1. Introduction

Malnutrition is a global problem of immense magnitude. The major affliction is however among children living in low-income settings (1), with severe acute malnutrition (SAM) affecting millions of children under 5 years of age (2). Furthermore, childhood malnutrition is associated with chronic diseases such as diabetes mellitus during adulthood and also reduces productivity through impaired working capacity and educational achievement (3).

Though SAM is known as a medical condition for over eight decades (4), some issues remain to be understood. For instance the uncertainties about the pathogenesis of nutritional oedema is reflected by the plethora of hypotheses ranging from dietary protein deficiency (5) to complex microbiota-nutrient interaction (6). Unfortunately, findings of the few intervention studies (7,8) are inconclusive.

The case fatality rate (CFR) of SAM is very high (9). In a review of data from 1950 to 1990s, mortality was typically 20-30% and ranged from 3.3% to 60%, with the highest levels being among those with oedematous malnutrition (10). In the same review only 15% of 67 facilities had CFR below 10% with most deaths attributed to outmoded and faulty practices. Aware of these facts, the investigators emphasized the indispensable need for a prescriptive standardized protocol in addition to addressing shortages of essential medical supplies.

With this background, the WHO protocol was introduced in 1999 and was highly advocated expecting to lower CFR to 5-10% (11). Routine use of broad spectrum antibiotics (12), judicious fluids therapy with initial low energy feeds (13) and timely treatment of hypoglycaemia (14) were cornerstones of the protocol. Nevertheless, implementation of the protocol with various degrees of contextualization showed inconsistent impact on outcome, as reviewed recently by Lenters *et al* (15). This systematic review found that using the WHO-based protocols, the CFR for inpatient treatment of SAM spanned from 3.4% to 35%. Notwithstanding the scarcity of high quality studies reported in this systematic review, the high mortality despite relative adherence to current management guidelines is puzzling.

Most deaths among patients with SAM occur within the first few days of treatment and are associated with indicators of fluid and electrolyte imbalances such as hyponatremia, hypokalaemia, congestive heart failure and oedema (16,17). This is not surprising since SAM leads to multiple fluid and electrolyte abnormalities (18), severe renal (19) and cardio-vascular (20) impairments. Moreover, the therapeutic diets create osmotic and water load on the body (11). Patients with SAM are vulnerable to rapid alteration of body fluids and thus their early mortality may depend on quality of triage, early detection and treatment of fluid-related complications.

Poor quality of care during management either due to shortage of essential medical facilities or absence of medical staff who understand the complex nature of the disease is documented in settings where SAM is treated (21). However, in Malawi intensive nursing care and frequent visits by a paediatrician failed to reduce mortality meaningfully (22). In Kenya CFR of 19% was reported in spite of adhering to the WHO guidelines insofar as staffing allowed, with 41% of death occurring within 72 h of admission. Although bacteraemia complicated 27% of all the deaths, 52% died before 48 h despite 85% in vitro antibiotic susceptibility of cultured organisms. The investigators also reported that regular staff training and an intensive period of temperature surveillance did not lower mortality. Bachou *et al* reduced unnecessary transfusions and IV infusions in accordance with the WHO guidelines and lowered the infusion-related deaths, but overall mortality did not improve (16).

Limitation in performance of currently used indicators of complications particularly hydration (dehydration or overhydration) could partly contribute to early deaths. A study from Kilifi Kenya supports this notion (23). In this study mortality was higher among children with SAM complicated with diarrhoea than those without diarrhoea (24% vs 14%). Of note, only one of the 325 children with a history of diarrhoea was found to be eligible for infusion therapy according to the standard protocol despite severe biochemical derangement and other features of shock.

Bradycardia, delayed capillary refill, weak pulse volume, and reduced or absent urine flow are reliable but very late signs of fluid loss, thus might explain the reported high mortality of SAM children associated with fluid therapy (23). In fact, the sensitivity and likelihood ratio of the WHO-recommended ‘‘danger signs’’ (lethargy, hypothermia, or hypoglycaemia) were found to be low, 52% and 3.4%, respectively (23). This clearly shows that reliance on oedema alone or in combination with other unreliable physical signs (cardio-respiratory) (24) might result in inadequate therapy.

Fluid disturbance is complex in all children with SAM and management requires a cautious approach especially if children have diarrhoea (25). Clinically, degree of pitting oedema, weight changes and signs of dehydration are used universally to monitor body fluid during treatment. Obviously, weight change does not distinguish between tissue- and fluid-related changes. Similarly, oedema is not sufficiently sensitive to tissue hydration since subclinical retention of sodium and water could occur before the threshold for oedema (26,27). Moreover, assessment of the amount and rate of change of oedema are very crude.

In patients with SAM, dehydration due to diarrhoea is often misdiagnosed and hence improperly treated leading to high mortality rates (28). Though the conventional physical assessment of dehydration are easy to perform and have high sensitivity (11), they are unreliable in severely malnourished patients. Extreme loss of subcutaneous fat per se may cause poor skin turgor and sunken eyes. On the other hand oedema may mask diminished skin turgor. Also behavioural abnormalities in both oedematous and non-oedematous SAM confound assessment of the mental state.

The above discussion ascertain the fact that SAM is a complex disease which requires improved understanding and monitoring (13,29). Actually in the recently updated WHO protocol issues of assessment and monitoring of hydration status, appropriate fluid strategy and monitoring approaches were identified as priority research areas (25). Therefore, it is pragmatic to explore ways of supplementing the conventional monitoring mechanisms with simple, valid and safe methods of evaluating hydration in order to enhance outcome of children with SAM.

Assessment of hydration in clinical settings is not easy but potential methods include measurement of plasma and urine osmolality, bioimpedance (BI), cardiovascular changes (e.g. heart volume and rate, liver enlargement), gallop rhythm, none of which is ideal (30). Unlike other methods BIM is nevertheless an easy, safe and simple bed-side technique (31–33). Besides predicting total body water (TBW) and derive estimate fat mass (FM), fat-free mass (FFM) or body cell mass (BCM), it predicts survival during treatment (34,35).

In its conventional application, bioimpedance method (BIM) requires population-specific equations for estimating body composition, an approach called bioimpedance analysis (BIA) (36,37). But, these equations are inaccurate in patients such as malnourished children who normally have body fluid imbalances (38). On the other hand, the use of primary BI parameters and vector analysis (BIVA) circumvents equation (39–41). It has been clinically validated in conditions such as sickle

cell disease (42), renal disease (43), hypertensive pregnancy (44), sepsis (45) and patients with HIV infection (35). Unfortunately, studies of BIVA approach in children with SAM are hard to find and the few available focused on validating equations or quantifying body compartments (46–48).

This thesis starts with a background on SAM with emphasis on major pathophysiologic changes relevant to body fluid abnormalities. Principles of BI are discussed subsequently. After describing the research methods, the main findings of the study are presented in three parts. The first part is on clinical predictors of oedema among children with SAM admitted to Jimma University Specialized Hospital (JUSH). In paper II, we compared TBW based on deuterium dilution technique with TBW based on BIA. The third part builds on the second and assessed the utility of primary BI parameters without equations in indexing hydration during treatment of SAM. Finally, synthesis and discussion of the main findings are provided followed by conclusions and recommendations for future researches regarding the application of BIVA in children with SAM.