Invited Article

Tailoring management of severe and complicated malnutrition: more research is required first.

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The implementation of reliable criteria for identifying malnutrition is of paramount importance for assessing the size of the problem and implementing proper management measures. The 2006 revisions to the weight and height growth standard references and mid upper arm circumference defining severe malnutrition criteria in children (from a cut of <11 cm to <11.5 cm)[1] resulted in an increase of cases identified as severely malnourished and thus eligible for integrated management for severe malnutrition recommended by the World Health Organization.[2] Even more imperative now is the question, raised by several observers in the past with respect to generic guidelines, does one size fit all?

An inherent challenge of developing guidelines for wide-ranging settings are the relevance and suitability of certain management components to the diverse circumstances and underlying co-morbidities underpinning the development of severe malnutrition. Whilst faulty case management is often attributed to high case fatality rates, the evidence for this is poor and other workers have suggested that outcome is largely dependent upon other antecedent factors including the frequency of additional life threatening complications.[3–7]

Although severe malnutrition continues to be a leading cause of childhood morbidity and mortality worldwide, the importance of generating robust and practical prognostic clinical and bedside markers to identify those at greatest risk has been relatively neglected. The paucity of prospective studies of unselected cohorts of children with severe malnutrition has resulted in a piecemeal accumulation of prognostic data; and matched by even fewer interventional research studies designed to inform future management guidelines.

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For example, the WHO-recommended 'danger signs' (lethargy, hypothermia, or hypoglycaemia) aimed at identifying those at high risk have been shown to not work in practice.[5] A prospective study including 15,191 observations of core temperature for example, recorded hypothermia (<36°C) on only 12 occasions (0.08%). Even when all three signs are taken together, they have a poor specificity and sensitivity of predicting early mortality (likelihood ratio 3.4% (95% confidence interval [CI] 2.2–5.1)).[8] Instead, comorbidities such as HIV and tuberculosis[6] as well as the complications of sepsis, shock, diarrhoea and severe electrolyte derangement define high-risk groups (case fatalities 23–34%)[5] requiring further research to improve the evidence-base for management.

Other than cases with cholera and dysentery, diarrhoea has been considered as a minor complication of malnutrition of little prognostic or therapeutic consequence. However, a recent prospective study of 1,206 unselected paediatric admissions with severe malnutrition in Kilifi, Kenya, demonstrated that 49% had diarrhoea (≥3 loose stools/day) at admission and a further 16 % developed diarrhoea after admission. In both these groups case fatality was substantially greater (21% and 18% respectively) compared to those without any diarrhoea during admission (12%).[9] Risk factors associated with poor outcome included bacteraemia and hyponatraemia (adjusted OR 6.1 (95% CI 2.3–16.3) P=0.001 and 4.6 (95% CI 2.0–10.6) P< 0.001 respectively).[9] That, 1) bacteraemia (largely enteric gram-negative organisms) complicates 12% of all cases of severe malnutrition(5) and 2) key parameters affecting clearance of enteral ciprofloxacin (oral clearance) were low sodium concentration and the high-risk category (shock, dehydration and diarrhoea),[10] implicates gut barrier dysfunction as an important factor in the pathogenesis of many cases of severe and complicated malnutrition.

Alterations in gut permeability and lactose intolerance in malnutrition have been previously reported[11]

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including children in several African countries[12–14] - and are likely to be more common than previously appreciated. Disruption of normal intestinal flora is known to cause impaired mucosal immunity and disrupted barrier function. This has a significant impact on tolerance to re-feeding as well as risk of subsequent sepsis, inflammation and organ dysfunction in severe malnutrition. Translocation of both endotoxin and viable enteric bacteria from the gut has been demonstrated in a variety of animal models, as well as in human illnesses associated with splanchnic hypoperfusion (including sepsis and critical illness). Translocated endotoxin[15] contributes to systemic inflammatory activation and organ dysfunction in children with malnutrition, further underlining the importance of restoring gut mucosal integrity at an early stage in the management of malnourished patients. This has substantial implications for syndromic management and likely to require a targeted care bundle once pathophysiology is better understood.

One key element of management requiring further research, and the subject of substantial and continuing controversy, are the treatment recommendations for rehydration and shock in the WHO malnutrition management guidelines, which include significant departures from the recommendations for non-malnourished children. They were based upon the firmly held view that severe malnutrition represents a state of 'reductive adaptation', in which sodium and water retention, expanded extracellular compartment, myocardial atrophy and a 'hypocirculatory state', are central to the pathophysiology, which could precipitate heart failure if intravenous fluids were given.[16–18] Supportive evidence for these conclusions and current recommendations include descriptive studies, not originally designed to answer the specific question of fluid resuscitation, reporting reduced mortalities following adoption of the fluid management guidelines but fail to account for the inherent biases of co-introduction of the whole package of care or other confounders.[19–21] Evidence for myocardial atrophy derived from radiographic studies showing reduced cardiothoracic ratios on x-rays,[22,23] echocardiography studies[24,25] and autopsies[26] – but have been countered by others suggesting that myocardial size was appropriate for overall body mass.[17,27,28] Kerpel-Fronuis disagreed with the argument for expanded extracellular space (ECF) who suggested this was spurious and only relative to intracellular compartment contraction evident in severe wasting.[29]

Recent interventional studies have challenged the notion these children have myocardial dysfunction intolerant to the fluid loading. In a comparative trial of oral rehydration solutions in 175 Bangladeshi children aged 6–36 months with cholera, including 149 cases with severe dehydration at enrollment who initially received 100 mL/kg of cholera saline, and recorded no events of fluid overload or heart failure.[30] They concluded that severe dehydration could be safely corrected intravenously by up to 100 ml/kg of isotonic fluid over 6 hours. A Phase II safety and efficacy trial in 62 Kenyan children with severe malnutrition aimed to establish whether hypovolaemic shock could be safely corrected by volume replacement with Ringer's Lactate (an isotonic crystalloid) compared to WHO-recommended half-strength Darrow's in 5% dextrose (HSD/5D), a hypotonic crystalloid fluid, given in similar volumes, but was terminated early after interim analysis. The trial included 41 children with shock and severe dehydrating diarrhoea and 20 with presumptive septic shock; overall 69% of the trial cohort had decompensated hypotensive shock.[31] Outcome was universally poor, characterised by persistence of shock, oliguria and high case fatality. No episodes of pulmonary oedema or fluid overload were reported. Isotonic fluid was associated with modest improvement in shock and survival when compared to HSD/5D but results were inconclusive.[31]

What is clear from the literature is that very few studies linked clinical status, physiological investigation and response to treatment in representative cohorts of children with severe malnutrition. Few have drawn on modern technology and contemporary understanding of paediatric critical illness to study myocardial status and haemodynamic response to fluid expansion. It is uncertain whether children with severe malnutrition have or develop features of cardiac dysfunction before or during treatment, and whether cardiac function differs between children with marasmus and kwashiorkor. Moreover, clinical studies have failed to demonstrate whether their findings are due to malnutrition per se or reflect other underlying co-morbidities. Further studies are needed that combine clinical, echocardiographic, and electrocardiographic findings with measurement of known biomarkers of cardiac dysfunction such as brain natriuretic peptide (BNP), Troponin I and myocardial depressant factors.

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