled trials (RCTs) constitute high-quality evidence. Observational studies without important limitations constitute low-quality evidence. The designated quality of evidence may be decreased if there are study limitations, inconsistent results or publication bias or if the evidence is indirect. Similarly, the designated quality of evidence also may be increased if there is a large magnitude of effect, plausible confounding that would reduce the demonstrated effect or a dose-response gradient.

Results

The database searches described above identified 475 articles. Of these, 466 were excluded as not relevant after screening the abstracts and titles, and 2 more were excluded after evaluating the full text of the articles, leaving 7 articles for inclusion in the final review.

Systematic review

The quality of data available for this PICO question was “Low” to “Very Low” since there were no prospective randomized trials in the target population. The observational studies that were found generally were not specific to children with SAM and often did not specifically report outcomes for this population of children, or they described outcomes after the implementation of treatment protocols for transfusions and infusions.

There was a paucity of studies and data relating to this question – no RCTs were identified. Seven observational studies or case series were found to contain data that were somewhat relevant – although none specifically was designed to assess the efficacy and safety of infusions or transfusions in malnourished children.

Lackritz and colleagues presented a case series in 1992 describing survival rates among children who were or were not transfused for anaemia at Siaya District Hospital in Kenya (*13*). An almost equal number of malnourished children – defined as weight-for-height <-2 z-score (WHZ) on the old National Center for Health Statistics (NCHS) growth standards (*14,15*) – received blood transfusions as those who did not, although no information is given about mortality or other outcomes among malnourished children specifically.

A brief report by English and colleagues at Kilifi District Hospital in Kenya demonstrated the overall effectiveness of blood transfusion for severe anaemia among hospitalized children (*16*). No indication was given of how many children were malnourished at the time of transfusion or their clinical status. However, they reported that 11/56 (20%) of the children who were transfused but died more than six hours after admission had severe protein energy malnutrition. Among those who died more than six hours after admission but were not transfused, 7/16 (44%) had severe malnutrition as their primary diagnosis.

Cheema and colleagues at Queen Elizabeth Central Hospital in Blantyre, Malawi, described the development of a paediatric blood transfusion protocol in which severely malnourished children were indicated to receive 5 ml/kg of red cells or 10 ml/kg of whole blood over four hours if the starting Hb was less than 4 g/dL or if it was 4–6 g/dL with other clinical indications for transfusion (*17*). The number of malnourished children in this report was very small, with seven children transfused before the introduction of this new protocol but no outcome information about them provided, and only two children included after the protocol was instituted, of whom one died.

Maitland and colleagues at Kilifi District Hospital in Kenya also attempted to identify which severely malnourished children were at the highest risk of death (*18*). In this series, children who received whole blood transfusions had a similar mortality rate as those who were not transfused, although more children who died early during their hospitalization had received blood transfusions compared to those that died late or survived (p=0.08).

Ahmed and colleagues presented an observational study in 1999 in Bangladesh describing decreased mortality, hypoglycaemia and need for intravenous fluids after the introduction of a standardized management protocol for severely malnourished children with diarrhoea (*19*). In this study, the standardized management protocol included a host of interventions, including an emphasis on the use of ORS, early feeding and aggressive replacement of stool water losses with additional oral fluid

boluses. In contrast to their traditional management, IV fluids were reserved for those with severe dehydration and only in the amount of 30–40 ml/kg over two hours. The major limitation of this study is that it was observational – the two different treatment protocols were administered over two different time periods – and thus the populations treated were somewhat different. Nevertheless, children treated with the standardized protocol had a lower death rate (OR 0.49, 95% CI 0.3–0.8) and less hypoglycaemia, although their overall length of hospitalization was similar.

Bachou and colleagues in Kampala, Uganda, presented an observational series of 220 hospitalized children with severe malnutrition, of whom 52 (24%) died (*20*). Clinician discretion determined whether children received blood or IV fluid therapy and only 11 children met World Health Organization (WHO) recommendations for transfusion (*4*) (of whom 7 were transfused) and 10 children met WHO recommendations for infusion (*4*) (of whom 9 were infused). From this study, the authors concluded that the main risk factors for mortality among hospitalized severely malnourished children included unnecessary blood transfusion and IV fluid infusions. These researchers, therefore, undertook a follow-up intervention study emphasizing "improved practice" in order to see if mortality could be reduced by following strict transfusion and infusion criteria (*21*). The introduction of a standardized protocol (transfusions for patients with Hb <4 g/dL or in septic shock; ReSoMal alternating with F75 feeds for diarrhoea; restrictions of IV fluids) did not lead to a decrease in overall mortality rates and actually led to an increase in duration from admission until discharge. However, the use of inappropriate blood transfusions and IV infusions decreased significantly in the post-intervention period and this was reflected in significantly lower mortality rates during the first week of hospitalization among children who received transfusions and/or infusions.

No studies were found that provided data to directly answer the PICO question, either with regard to blood transfusions or IV fluid infusions. See Table 1 for a summary of studies on whether half strength Darrow's/5% dextrose (HSD/5D) vs. Ringer's lactate (RL) should be used in children with severe acute malnutrition and shock.

Summary

In summary, there have been no prospective trials published to inform the use of IV fluid infusions for dehydration or blood transfusions for anaemia among hospitalized children with SAM. This leaves a large evidence gap when attempting to guide management recommendations for frontline care providers and leaves us to rely upon observational studies and case series.

The observational studies identified do show that children who are given IV fluids even when not dehydrated or given blood products even when not severely anemic (Hb less than 4–5 g/gL) have higher mortality than those who meet appropriate criteria for infusions or transfusions. However, the inherent limitations of case series and observational studies make it difficult to draw strong conclusions from this type of study. Without randomization and contemporaneous side-by-side treatment of children who do receive and children who do not receive these interventions of interest, the study populations will be different in a range of known and unknown ways, including (but not limited to): (i) the etiology of dehydration and anaemia; (ii) the severity of dehydration and anaemia; (iii) the etiology of SAM; (iv) the severity, duration and type of malnutrition (kwashiorkor vs marasmus); (v) the rate of complications and superinfections such as HIV, malaria, hookworm and bacteraemia; (vi) the amount of nursing care received (*22*); and (vii) the nutritional, anti-infective, psychological, environmental and other interventions administered during different time periods.

Despite these significant limitations, a consistent pattern emerges in the observational studies that suggest that limiting the use of IV infusions and blood transfusions in children who are not severely dehydrated or anemic children is effective in decreasing mortality rates among these "less sick" children. Whether this decrease in mortality is because of the more judicious use of the infusions and transfusions themselves or whether it is a result of the complete package of interventions provided cannot be determined given the observational nature of the studies. In addition, the variety and unpredictability of clinician discretion in determining whether to give these interventions is subject to significant bias as it is quite possible that the children who died despite these interventions were the ones who were a priori "sicker" and thus prompted the clinicians to initiate these interventions in the first place.

Conclusions

There are no prospective clinical trials available to answer the PICO question of interest in this review. Seven observational studies were identified, all of "Low" or "Very Low" quality with regard to the question at hand. Nevertheless, some insight into the management of dehydrated and anemic children can still be gleaned from these studies. It seems likely that giving inappropriate IV infusions (i.e. to those children without severe dehydration or those children who are able to tolerate oral rehydration) and inappropriate blood transfusions (i.e. to those children without severe anaemia, Hb <4–5 g/dL, or symptomatic complications such as respiratory distress or shock) increases the likelihood of death.

Reducing the rate of these inappropriate transfusions is likely to decrease mortality rates and also help conserve limited resources. (Admittedly, the increasing availability of improved blood banking resources and protocols in recent years might decrease the risk associated with blood transfusion relative to the time when the studies included in this review were conducted.)

The principle of limiting infusions and transfusions to only the sickest children with malnutrition is consistent with years of experience in managing non-malnourished hospitalized children (*6*), especially in settings without the resource for close hemodynamic monitoring and without the ability to intervene aggressively in cases of pulmonary oedema, cerebral oedema, heart failure and fluid overload. The balance between the lifesaving power of IV fluids and blood products for children with dehydration, anaemia and hypovolaemic shock and the negative effects of overhydration and fluid overload is a major issue with respect to the question of when to administer these therapies, to whom and how quickly. In the absence of prospective clinical trial evidence at this time, the best recommendation that can be made based on the observational studies reviewed here is to limit IV fluid hydration to children with severe dehydration and to limit the administration of blood products to children with Hb less than 4–5 g/dL or complications such as respiratory distress.

Further research

Future research evaluating the effects of infusions and transfusions on mortality, nutritional recovery and length of hospitalization in children with SAM is necessary. Ideally, such a study would be an RCT that would determine whether children receive these interventions without being subjected to clinician discretion (assuming certain baseline consistent criteria for dehydration and anaemia are satisfied). Aside from the straightforward question about receiving the intervention or not, areas for further study also could include the volume of blood of IV fluid given, the rate at which it is given, the type of fluid given and also whether ancillary therapies such as furosemide impact outcomes. It seems likely that an RCT such as this would be extremely complicated and possibly unethical in these resource-poor settings. Prospective observational cohort studies thus might be the most feasible, with careful attention to complete and standardized data gathering and a rigorous protocol to follow, while some children receive these interventions whereas simultaneously others do not.

Table 1

Question: Should half-strength Darrows/5% dextrose versus Ringer's lactate be used in children with severe acute malnutrition and shock?
Settings: Hospital

Quality assessment							Number (%) of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Half-strength Darrows/5% dextrose	Ringer's lactate	Relative (95% CI)	Absolute	Quality	Importance
Mortality until the end of hospitalization												
1	Randomized trials	Very serious[a]	No serious inconsistency[b]	No serious indirectness	Serious[c]	None	15/26 (57.7)	13/29 (44.8)	RR 1.29 (0.76 to 2.17)	130 more per 1000 (from 108 fewer to 524 more)	+ VERY LOW	CRITICAL
Shock unresolved at 8 hours												
1	Randomized trials	Very serious[a,d]	No serious inconsistency[b]	No serious indirectness	Serious[c]	None	15/22 (68.2)	14/25 (56)	RR 1.22 (0.78 to 1.91)	123 more per 1000 (from 123 fewer to 510 more)	+ VERY LOW	CRITICAL

Shock unresolved at 24 hours												
1	Randomized trials	Very serious[a,d]	No serious inconsistency[b]	No serious indirectness	Serious[c]	None	14/18 (77.8)	14/25 (56)	RR 1.39 (0.91 to 2.13)	218 more per 1000 (from 50 fewer to 633 more)	+ VERY LOW	CRITICAL
Oliguria at 8 hours												
1	Randomized trials	Very serious[a,d]	No serious inconsistency[b]	No serious indirectness	Very serious[e]	None	9/22 (40.9)	3/25 (12)	RR 3.41 (1.05 to 11.03)	289 more per 1000 (from 6 more to 1000 more)	+ VERY LOW	CRITICAL
Oliguria at 24 hours												
1	Randomized trials	Very serious[a,d]	No serious inconsistency[b]	No serious indirectness	Serious[c]	None	8/18 (44.4)	6/25 (24)	RR 1.85 (0.78 to 4.41)	204 more per 1000 (from 53 fewer to 818 more)	+ VERY LOW	CRITICAL
Tachycardia at 8 hours												
1	Randomized trials	Very serious[a,d]	No serious inconsistency[b]	No serious indirectness	Very serious[e]	None	7/22 (31.8)	2/25 (8)	RR 3.98 (0.92 to 17.18)	238 more per 1000 (from 6 fewer to	+ VERY LOW	CRITICAL

										1000 more)		
Tachycardia at 24 hours												
1	Randomized trials	Very serious[a,d]	No serious inconsistency[b]	No serious indirectness	Very serious[e]	None	8/14 (57.1)	4/25 (16)	RR 3.57 (1.31 to 9.77)	411 more per 1000 (from 50 more to 1000 more)	+ VERY LOW	CRITICAL

CI: confidence interval; RR: risk ratio

[a] Several limitations: non-blinded, small sample size (61 children), assessment restricted to the hospitalization period without further follow-up. One study arm was dropped.

[b] Only one study.

[c] Wide confidence intervals.

[d] Outcomes only presented for survivors and not for all those randomized.

[e] Very wide confidence intervals.

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