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Utility of bio-electrical impedance vector analysis for monitoring treatment of severe acute malnutrition in children

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Abstract

**Background & Aims:** Change in hydration is common in children with severe acute malnutrition (SAM) including during treatment, but is difficult to assess. We investigated the utility of bio-electrical impedance vector analysis (BIVA), a quick non-invasive method, for indexing hydration during treatment.

**Methods:** We studied 350 children 0-5-14 years of age with SAM (mid-upper arm circumference <11·0 cm or weight-for-height <70% of median, and/or nutritional oedema) admitted to a hospital nutrition unit, but excluded medically unstable patients. Weight, height (H), resistance (R), reactance (Xc) and phase angle (PA) were measured and oedema assessed. Similar data were collected from 120 healthy infants and preschool/school children for comparison. Means of height-adjusted vectors (R/H, Xc/H) from SAM children were interpreted using tolerance and confidence ellipses of corresponding parameters from the healthy children.

**Results:** SAM children with oedema were less wasted than those without (p< 0·001), but had BIVA parameters that differed more from those of healthy children (P<0·05) than those non-oedematous. Initially, both oedematous and non-oedematous SAM children had mean vectors outside the reference 95% tolerance ellipse. During treatment, mean vectors migrated differently in the two SAM groups, indicating fluid loss in oedematous patients, and tissue accretion in non-oedematous patients. At admission, R/H was lower (oedematous) or higher (non-oedematous) among children who died than those who exited the hospital alive.
Conclusions: BIVA can be used in children with SAM to distinguish tissue- vs. hydration-related weight changes during treatment, and also identify children at high risk of death enabling early clinical interventions.

Keywords: bio-electrical, impedance, BIVA, severe acute malnutrition, hydration
Introduction

Mortality from severe acute malnutrition (SAM) is still high, especially among children with oedema. Most deaths occur during the early phase of in-patient treatment and are associated with complications, mainly infections and fluid and electrolyte abnormalities. It is crucial therefore to monitor treatment intensively with reliable and preferably technically simple methods to improve outcome. The challenge however is that SAM-related physical and physiological changes compromise the application and accuracy of most of the available techniques.

It is well established that altered hydration can confound the assessment of malnutrition, as excess fluid retention inflates both body weight and other routinely sampled somatic traits, such as mid-upper arm circumference. However, before this issue can be addressed, it is also critical to identify improved ways for assessing hydration status, and its variability during treatment. For instance, change in the degree of clinically detectable oedema is used to distinguish between tissue- and fluid-related weight changes. Though both oedema and weight measurements are simple, in routine clinical practice both are prone to significant error due to a combination of factors including unstandardized procedures, poor clinical skills, faulty equipment or recording errors. Moreover, peripheral oedema is undetectable until interstitial fluid volume is significantly elevated and hence is insensitive for early detection of fluid retention. Conversely, children with SAM can develop dehydration with minimal clinical signs. Also, the validity of other clinical indicators including irritability, poor skin turgor or enlarged liver is poor as they are associated with non-oedematous SAM as well.
There are other more valid and operator-independent methods for clinical use including plasma osmolality, urine osmolality and bio-electrical impedance (BI) methods. BI has the advantage over other methods of being rapid, inexpensive, non-invasive, and a safe bedside procedure. The conventional BI approach involves the prediction of total body water from the impedance (Z) index (calculated as the square of height divided by Z). However, this approach requires population-specific equations, furthermore the method assumes normal physiological state, hence conventional BI is often invalid in disease states where physiological state is disturbed, including SAM. To circumvent these challenges, a semi-qualitative approach called BI vector analysis (BIVA) has been found useful for differentiating between tissue- and fluid-related weight changes in various clinical conditions. With fewer assumptions, BIVA allows indexing and visualization of relative hydration status and assessment of body cell mass (BCM) reflecting cellular function.

To date, most BIVA studies of disease states have addressed adults, for example with renal diseases or anorexia nervosa, and few are from low-income countries. The use of BI or BIVA methods to study children with SAM remains rare. In this study, we investigated the utility of BIVA and primary BI parameters among children with SAM treated with standard protocols at a hospital in a low-income setting.
Materials and Methods

Study setting and subjects

The study was conducted in the Nutrition Rehabilitation Unit (NRU) of Jimma University Specialized Hospital, Ethiopia, from November 2009 to September 2011. Eligible children were those 0.5-14 years of age with SAM, defined as MUAC <11.0 cm or weight-for-height (WFH) <70% of the median of the NCHS growth reference and/or nutritional oedema. Children with life threatening illness such as shock or who were readmitted with SAM were excluded. Children below 6 months of age were excluded as the diagnosis and treatment of SAM in this age group is still not well standardized. Children were treated according to WHO-based guidelines.

Data collection

Children were weighed naked or with minimal clothing using a pediatric scale (Tanita BD 815 MA, Tokyo, Japan) and the weight recorded to the nearest 10g. For children less than 2 years of age or not able to stand, length was measured supine using a length board (SECA 416, Hamburg, Germany) and recorded to the nearest 0.1 cm. When length was measured in children older than 2 years of age, 0.5 cm was subtracted from the length. In older children, height was measured using a free-standing stadiometer (SECA 214, Hamburg, Germany) and recorded to the nearest 0.1 cm. MUAC was measured using a paper strip (SECA 2012, Hamburg, Germany) and recorded to the nearest 0.1 cm. Pitting oedema was checked by gentle pressure with the thumb on the feet for 3-5 seconds. Information on infections diagnosed at admission were copied from the child’s clinical record.
BI measurement was performed in all children. The protocol has been described previously but in brief it measures the opposition or impedance (Z) of the body to an alternating electric current. Impedance has two components: resistance (R) and reactance (Xc). R is the decrease in voltage reflecting conductivity through ionic solutions and Xc is the delay in the flow of current measured as a phase-shift, indicating mainly dielectric properties of cell membranes. The phase angle (PA) is the angle the impedance vector forms relative to the R vector 
\[ \text{atan}(Xc/R) \times \frac{180}{\pi} \].

Though the exact determinants of electrical properties of the normal human body remain poorly understood, BI method is based on the assumption that the body is a network of resistors (physiological fluids) and capacitors (cell membranes). In brief, R represents opposition of alternate electrical current that flows through physiological fluids by the movement of ions, while Xc reflects the charging of cell membranes and other interfaces. Resistance is inversely related to the amount of total body water and thus fat-free mass, whereas Xc is directly related to BCM.

BI parameters (R, Xc and PA) were measured at 50kHz using a Quadscan 4000 analyser (Bodystat, UK), multi-frequency and phase-sensitive, that emitted 200 Micro Amps root mean square alternating current. In addition to measuring the raw impedance values at four frequencies (5, 50, 100 and 200), the machine generated estimated values of including volume and distribution of body water, nutrition indices and prognostic health indicators. Using protocols described previously, self-adhesive disposable electrodes were attached at the right hand.
and foot, injecting leads were connected to the electrodes just behind the fingers and toes and the measuring leads were then connected to the electrodes on the right wrist and right ankle. Measurements were taken in triplicate, each spaced 5 minutes apart, while children were supine on a stretcher with limbs abducted from the body. The technical error of the mean, calculated on baseline data using the formula of Ulijaszek and Kerr (24), was as follows: Resistance 9.4 ohms; Reactance 2.0 ohms; Phase angle 0.18 degrees. These values are very small relative to both the standard deviation of the same variables at baseline (Resistance 254.1 ohms; Reactance 16.5 ohms; Phase angle 1.12 degrees) and their longitudinal changes during treatment.

Children (0·5-14 years of age) with WFH or body mass index-for-age (BMI, kg/m$^2$) and height-for-age (HFA) within ± 2SD of WHO growth standard were assessed using the same BI analyser and similar procedures. These apparently healthy children were recruited from vaccination attendees, children in day-care centres, and primary schools.

Caretakers were given verbal and written information about the study before consenting on behalf of their child. The Research Ethical Review Committee of Jimma University approved the study. Two research nurses collected the data.

Statistics and data handling

Descriptive statistics

Data were double-entered into EpiData version 3·1 (EpiData Association, Odense, Denmark) and analyzed with Stata/IC 12·1 (StataCorp, Texas, USA). Anthropometric z-scores were based
on WHO child growth standards and were calculated in Stata and WHO Anthro Plus v 1.0.3 (WHO, Geneva, Switzerland). Data were stratified by the presence of oedema at admission and patient hospital exit status (recovery, self-discharge or death). R and Xc were indexed to height by division, giving R/H and Xc/H. Continuous data were presented as mean ± standard deviation, median (IQR); categorical data were presented as n (%). Two-sample t-tests and chi-squares test were used to compare healthy children with children having SAM.

Regression analysis

Height-adjusted values of BI parameters were the dependent variables. Covariates associated with changes in the BI parameters over time were identified using linear mixed-effects regression analysis. The covariates considered were age, sex, presence of nutritional oedema at admission, co-diagnosis, and days of hospitalization before enrolment (stabilization period). None of these were time-dependent. Both linear and quadratic trends were included in the model.

To investigate whether changes in BI parameters during treatment depended on oedema at admission, time-oedema interactions were evaluated. Correlation between measurements on the same subject was described by means of subject-specific random effects. Simple linear regression was used to evaluate the association of baseline BI parameters with patients’ exit status; the model included all the above covariates. All final models were established using forward selection.

Vector analysis

BIVA was performed by RXc graph method (13) using a customized Excel program. (26) Vectors of children with SAM were compared with vectors of healthy children using the “RXc
mean graph”; the relationship of R/H, Xc/H, and PA. We plotted vectors over time on “RXc graph tolerance ellipses” and interpreted their trajectory. Generally the 75% tolerance ellipse represent bioelectrical thresholds or normal tissue impedance; displacements along the major axis of the ellipse show changes in tissue hydration whereas vectors following the minor axis (above or below the major axis) indicate soft tissue or BCM. (27) Vectors of group-means were compared by Hotelling’s T-squared ($T^2$) generalized means test. Changes during treatment in BMI-for-age z-score and the BI parameters were shown by mean and 95% confidence interval plots over five time points during treatment:0, 7th, 14th & 21st days.
Results

During the study period, 527 children with SAM (0·5 to 14 years of age) were admitted to the paediatric ward at the study site. We excluded 176 (33·4%) children since they were medically unstable. One child was omitted from analysis due to incomplete BI data. The studied and excluded children had comparable mean age (1·6 months, 95% CI, -4·2, 7·4), sex distributions (38·6 % v. 43·3 % girls, p=0·30) and proportions with oedema (66·1 % v. 61·1 %, p=0·26). Out of those excluded children, 105 (60·6%) had exit-status data, which showed that they had lower recovery rate (69·5% vs. 85·9%, p<0·01) and higher mortality (20·0% vs. 3·4%, p<0·001) compared to those studied.

Table 1 shows that non-oedematous children were younger than non-oedematous children (median age, 26 vs. 36 months, p=0·04), needed more stabilization time (mean days, 8 vs. 5, p<0·001) and also had a higher proportion with clinical infection (51% vs. 43%, p<0·001). But, stunting was comparable between the two groups (mean HAZ, -3·3 vs. -3·2, p=0·70). Table 2 compares the BIVA values between healthy children and children with SAM at enrollment and also within SAM by presence of oedema. Variability of parameters was higher among children with SAM than healthy children. SAM children had higher R/H than healthy children (-204, 95%CI -277 to -131) while their Xc/H (19, 95%CI 15-23) and PA (1·5, 95%CI 1·3-1·7) were lower. The oedematous SAM group had the lowest R and Xc as also displayed in Figure 1B by the shortest vector with the least slope.

The four graphs in Figure 2 show trends in both BMI and BIVA parameters during treatment. It is evident that though BMI and BIVA parameters have improved significantly over the four
weeks of treatment, they did not normalize. Interestingly, the change in resistance was divergent by oedema status whereas, expect for slope, the trends in reactance and phase angle did not differ by oedema status. Children with oedema had weight loss in the first two follow-up weeks, followed by weight catch-up. The regression results in Table 3 further demonstrate the temporal relationship between oedema and BI parameters within and between SAM groups during the course of nutritional therapy. Weight losses were accompanied by significant increases in both R/H (B = 19, 95%CI 13, 25) and Xc/H (B = 0·71, 95%CI 0·26-1·2) However, both of these changes slowed in rate during the catch-up period. In children without oedema, weight increased linearly throughout treatment and this was accompanied by steady but insignificant reduction in R/H (B = -2·8 95%CI -6·4 to 0·87) and increase in Xc/H (B = 0·13, 95%CI -0·16 to 0·41) over time.

The changes in BI parameters are better visualized in their vector trajectories (Figure 3). Of note, vectors of both oedematous and non-oedematous children were notably outside the reference 95% tolerance ellipse (Figure 3A). Subsequently, the vector of oedematous children migrated towards the centre along the major axis of ellipses, demonstrating increased R/H and Xc/H. As noted in Figure 3B the trajectory had faster pace initially. The vector migration in non-oedematous children was also in a central direction, but unlike in the oedematous children it followed the minor axis, showing a reduction in R/H and an increase in Xc/H. Additionally, compared with the oedematous children, the pace of migration was slower and more uniform in non-oedematous children throughout the treatment period.

On one hand, children who had no clinical infection had higher mean PA than children who had at least one recorded infection (mean PA, 2.52 vs. 2.38, 95%CI: 0.12-0.16). On the other hand, PA was 0.036 higher by each additional day of stabilization (95%CI:0.02-0.05, p<0.001).
Finally, though this study excluded medically unstable children, twelve deaths were recorded, nine of them among children who had oedema at enrollment. Most of these deaths occurred before the second BI measurement (data not shown). As shown in Table 4 and Figure 4, extremely low and extremely high baseline resistance predicted death in oedematous and non-oedematous children, respectively.
Discussion

This study described changes in BIVA parameters of children with SAM during in-patient treatment using two main analytical approaches. The first one, BIVA showed that children with SAM initially had grossly deranged BI values which improved during the course of treatment. The vector also easily identified the predominantly fluid-related weight changes in oedematous children whilst in non-oedematous children it showed tissue accretion. Second, comparison of the means (actual and adjusted for covariates) of individual raw parameters (R, Xc and PA) between healthy and SAM and within SAM has also provided the aforementioned information. Finally, extremes of R values at admission were found to be associated with death.

The initial data points clearly show that BIVA parameters are severely affected in children with SAM, and also have increased variability. The increased variability by itself is useful clinical information. Among healthy individuals, BIVA variability can arise from normal variation in tissue structure and adipose tissue content. (22) However, in disease states, cellular changes due to morbidities and body composition abnormalities may increase this variability (28), hence explaining the greater heterogeneity of SAM children compared with healthy children. Change in variability could be when examining group data from epidemiologic studies.

The most interesting observation in this study has come from the vector trajectories that accompanied the weight changes. Theoretically, changes in R and Xc represent changes in body fluid and tissue (BCM), respectively. (12,37) The trajectory of oedematous children indicates a combination of major loss of excess fluid and minor lean tissue accretion, a pattern found in nephrotic patients losing oedema. (13) The trajectory among non-oedematous children represents
gain in BCM with increasing hydration. Though less pronounced, this trajectory is similar to findings in HIV/AIDS patients. (13) Of note, the finding of weight gain accompanied by insignificant vector movement may indicate accelerated body-fat which often initially accompanies refeeding. (30)

When examining the individual BIVA parameters, oedematous children had lower values despite having higher BMI even after loss of oedema. The lower R could be explained by the combination of larger muscle mass and excess fluid collection which is manifested as oedema. In addition for a given body water, individuals with more fluid in extremities will have lower R since the limbs contribute approximately to half of total body R. (31) (32) Cirrhotic patients with oedema have shorter impedance vectors than cirrhotic patients without oedema whereas impedance vectors between those with or without ascites did not differ. (33)

In the oedematous children, consistent and significant increase in R was noted during treatment. This change was rapid during the period of weight loss and may show progressive increase in tissue specific resistivity (ρ), a constant that is inversely related to the concentration of free ions. (34) Further support for this explanation comes also from the simultaneous increase in the Xc which indicates an increase in BCM. Extreme alterations in the amount and composition of extracellular fluids in oedematous children (35) may modify ρ of the body. Considering the direct relationship between R and wasting, higher R in children without oedema indicates their extreme wasting. Xc and PA may reflect ‘cellular health’. (36) The significantly low Xc and PA values of children with SAM compared with the healthy children specially among oedematous children may show cellular and membrane dysfunctions described in SAM. (37)
PA has been shown as a prognostic indicator in various clinical conditions among young age groups; lower PA indicates poor clinical outcome in critically ill children (38–41) and has been used to assess response to different nutritional therapies in young children with severe-acute malnutrition. In this study, we have found that SAM children with at least one type of infection had lower PA than those without. On the other hand, PA was directly related with the number of days SAM children required to stabilize before enrollment. The higher PA could be a proxy indicator for better clinical stabilization. However, as PA varies with age in children, age-specific z-scores calculated from population-specific reference data may be the best way to approach this issue (42).

The relationship between baseline R and patient outcome indicates a prognostic value of BIVA parameters, with oedema further influencing the direction of this relationship. The extremely low values of R in oedematous children might indicate severe tissue over-hydration (43) while extremely high R in children without oedema indicates extreme wasting compared within their group of those who were alive at exit. Considering that medically unstable children were excluded from this study, it is possible that BI could outperform clinical parameters in identifying SAM children at high risk of death. However, it is important to investigate the performance of BIVA as a triage tool compared with the standard appetite test and other clinical indicators. If proven to function well, its objectivity and simplicity could give it an edge over other methods.
In terms of additional practical application of BIVA parameters, combining anthropometric measurements and BIVA may broaden and optimize aspects of patient evaluation specially assuming that repeated BI measurements assess nutritional status, hydration, and “cellular health” simultaneously. As noted above, BIVA can clearly distinguish whether acute weight change is due to fluid change or tissue accretion. Even though accurate quantification is unlikely to be made, there is a potential for continuous tracking of relative changes. This, combined with other clinical parameters could guide clinical interventions. For instance, in a clinically deteriorating child a fall in R without detectable change in oedema status could signal excess fluid accumulation. At the same time, accompanying change in Xc or PA could be clues for underlying factors like infection which can affect ‘cellular health’.

In both types of SAM, the BIVA values for R, Xc and PA were all well outside the reference range and did not normalize. Based on this finding BIVA should be considered as a tool for monitoring post-SAM children. Assuming that BIVA parameters will normalize if and when nutritional status and general health improve, vector and/or the individual parameters can be assessed regularly to monitor children who have been discharged from SAM treatment programs.

This study has certain limitations. The exclusion of critically ill children from the study limited the assessment of BIVA approach in this group. It would have been of value to compare the BIVA data with another indicator of hydration (e.g. deuterium or bromide dilution or serum osmolality). A systematic clinical investigation (imaging, microbiologic, and blood chemistry) of the patients would have enhanced clinical interpretation of the BIVA data. Finally, as calibration device was not available for the BIA analyzer in this study, it was not possible to provide...
calibration data. Strengths include the large sample size, the protocol of measuring BIVA parameters in triplicate and the inclusion of a healthy comparison group.

In conclusion, our study demonstrates the utility of BIVA for indexing tissue- vs. fluid-related weight changes in children with SAM during in-patient treatment. Moreover, BIVA may predict survival of children hospitalized for SAM. More studies should be done to understand the biological correlates of BI changes in conditions like SAM which are associated with multisystem and complex pathophysiological changes. Furthermore, future studies should identify BIVA patterns and its associated factors in medically unstable or critically sick children with SAM. This will contribute to evaluate the usefulness of BI in patient triage. Finally, it is important to investigate the timing for normalization of BI and the determinants.

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Statement of Authorship

TG, PK, KFM, CM, HF and JW were involved in the conception and design of the study. TG and PK contributed to acquisition of data. TG, PK, KFM, CM, GSA, CR, HF and JW contributed
to analyses and interpretation of the data. TG was responsible for writing up of the paper while all authors reviewed, contributed to, and approved the final manuscript.

Conflicts of interest

All authors declare no conflict of interest.

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References


480 42. Wells JCK, Williams JE, Quek RY, Fewtrell MS. Bio-electrical impedance vector analysis: testing Piccoli’s model against objective body composition data in children and adolescents. European Journal of Clinical Nutrition [Internet]. 2018 Aug 30; Available from: https://doi.org/10.1038/s41430-018-0292-x

Fig. 1 Scatter and RXc mean graph of baseline R/H and Xc/H of healthy children and children with severe acute malnutrition, where R is resistance, Xc reactance and H height.

Fig 1A shows oedema-specific distribution of data points compared with the healthy children and fig 1B displays the position of vector means of the three groups. The oedematous children have the shortest vector with the least phase angle (slope) – related indirectly with relative volume of body water. The oedematous children have the shortest vector with the least slope. Separate 95% confidence ellipses of two mean vectors is equivalent to a significant Hotelling’s T2 test, P<0.05.

Fig. 2 Trends in body weight and bio-impedance during treatment in children with severe acute malnutrition

The estimated means and 95%CI (error bars) of body mass index z score, height indexed resistance and reactance, and phase angle were generated using linear mixed-effects regression after adjusting for covariates including age. The horizontal dash lines indicate reference values.

Fig 3. Oedema-specific trajectories of weekly mean impedance vectors (R/H and Xc/H) of children with severe acute malnutrition treated at Jimma University Hospital, where R is resistance, Xc reactance and H height.

Fig 3A shows tolerance ellipses based on data from age-matched healthy children. Fig 3B zooms-in the vectors shown in fig x1 which were measured weekly over the treatment period. The error bars represent 95%CI. Among oedematous children, the vector migrates to the center mainly along the major axis of ellipses starting outside the 95% tolerance ellipse and thus
indicates combined major loss of excess fluid and minor lean tissue accretion (i.e. increasing in both R and Xc, but mainly R). The migration pattern among non-oedematous children is to the center principally along the minor axis and hence represents gain in cell mass (lean tissue) with increasing hydration (i.e. reduction in R and increase in Xc).

**Fig 4.** Oedema-specific trajectories of weekly mean impedance vectors (R/H and Xc/H) of children with severe acute malnutrition treated at Jimma University Hospital, where R is resistance, Xc reactance and H height.

The border for “reference” children represents 95% tolerance ellipse and was based on data from age-matched healthy children. The data points outside the trajectories were from deaths in oedematous and non-oedematous groups. They were only baseline and hence are to be compared with similar data points of their respective groups.
Table 1. Selected characteristics of healthy children and children with severe acute malnutrition (SAM)

<table>
<thead>
<tr>
<th></th>
<th>Healthy</th>
<th>Non-oedematous</th>
<th>Oedematous</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=120</td>
<td>n=136</td>
<td>n=214</td>
<td></td>
</tr>
<tr>
<td>Age, month</td>
<td>38 (22 - 82)</td>
<td>29 (14 - 60)</td>
<td>36 (24 - 60)</td>
<td>0.04</td>
</tr>
<tr>
<td>Male sex</td>
<td>60 (50.0)</td>
<td>76 (56.0)</td>
<td>122 (57.0)</td>
<td>0.84</td>
</tr>
<tr>
<td>BMI-for-age z-score</td>
<td>-0.1 ± 1.0</td>
<td>-3.6 ± 1.3</td>
<td>-1.7 ± 1.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight-for-age z-score</td>
<td>-0.3 ± 0.8</td>
<td>-4.3 ± 1.2</td>
<td>-3.2 ± 1.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Height-for-age z-score</td>
<td>-0.5 ± 1.0</td>
<td>-3.3 ± 1.7</td>
<td>-3.2 ± 1.6</td>
<td>0.70</td>
</tr>
<tr>
<td>Weight-for height z-score</td>
<td>0.1 ± 0.1</td>
<td>-3.6 ± 1.2</td>
<td>-1.7 ± 1.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clinical Infections</td>
<td>-</td>
<td>51 (37.5)</td>
<td>43 (20.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Days to stabilization</td>
<td>-</td>
<td>8 ± 8.2</td>
<td>5 ± 5.5</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are median (IQR) or number (%) or mean ± standard deviation; z-scores were calculated using WHO growth standard; "a only for children <5 years of age; b ≥1 clinically diagnosed infections during admission, c number of days between hospital admission and enrolment into study.
Table 2. Baseline bio-impedance values of children with severe acute malnutrition (SAM) and healthy control children

<table>
<thead>
<tr>
<th></th>
<th>Healthy</th>
<th>SAM</th>
<th>SAM Non-oedematous</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=120</td>
<td>n=350</td>
<td>Diff (95%CI)</td>
</tr>
<tr>
<td>Resistance (R), ohm</td>
<td>826 ± 109</td>
<td>888 ± 252</td>
<td>-62 (-109,-15)</td>
</tr>
<tr>
<td>Reactance (Xc), ohm</td>
<td>62 ± 13</td>
<td>37 ± 16</td>
<td>25 (22, 28)</td>
</tr>
<tr>
<td>Phase angle, degree</td>
<td>4.3 ± 1.0</td>
<td>2.5 ± 1.1</td>
<td>1.8 (1.6,2.0)</td>
</tr>
<tr>
<td>R / height, ohm/m</td>
<td>878 ± 246</td>
<td>1082 ± 382</td>
<td>-204 (-277,-131)</td>
</tr>
<tr>
<td>Xc / height, ohm/m</td>
<td>64 ± 8.0</td>
<td>45 ± 21</td>
<td>19 (15, 23)</td>
</tr>
</tbody>
</table>

Data are mean ± standard deviation of tetra-polar whole-body impedance measured at 50 kHz
Table 3. Estimated coefficients (95%CI) of changes in bio-impedance parameters among 350 children during treatment for severe acute malnutrition

<table>
<thead>
<tr>
<th></th>
<th>Resistance /height</th>
<th>Reactance /height</th>
<th>Phase angle</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Linear slope</strong>a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-oedematous</td>
<td>-2.8 (-6.4, 0.87)</td>
<td>13 (-0.16, 0.41)</td>
<td>0.007 (-0.015, 0.028)</td>
</tr>
<tr>
<td>Oedematous</td>
<td>19 (13, 25)</td>
<td>0.71 (0.26, 1.2)</td>
<td>0.009 (-0.025, 0.043)</td>
</tr>
<tr>
<td><strong>Quadratic slope</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-oedematous</td>
<td>-0.01 (-0.11, 0.09)</td>
<td>0.002 (-0.006, 0.01)</td>
<td>0.0001 (-0.0005, 0.0001)</td>
</tr>
<tr>
<td>Oedematous</td>
<td>-0.30 (-0.46, -0.14)</td>
<td>-0.016 (-0.03, -0.004)</td>
<td>-0.004 (-0.001, 0.0001)</td>
</tr>
</tbody>
</table>

Multiple mixed-effects models: interaction between oedema at admission and follow-up days adjusted for age, sex, hospital stay for stabilization before enrollment and co-diagnosis (≥1 infection diagnosed during admission);a Resistance and reactance are Ohm/meter and phase angle is in degree.
Table 4. Relationship between baseline bio-impedance and hospital exit status of children with severe acute malnutrition

<table>
<thead>
<tr>
<th></th>
<th>Resistance/height</th>
<th>Reactance/height</th>
<th>Phase angle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recovered *a</td>
<td>Ref.</td>
<td>Ref.</td>
<td>Ref.</td>
</tr>
<tr>
<td>Self-discharged</td>
<td>16 (-106, 137)</td>
<td>2.5 (-5.9, 10.9)</td>
<td>0.24 (-0.44, 0.92)</td>
</tr>
<tr>
<td>Died</td>
<td>655 (345, 967)</td>
<td>4.2 (-17.1, 25.4)</td>
<td>-0.34 (-2.5, 1.6)</td>
</tr>
<tr>
<td>Died*oedematous</td>
<td>-801 (-1161, -441)</td>
<td>-16.2 (-40.8, 8.3)</td>
<td>-0.22 (-3.1, 2.7)</td>
</tr>
<tr>
<td>Self-discharge*oedematous</td>
<td>-26 (-210, 158)</td>
<td>-2.1 (-14.8, 10.5)</td>
<td>-0.11 (-1.0, 0.83)</td>
</tr>
</tbody>
</table>

*aCoefficient (95%CI) after adjustment for age, sex, days of hospital stay for stabilization before enrollment and co-diagnosis (≥1 infection diagnosed during admission). Recovered (n=296): medical discharge after attaining weight for height ≥ 85% of median and/or complete resolution of pitting pedal oedema, self-discharged (n=42): discharge against medical advice ‡ and died (n=12). Resistance and reactance are Ohm/meter and phase angle is in degree.
Fig. 1 Scatter and RXc mean graph of baseline R/H and Xc/H of healthy children and children with severe acute malnutrition, where R is resistance, Xc reactance and H height. Fig 1A shows oedema-specific distribution of data points compared with the healthy children and fig 1B displays the position of vector means of the three groups. The oedematous children have the shortest vector with the least phase angle (slope) – related indirectly with relative volume of body water. Separate 95% confidence ellipses of two mean vectors is equivalent to a significant Hotelling’s T2 test, P<0.05.
Fig. 2 Trends in body weight and bio-impedance during treatment in children with severe acute malnutrition. The estimated means and 95%CI (error bars) of body mass index z score, height indexed resistance and reactance, and phase angle were generated using linear mixed-effects regression after adjusting for covariates including age. The horizontal dashed lines indicate reference values.
Fig 3. Oedema-specific trajectories of weekly mean impedance vectors (R/H and Xc/H) of children with severe acute malnutrition treated at Jimma University Hospital, where R is resistance, Xc reactance and H height. Fig 3A shows tolerance ellipses based on data from age-matched healthy children. Fig 3B zooms-in the vectors shown in fig x1 which were measured weekly over the treatment period. The error bars represent 95%CI. Among oedematous children, the vector migrates to the centre mainly along the major axis of ellipses starting outside the 95% tolerance ellipse and thus indicates combined major loss of excess fluid and minor lean tissue accretion (i.e. increasing in both R and Xc, but mainly R). The migration pattern among non-oedematous children is to the centre principally along the minor axis and hence represents gain in cell mas (lean tissue) with increasing hydration (i.e. reduction in R and increase in Xc).
Fig 4. Oedema-specific trajectories of weekly mean impedance vectors (R/H and Xc/H) of children with severe acute malnutrition treated at Jimma University Hospital, where R is resistance, Xc reactance and H height. The border for “reference” children represents 95% tolerance ellipse and was based on data from age-matched healthy children. The data points outside the trajectories were from deaths in oedematous and non-oedematous groups. They were only baseline and hence are to be compared with similar data points of their respective groups.