

Conference on ‘Malnutrition matters’

Symposium 5: Joint BAPEN and Nutrition Society Symposium on ‘Feeding size 0: the science of starvation’ Severe malnutrition: therapeutic challenges and treatment of hypovolaemic shock

Kathryn Maitland

KEMRI-Wellcome Trust Programme, PO Box 230, Kilifi, Kenya

The systematic failure to recognise and appropriately treat children with severe malnutrition has been attributed to the elevated case-fatality rates, often as high as 50%, that still prevail in many hospitals in Africa. Children admitted to Kilifi District Hospital, on the coast of Kenya, with severe malnutrition frequently have life-threatening features and complications, many of which are not adequately identified or treated by WHO guidelines. Four main areas have been identified for research: early identification and better supportive care of sepsis; evidence-based fluid management strategies; improved antimicrobial treatment; rational use of nutritional strategies. The present paper focuses on the identification of children with sepsis and on fluid management strategies.

Severe malnutrition: African children: Identification of sepsis: Fluid management strategies

The WHO consider that a mortality rate of >20% for children with severe malnutrition, a situation that is common in many hospitals in sub-Saharan Africa, is unacceptable^(1–5). High case-fatality rates are often attributed to insufficient staff training and poor compliance with the recommended protocols^(6–12). The WHO has developed consensus management guidelines⁽²⁾ that include a stabilisation phase during which life-threatening problems are identified and treated, a staged introduction of milk-based nutritional rehabilitation, micronutrient and vitamin supplementation and empirical use of antimicrobial and anti-helminth treatments. It is argued that with strict adherence to these guidelines the mortality should be <5%^(13,14). Whilst high case-fatality rates are often attributed to faulty case management, the evidence for this assertion is poor and other workers have suggested that outcome is largely dependent on other antecedent factors, including the frequency of additional life-threatening complications^(4,15–18).

The current guidelines have largely been based on expert or consensus opinion. Consequently, there are several

aspects that are controversial^(3,15). A major challenge is that they have been developed to be relevant to many varying contexts and geographic settings that include: diverse populations such as those exposed to displacement (refugees) where acute starvation in previously healthy populations may be compounded by diarrhoea in unsanitary settings⁽¹⁹⁾; acute malnutrition secondary to epidemics of cholera, dysentery⁽¹³⁾ or measles; cases admitted from populations with stable endemic undernutrition. In the latter situation, because of the high rates of comorbidity, successful treatment may not be guaranteed by strict compliance with current management guidelines alone.

At Kilifi District Hospital, on the coast of Kenya, severe malnutrition is a common cause of admission; 400–500 paediatric cases are treated annually. The current management approaches the gold standard recommended by the WHO⁽²⁾. However, in-hospital mortality remains at approximately 20%⁽¹⁷⁾ and has been stable over time despite in-service training and expansion of the dedicated nutrition team. More careful adherence to WHO recommended

Abbreviations: ORS, oral rehydration solution; ReSoMal, rehydration solution for malnutrition.

Corresponding author: Dr Kathryn Maitland, fax +254 415 22390, email kmaitland@kilifi.kemri-wellcome.org

management^(6,9) could be achieved by a considerable investment in health personnel, but without a careful re-examination of current management recommendations this approach is unlikely to impact substantially on the outcome for those at greatest risk of dying.

Every cohort of children with severe malnutrition will comprise subgroups with different antecedent risk factors. It is recognised that in Kilifi District Hospital the largest group comprises children with uncomplicated malnutrition who have accessed hospital care for nutritional rehabilitation alone. For these children the management and inpatient survival approaches the standard recommended by the WHO guidelines⁽²⁾. Nevertheless, a substantial group of children present to hospital with severe illness and life-threatening complications. An acute medical or nutritional decompensation, and more often the combination, underpin their hospitalisation and represent a major challenge to successful management.

At Kilifi District Hospital a prospective study of children with severe malnutrition has been conducted over the last decade, which has identified a number of areas of concern in relation to management; early mortality being of particular concern, as >40% of deaths have been found to occur within 72 h of admission⁽¹⁷⁾. This finding suggests that triage, early identification and adequate treatment of life-threatening complications are inadequate and need more careful scrutiny.

Factors contributing to poor outcome

A retrospective review, conducted in 2006, has identified a number of important factors that contribute to poor outcome and highlights the therapeutic challenges encountered⁽¹⁷⁾, which include:

- (1) invasive bacterial infection: bacteraemia was found to complicate 27% of all deaths; 52% dying before 48 h, despite 85% *in vitro* antibiotic susceptibility of cultured organisms;
- (2) early deaths were frequently found to be complicated by features of hypovolaemic shock or dehydrating diarrhoea at admission;
- (3) very few children were identified as shocked or requiring intravenous fluids because of the very stringent criteria for fluid resuscitation specified in the WHO guideline⁽²⁾;
- (4) high mortality was found for those patients with severe dehydration and severe electrolyte derangements;
- (5) more than one life-threatening complication was frequently found to complicate the hospital admission.

Furthermore, on review it was found that the WHO danger signs⁽²⁾ lack the sensitivity and specificity to identify those patients at greatest risk of early mortality. In 2005 the Kilifi Severe Malnutrition Research Programme was established in order to systematically evaluate the current WHO management guidelines⁽²⁾. A major programmatic theme is to identify areas that require further research with the aim of providing a broader evidence base for future recommendations.

Gastroenteritis and dehydrating diarrhoea

Profuse watery diarrhoea, defined as three or more loose stools per d, often complicates severe malnutrition⁽²⁰⁾. Management of diarrhoea and dehydration continues to be a controversial issue in the treatment of severe malnutrition. The difficulty of differentiating the signs of acute dehydration from chronic features of malnutrition has been recognised but poorly evaluated physiologically⁽²⁾. Some studies have shown that the presence of diarrhoea predicts poor outcome^(4,17,21), especially when complicated by other features of severity, whereas other studies have shown little impact on successful rehabilitation⁽¹³⁾. It has been shown previously that both community- and nosocomial-acquired diarrhoea are major challenges to the successful management of Kenyan children hospitalised with severe malnutrition, with the highest mortality occurring in the groups with clinical signs of severe dehydration and impaired perfusion⁽¹⁷⁾.

WHO recommended management

Diarrhoea and dehydration at Kilifi District Hospital are managed in accordance with WHO policy⁽²⁾. In brief, this procedure includes the provision of an oral rehydration solution (ORS) with a reduced Na content (rehydration solution for malnutrition; ReSoMal; for details, see World Health Organization⁽²⁾), micronutrient and vitamin supplementation, antibiotics and starter 'F75' milk-based feeds (for details, see World Health Organization⁽²⁾). ReSoMal is provided on the ward following initial observed rehydration and carers are encouraged to give additional ReSoMal for every loose stool. For children too weak or unable to rehydrate orally a nasogastric tube is inserted for enteral rehydration and feeding. Intravenous rehydration is reserved for children developing advanced shock, as stipulated in the WHO guideline⁽²⁾, which is defined as impaired consciousness together with capillary refill >3 s, a weak pulse volume and a temperature gradient (cool hands and feet).

The results of the 2-year prospective study (June 2005–May 2007) include 667 children with severe malnutrition (10% of all hospital admissions). A total of 325 children (49%) were admitted with a history of diarrhoea, of which seventy-seven (24%) died compared with 14% of the 342 cases that were uncomplicated by diarrhoea (χ^2 10.2, $P < 0.001$). Table 1 demonstrates the admission characteristics for the 325 children with severe malnutrition complicated by diarrhoea. Of note is the poor performance of the WHO danger signs⁽²⁾ to identify those children at risk of dying and the limited number that would qualify for intravenous rehydration. Despite severe biochemical derangement and other features of shock only one child of the 325 with a history of diarrhoea was found to be eligible for intravenous fluid rehydration at admission. Fatal cases were more frequently found to be complicated by clinical evidence of dehydration or impaired perfusion, severe acidosis or electrolyte imbalance and invasive bacterial infection. Notably, HIV status was not found to be a predictor of poor outcome. A further ninety-eight children were found to develop diarrhoea after admission ('nosocomial diarrhoea'), of whom twenty-one died (21%).

Table 1. Admission features of 325 children with severe malnutrition complicated by diarrhea

Feature	Cases with feature	
	<i>n</i>	%
WHO treatment indicators ⁽²⁾		
Shock definition	1	0.5
Danger signs (lethargy, hypothermia or hypoglycaemia)	73	22
Bedside assessment		
Severe dehydration signs	112	35
Capillary refill >2 s	27	8
Weak pulse volume	32	8
Any impairment of consciousness	16	4
Laboratory		
Acidosis (base deficit >10 mmol/l)	117	36
Hyponatremia, (<125 mmol/l)	29	8
Hypokalaemia, (<2.5 mmol/l)	133	31
Elevated creatinine, (>80 mmol/l)	47	14.5
Bacteraemia (admission culture)	28	8

It was noted that in both groups a number of children developed profuse osmotic diarrhoea. This condition led to a rapid collapse (often within hours of the development of severe diarrhoea) with features of haemodynamic decompensation, severe electrolyte abnormalities, metabolic acidosis and ultimately death. Osmotic diarrhoea has been reported before in Aboriginal communities with a tropical enteropathy (with similar complications on feeding)^(16,22) and these previous observations have parallels with the findings at Kilifi District Hospital.

Therapeutic challenges: intravenous rehydration

In children without anthropometric or clinical signs of malnutrition any one of these complications would ordinarily prompt urgent intravenous fluid resuscitation and rehydration. Under the current WHO guidelines⁽²⁾ intravenous fluid resuscitation is reserved for too few cases with signs of advanced shock, when it is probably too late and thus fluid resuscitation is often associated with high mortality. Similar observations have been reported, with advice for the targeted use of isotonic fluids in those patients with any feature of shock⁽¹⁶⁾.

Therapeutic challenges: oral rehydration

The use of the standard WHO ORS^(2,13) with 90 mmol Na/l for severely-malnourished children has been cautioned because of its relatively high concentration of Na and low K concentration (Table 2). As a result of the adaptive state of severe malnutrition there is a concern that ORS containing large quantities of Na may result in further increases in intracellular Na and the risk of fluid overload and heart failure^(20,23). In a randomised trial of Bangladeshi children with severe malnutrition in which the efficacy and safety of ReSoMal was compared with that of the standard WHO ORS similar efficacy was demonstrated for correcting dehydration, but ReSoMal was found to be associated with a more beneficial effect on K status, with most

Table 2. Standard composition (mmol/l) of oral rehydration solutions (ORS)

	Standard WHO ORS ⁽²⁾	Reduced-osmolarity ORS		
		ReSoMal ⁽²⁾	New WHO reduced osmolarity ORS ^(25,26)	Dioralyte
Glucose	111	105	75	90
Na	90	45	75	60
Chloride	80	40	65	60
K	20	40	20	20
Citrate	10	10	10	10
Osmolarity	311	240	245	240

ReSoMal, rehydration solution for malnutrition.

children correcting hypokalaemia by 24 h. However, hyponatraemia was reported to persist in 25% of the children treated with ReSoMal, which was complicated by the development of seizures⁽²³⁾. The interpretation of the study findings may be complicated by the presence of *Vibrio cholera* in 30% of the study population. Nevertheless, ReSoMal has subsequently been adopted into the present guideline as the standard ORS for children with severe malnutrition⁽²⁾.

Since this trial the WHO has changed the formulation for ORS for non-malnourished children^(24,25) (see Table 2). For a number of reasons, including the potential safety concerns of ReSoMal together with the author's observations that mortality remains high on current management and the introduction of an ORS with lower Na content and higher K, prospective evaluation is warranted in comparing ReSoMal against the new standard WHO ORS. Ultimately, there are programmatic and logistic advantages to using a single solution around the world for all causes of diarrhoea in all ages irrespective of nutritional status.

Treatment of hypovolaemic shock: phase I and II clinical trials

WHO guidance on fluid resuscitation

Current WHO guidelines recommend that children with severe malnutrition should not routinely receive intravenous fluids⁽²⁾. Fluid resuscitation should be reserved for those with signs of decompensated shock (cool peripheries, capillary refill time >3 s, a rapid and weak pulse and impaired consciousness). In this situation treatment guidelines recommend an initial bolus of half-strength Ringers lactate, half-strength Darrow's solution or 0.45% (w/v) saline followed by whole-blood transfusion if the child fails to improve^(2,20).

Are the guidelines evidence based?

The recommendations for children with severe malnutrition are based on two largely unproven concerns. First, in simple terms, children with severe malnutrition retain Na (and water) and therefore infusions of Na-rich crystalloidal solutions may be detrimental, leading to salt and

water overload. Second, children with severe malnutrition have impaired cardiac function and incipient heart failure. These rationale have been advanced to discourage the use of isotonic or 'Na-rich' resuscitation fluids or ORS.

Limitations of treatment guidelines

Although hypotonic solutions may correct intracellular volume depletion (dehydration), the crystalloid solutions recommended by the current guidelines for correction of shock in severe malnutrition⁽²⁾ are not recognised in contemporary paediatric critical care practice. Paradoxically, hypotonic fluids represent a much greater risk of fluid overload because of rapid equilibration of water across the extracellular and intracellular compartments, following the osmotic gradient, leading to a proportionately greater expansion of the intracellular compartment relative to the intravascular compartment. Hence, they have a limited effect on expanding the circulating volume or correction of shock. Furthermore, the recommendation for using blood as a volume expander is physiologically unsound and overlooks the literature relating to emergency transfusion, which is frequently unobtainable in sub-Saharan Africa even for children with severe life-threatening anaemia, many of whom die awaiting transfusion^(26,27).

Standard of care: paediatric critical care approach

Cardiac output and organ perfusion in critically-ill children are dependent on the extent of filling of the intravascular compartment. In paediatric and neonatal shock reversal of early stages of shock has been shown to be associated with improved outcome⁽²⁸⁾. Conversely, delayed intervention or treatment of late decompensated shock is frequently associated with a very poor outcome⁽²⁹⁾. The optimal fluid and electrolytes for resuscitation require consideration of two major aspects of critical illness physiology. First, what is the extent and nature of any deficits in fluid and electrolytes? Second, does diminished intravascular volume also contribute to clinical presentation thus reducing cardiac output and impairing organ perfusion? While simple electrolyte solutions given either intravenously or orally are appropriate where excess water and electrolyte depletion are involved, principally as a result of dehydration (intracellular losses), in other conditions such as septic shock that involve the loss of intravascular volume (both relative and absolute) the optimal solutions include isotonic crystalloidal or colloidal solutions. These solutions are necessary to restore the filling of the intravascular compartment, restore cardiac output and optimise perfusion to vital organs.

Prospective studies

Two trials have been conducted to examine volume expansion in severely-malnourished children with shock secondary to diarrhoea or severe sepsis. They were conducted in two phases and aimed to provide detailed data on malnourished children with features of hypovolaemia. In the first phase a single-arm prospective study examined the safety and efficacy of the current WHO shock treatment

protocol⁽²⁾ in up to twenty children with severe malnutrition. In the second phase a phase II randomised controlled trial was conducted to examine the safety and efficacy of different intravenous replacement regimens compared with the standard WHO protocol (control).

Phase I intervention. The single-arm trial was conducted on the high-dependency unit with continuous haemodynamic monitoring and comprehensive input–output fluid balance. The WHO recommended treatment⁽²⁾ was followed that includes an initial bolus (15 ml/kg) of half-strength Ringers lactate (Na content 70 mmol/l) given over 1 h, and if the child improves an additional bolus of 15 ml/kg is given over 1 h. If the child does not improve after 1 h 10 ml whole blood/kg is given, irrespective of Hb.

Phase I results. Recruitment was terminated after six of the seven (86%) children enrolled into this study died. The seventh child died later, after transfer from the high-dependency unit. Most deaths were a result of uncorrected shock; however, a number of treatment challenges were noted that were corrected for in phase II. In particular, feeding was commenced only after the child had been stabilised and ileus had been excluded and was withheld in those children developing osmotic diarrhoea.

Phase II safety and efficacy randomised controlled trial. This trial compared the WHO recommended treatment for shock (for details, see phase I intervention) with full-strength Ringers lactate (Na 154 mmol/l) in the group with diarrhoea and in the group with septic shock a three-arm trial compared the WHO treatment with 5% (w/v) albumin or full-strength Ringers lactate. In those receiving full-strength Ringers lactate or 5% (w/v) albumin the initial bolus of 15 ml/kg was infused over 1 h, and this treatment was repeated if the child remained in shock. It was recognised that this approach was exceptionally cautious, but an attempt was made not to introduce a potential imbalance in the volumes received compared with the current WHO guideline.

Phase II trial summary. In a planned interim analysis mortality across the trial was noted to be high; thirty-three of the sixty-one children died (54%). There was a non-significant trend towards a higher mortality in the WHO arm compared with the Ringers lactate arm. In all arms (WHO, Ringers lactate and albumin) the safety of the intervention fluids was demonstrated. In particular, no clinical features of fluid overload–pulmonary oedema (defined as bilateral basal crepitations and an O₂ saturation of <90% on air) or evidence of cardiac failure were observed. We concluded that fluid resuscitation with an isotonic solution should be re-evaluated prospectively in dose-escalation studies or by end-point-directed treatment.

Myocardial function and response to treatment

Optimal cardiac function is important for the maintenance of haemodynamic stability. Myocardial dysfunction and alterations of vascular tone are major complications in severely-ill patients and play a major role in patient morbidity and mortality^(30,31). Alterations in normal cardiac and haemodynamic function are exacerbated by perturbations of acid–base balance, electrolytes and micronutrients

and relative adrenal impairment. If treated early enough these factors are amenable to rapid correction by commonly-available therapies such as fluid resuscitation to correct shock and correction of hypoglycaemia and of electrolyte imbalance (hypokalaemia and hypocalcaemia).

In severe malnutrition there are limited data on cardiac function in children, with conflicting conclusions^(32–36). A study in Jamaica concluded, on the basis of reduced cardiac output, that there was marked impairment of cardiac function⁽³²⁾. A study on Zairian children indicated that many children have signs of an ‘adaptive hypocirculatory state’ and some show frank peripheral circulatory failure comparable with hypovolaemic shock^(33,37). Neither of these studies examined the response to volume expansion or other therapies.

Cardiac output studies

Two-dimensional echocardiographic examinations using GE Logiq book portable echocardiography (GE Medical Systems UK, Chalfont St Giles, Bucks., UK) have been undertaken as well as Doppler assessment of cardiac output using an ultrasound cardiac monitor (USCOM ultrasonic cardiac output monitor; USCOM Ltd, Sydney, NSW, Australia; Fig. 1), which uses anthropometric data to compute systemic vascular resistance. Initial examinations were conducted in children with clinical features of shock just before or after fluid resuscitation stabilisation of the child.

Evidence of cardiac failure is not supported by the findings. Markedly reduced cardiac output concurrent with increased systemic vascular resistance was observed (Fig. 2). This finding is frequent in children with septic shock⁽³⁸⁾, and was supported by evidence of reduced preload (data not shown). Taken together with the finding of the fluid trial these results point to substantial volume depletion and reduced cardiac output.

Lessons learned from feeding the size O

There are many parallels in these findings with the experience of nutrition experts managing severely-malnourished

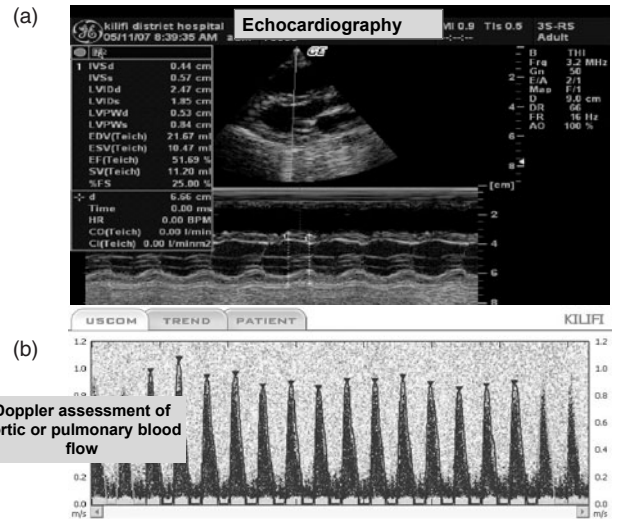


Fig. 1. An example of readings from (a) two-dimensional echocardiographic examinations of children with clinical features of shock undertaken just before or after fluid resuscitation stabilisation using GE Logiq book portable echocardiography (GE Medical Systems UK, Chalfont St Giles, Bucks., UK) and (b) Doppler assessment of cardiac output (aortic or pulmonary blood flow) using an ultrasound cardiac monitor (USCOM ultrasonic cardiac output monitor; USCOM Ltd, Sydney, NSW, Australia).

populations with complex causes of starvation. In the 2008 meeting of BAPEN a dedicated session on feeding the size 0 has enabled some comparisons to be made (for example, see Cockfield & Philpot⁽³⁹⁾). What is apparent is that there are many lessons to be learned across the specialities, from Africa to UK and vice versa. The clinical experience of managing severe malnutrition in Africa, which is complicated by severe electrolyte perturbations, shock and complex complications of gastroenteritis, have also been highlighted in the management of difficult complex gastroenterological and nutritional problems and the refeeding syndrome⁽⁴⁰⁾. The risk of development of the refeeding syndrome was discussed and common factors identified,

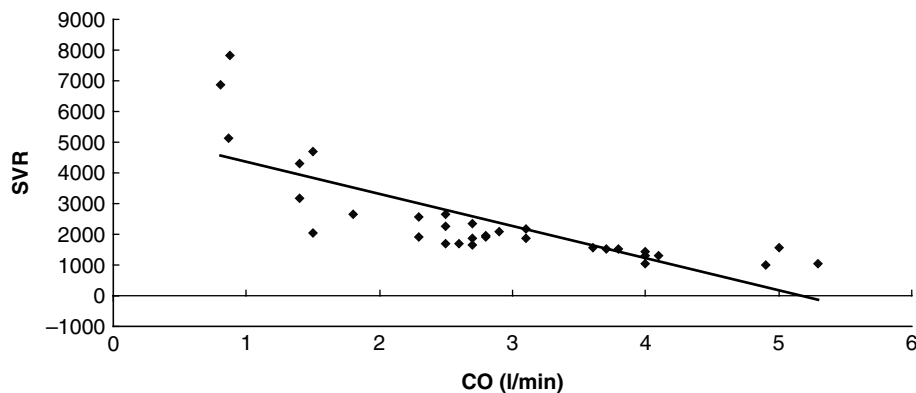


Fig. 2. Simultaneous measurement of cardiac output (CO; using an ultrasound cardiac monitor (USCOM ultrasonic cardiac output monitor; USCOM Ltd, Sydney, NSW, Australia)) and systemic vascular resistance (SVR; which is computed by the USCOM ultrasonic cardiac output monitor using anthropometric data) in children with clinical features of shock just before or after fluid resuscitation stabilisation, which shows evidence of underfilling of the intravascular compartment.

including the severity of the underlying malnutrition, over-aggressive nutritional support in the early stages before adequate supplements of phosphate, thiamine, K and Mg and associated conditions that exacerbate micronutrient, electrolyte and mineral depletion⁽⁴⁰⁾.

Summary

Resolving some of the complex and unresolved clinical therapeutic issues of African children with severe malnutrition requires a multidisciplinary approach that may benefit from including international experts in nutrition, gastroenterology, paediatric sepsis and critical care. This approach could be the basis on which to develop a programme of severe malnutrition research to address the fundamental scientific and treatment gaps that result in high in-hospital mortality in children with severe malnutrition in Africa. Valuable lessons may be learned by sharing experiences with specialists managing complex nutritional problems on both sides of the equator.

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