Beyond Z-scores: Measures to Advance Prevention and Treatment Outcomes in Child Malnutrition

Summary of Proceedings from a Symposium at the International Congress of Nutrition, Buenos Aires, Argentina on October 16, 2017

A Report from the Food Aid Quality Review

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<td>BIA</td>
<td>Bio-electrical Impedance Analysis</td>
</tr>
<tr>
<td>DCHA</td>
<td>Bureau for Democracy, Conflict and Humanitarian Assistance</td>
</tr>
<tr>
<td>DIAAS</td>
<td>Digestible Ileal Amino Acid Score</td>
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<tr>
<td>DXA</td>
<td>Dual-energy X-ray Absorptiometry</td>
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<td>EED</td>
<td>Environmental Enteric Dysfunction</td>
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<td>FAQR</td>
<td>Food Aid Quality Review</td>
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<td>FFP</td>
<td>The Office of Food for Peace</td>
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<td>ICN</td>
<td>International Congress of Nutrition</td>
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<td>MAM</td>
<td>Moderate Acute Malnutrition</td>
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<tr>
<td>MUAC</td>
<td>Mid-Upper Arm Circumference</td>
</tr>
<tr>
<td>PDCAAS</td>
<td>Protein Digestibility Corrected Amino Acid Score</td>
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<tr>
<td>SAM</td>
<td>Severe Acute Malnutrition</td>
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<td>USAID</td>
<td>United States Agency for International Development</td>
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<tr>
<td>WHZ</td>
<td>Weight-for-Height Z-score</td>
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I. EXECUTIVE SUMMARY
There is a growing imperative to measure the nutrition and health impact of food-based humanitarian assistance with more precision to better inform policy and practice. For many decades, researchers and programmers have relied mainly on anthropometric Z-scores and related cutoffs to determine the nutritional status of children to assess the impact of interventions. However, Z-scores may fail to distinguish important physiological or cognitive factors which can bias the interpretation of health, malnutrition or recovery. A symposium was organized at the 2017 International Congress of Nutrition (ICN) in Buenos Aires, Argentina, to consider three measures which add important contextual information and have implications for how we approach the treatment and prevention of child malnutrition. This paper provides a summary of the Symposium and key messages on research priorities, policy implications and programming guidance.

Several experts were asked to offer their perspectives on each of the three measures considered. The first measure was body composition, i.e. the proportion of lean and fat mass, which can be more useful than weight or height in predicting certain health outcomes. The second measure was environmental enteric dysfunction (EED), whose presence has been shown to be a predictor of child undernutrition. The third measure was dietary protein quality combined with biomarker serum amino acids, which have been shown to be associated with child malnutrition. Current research is being conducted on the use and interpretation of these three measures in the context of malnutrition. However, similar challenges remain among all three. The technology required to evaluate these three measures remains costly and highly-trained technicians are needed. In addition, there is ongoing debate as to which evaluation methods are the most accurate and meaningful. Furthermore, while these measures are being explored, they are still not the main drivers in making decisions about a program’s effectiveness.

The Symposium discussed efforts to treat or prevent child malnutrition which need to move beyond measurement of Z-scores to determine treatment methods and understand the effects of food-based interventions. Further efforts are needed toward accessible technology, accepting the use of these new measures, and understanding how they should be interpreted. In the meantime, we should be taking what is already known about these three key areas into urgent consideration in research, policy and programming.

II. BACKGROUND
The United States Agency for International Development (USAID) spends upwards of $1.4 billion U.S. dollars per year on Title II emergency and non-emergency food aid, more than 1 million metric tons (1). As the need for food aid increases globally in the context of resurging famines and a rising number of hungry people, there is a growing imperative to measure the nutritional impact of this large dimension of humanitarian assistance with more precision and policy-implementing value. Tufts University’s Food Aid Quality Review (FAQR) is a project supported by USAID which examines the effectiveness of food aid in addressing prevention and treatment of child malnutrition.
For many decades, nutritionists have relied mainly on anthropometric measurements of height and weight—further transformed into height-for-age or weight-for-height percentiles or Z-scores—to determine nutritional status in children. However, anthropometric Z-scores fail to distinguish important dynamic and contextual factors which will greatly affect the success of interventions to treat or prevent malnutrition, as well as future implications of these interventions. In addition, there are contextual factors which can influence the potential effect of a supplementary food intervention on growth, such as the presence of EED, an as-yet undefined structural and functional change to the gut which impairs absorption of nutrients. Furthermore, the nutritional quality of the diet and related biomarker status is not reflected in Z-scores. In the case of protein, there is a complex combination of factors, including the food matrix, processing, and amino acid profile, which can impact its quality, absorption and utilization in the body for growth and other functions.

These three areas—body composition, EED and protein quality—represent some of the newer measures which give us more information about malnutrition, its context, potential target beneficiaries, outcomes and the impact of our food aid interventions. The purpose of this Symposium was to discuss the status of these newer indicators and move the agenda forward on research priorities, policy implications and program guidance.

III. SUMMARY OF PRESENTATIONS

BODY COMPOSITION
Presenters: Cornelia Loechl, International Atomic Energy Agency, Vienna, Austria and Susan Roberts, Tufts University, Boston, U.S.A. (presented by Dr. Irwin Rosenberg in her absence)

Key Points
• Lean mass and fat mass, rather than weight alone, are more useful for nutritional evaluation.
• Newer technologies are able to determine body composition in the field. They will make body composition measures more affordable and accessible. However, they need to be validated against reference methods.

Currently, interventions to treat moderate acute malnutrition (MAM) or severe acute malnutrition (SAM) rely on weight-for-height Z-score (WHZ) and/or mid-upper arm circumference (MUAC) both to screen individual children for treatment and to determine “recovery” from malnutrition. However, determination of body composition, i.e. the proportion of lean and fat mass, in the context of treatment of acute malnutrition may be more useful in the definition of healthy recovery and prediction of later relapse or health outcomes. The risk for obesity and chronic disease may be programmed by events early in life, and there is a positive association between greater rate of weight gain in early infancy and later fat mass and central fat distribution (2,3). While there is concern that supplementary foods for treatment of MAM may increase fat tissue (4), two recent studies using the newer technology of deuterium dilution have shown that supplementary foods are not associated with excess fat deposition during treatment of MAM (5,6).
There are a number of methods to assess body composition, each with varying strengths and weaknesses (Table 1). Despite its important implications in the treatment of malnutrition, evaluation of body composition is not often included in interventions, especially in a low-resource setting, where it can be challenging for several reasons, including:

- Costs associated with equipment, materials and/or adequate training for staff are high;
- Detection of very small differences in body composition to evaluate changes over short periods of time can be difficult with existing technology;
- Hydration factor varies with age and physiological states (e.g. pregnancy, severe acute malnutrition with edema and other clinical conditions); and
- Data on “normal” body composition is limited (e.g. for different ethnic groups).

Over time, costs of more technology-heavy body composition assessment methods such as deuterium dilution will decrease. In addition, more partnerships with groups which have funding and technological capacity will be needed both to refine methods and to build an evidence base around their use. At the same time, low-cost, lower-tech methods such as MUAC and skinfolds should still be used but they should be combined with functional tests such as muscle strength.

**Table 1: Methods and Challenges in Assessing Body Composition**

<table>
<thead>
<tr>
<th>Method</th>
<th>Challenges</th>
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<tbody>
<tr>
<td>DXA</td>
<td>It is difficult for remote and pediatric populations because it requires a large scanner, the individual must lie completely still for several minutes and it involves a dose of radiation.</td>
</tr>
<tr>
<td>Deuterium dilution</td>
<td>This is expensive and time-consuming to conduct in large-scale population studies. Deuterated water is costly. Collection of urine or saliva is needed. Assumptions about hydration status may result in inaccurate estimates (especially in the context of edema).</td>
</tr>
<tr>
<td>Bio-electrical impedance analysis (BIA)</td>
<td>The BIA machine is simpler to use in the field but has a large margin of error (+/- 200 g lean tissue in malnourished infants). While this does not lend itself to detecting small changes over time, it could be used for cross-sectional evaluation.</td>
</tr>
<tr>
<td>Skinfold and MUAC measurements</td>
<td>Skinfold and MUAC measurements can be useful field methods if done correctly but they are sensitive to field errors and differences across assessors. There is potential to combine these methods to estimate muscle mass.</td>
</tr>
<tr>
<td>Body cell mass</td>
<td>This technique uses sodium iodide detectors and is independent of hydration changes but currently requires a large non-portable scanner so is not suitable for field studies.</td>
</tr>
<tr>
<td>Creatine dilution to determine muscle mass</td>
<td>This technique is promising but still under development for use in malnourished infants.</td>
</tr>
<tr>
<td>Future technologies</td>
<td>Newer technologies such as mobile phone and photo applications may combine low-cost portability and ease of use.</td>
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</tbody>
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ENVIRONMENTAL ENTERIC DYSFUNCTION (EED)

Presenters: Dr. Irwin Rosenberg, Tufts University, Boston, U.S.A. and Tahmeed Ahmed, International Centre for Diarrhoeal Disease Research, Bangladesh, Dhaka, Bangladesh

Key Points

- Environmental enteric dysfunction (EED) is an often subclinical inflammatory, malabsorptive disorder of the gut, increasingly linked with child stunting.
- Non-invasive technologies to determine and quantify EED are still in development.
- The relationship between EED and supplemental foods is yet to be elucidated, but future food-based interventions will need to take factors related to EED into account in order to be more effective.

Globally, one-quarter of children are stunted (more than one-third in sub-Saharan Africa and South Asia) but we have yet to make a large impact in stunting rates through targeted nutritional interventions alone. EED may be a causative factor in stunting and a factor preventing nutritional interventions from being effective.

In the 1960s, new methods available to biopsy the small bowel revealed differences in mucosal structure between Western adults and adults in tropical, developing countries, including shortened villi, mucosal inflammation and reduced absorptive function. Similar changes occurred in expatriates living in tropical environment—minimal symptoms, some weight loss—which was named tropical sprue or enteropathy. These changes reversed without any intervention after the individuals returned home. The cause was unclear but environmental factors were implicated. However, due to uncertain relevance, interest in EED waned for several decades.

Today, EED is better defined but characterized as an acquired functional and structural change of the intestine (perhaps just the small bowel) in the absence of overt illness. It may be due to factors encountered in the environment of still-unknown type related to microbial contamination, diet, toxicity in water or food, or others factors yet to be identified. Poor sanitation and hygiene, as well as fecal contamination of the domestic environment have been shown to be associated with EED.

Recently, interest in EED has increased, as appears to be a reversible cause of malnutrition and stunting. EED which begins early in life can result in growth faltering due to malnutrition, predisposed susceptibility to infection with pathogens and increased severity of their consequences. The strongest evidence for EED was the association between enteropathogens and linear growth mediated through systemic inflammation (7). Several recent studies have shown varying indicators of EED associated with poor nutritional status and linear growth (8-10). It has also been found that the gut microbiome is different between healthy and malnourished children (11) and impaired gut microbiota development is causally related to undernutrition (12). EED is potentially reversible; it could be as important as reducing exposure to pathogens/contaminated environments (13) or improving response to oral vaccines in our efforts to reduce child malnutrition. However, this condition is difficult to diagnose, as children with EED may not show overt symptoms of gut infection, such as diarrhea (14).
All the current assessment methods (Table 2) involve obtaining subjects’ serum, urine and/or feces. Serum is more invasive, but urine and feces can be challenging to collect, especially from very young children. Moving forward, a standard definition of EED is needed. New studies using this definition could provide clues to the relevance of EED as antecedent cause for malnutrition and increased infection. Clues to etiologic factors may be obtained so intervention studies can be planned; evidence is needed on how supplemental foods impact EED and, conversely, how EED impacts effectiveness of nutrition interventions. Remedies for EED could increase optimum utilization of food, perhaps by harnessing the gut microbiota. A new cost-effective strategy to combat EED and its consequences may result, particularly effective if applied right after birth (or before) to reduce impacts during rapid growth and development of infants and children. Finally, biomarkers for EED are now available but still need more work for optimization in terms of validation and field-friendly measures.

**Table 2: Methods for Assessing Biomarkers of EED**

<table>
<thead>
<tr>
<th>Domain</th>
<th>Biomarker</th>
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<tbody>
<tr>
<td>Intestinal absorption</td>
<td>Mannitol recovery</td>
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<tr>
<td>Intestinal barrier function</td>
<td>Lactulose recovery</td>
</tr>
<tr>
<td>and permeability</td>
<td>a-1 antitrypsin, neopterin, myeloperoxidase, CD53, HLA-DRA, MUC12, CDX1,</td>
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<tr>
<td></td>
<td>S100A8, REG1A, TNF; Fecal host mRNA</td>
</tr>
<tr>
<td>Intestinal inflammation</td>
<td>I-FABP</td>
</tr>
<tr>
<td>Enterocyte damage</td>
<td>REG-1B</td>
</tr>
<tr>
<td>Intestinal regeneration</td>
<td>EndoCAb, LPS, sCD14, sCD163</td>
</tr>
<tr>
<td>Microbial translocation</td>
<td>C-reactive protein, alpha-glycoprotein</td>
</tr>
<tr>
<td>Systemic inflammation</td>
<td>Insulin-like growth factor-1</td>
</tr>
<tr>
<td>Growth hormone activity</td>
<td>Lactulose:Mannitol ratio</td>
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<tr>
<td>Combined indicators</td>
<td>EE Score (2 x AAT category + 2 x MPO category + 1 x NEO category)</td>
</tr>
</tbody>
</table>

**PROTEIN QUALITY**

Presenters: Anura Kurpad, St. John’s College, Bangalore, India and Ricardo Uauy, London School of Hygiene and Tropical Medicine, London, U.K.

**Key Points**

- Inadequate dietary protein quality is associated with stunting.
- Current methods of assessing dietary protein quality are complex, have questionable accuracy and may vary across individuals and contexts.
- There is a need for simpler assessment of protein quality to target strategies to improve dietary protein quality to address malnutrition and stunting.

Young children in developing countries are often at risk of nutrient deficiencies due to a diet heavily reliant on staple crops. This includes high-quality protein—the ability of a food or diet to meet human protein and amino acid requirements—which is often overlooked and is implicated in growth. Amino acids are necessary for a myriad of metabolic processes,
including growth, tissue repair, immune functioning and cognition. Unmet protein needs can result in growth retardation and stunting. This can affect infants both before and after birth. Risk of country-level population protein inadequacy calculated from food balance sheet data using utilizable protein, but not total protein, is associated with stunting rates (15). At the individual level, low circulating amino acids are associated with stunting (16).

The main challenges for protein digestibility corrected amino acid score (PDCAAS) and newer digestible ileal amino acid score (DIAAS) are the availability of human fecal and ileal digestibility data (Table 3). Ileal digestibility represents the true digestibility of protein, since it is not confounded by colonic bacteria which could fix nitrogen. This is further complicated by the lack of data for children, who may have different digestion of protein compared with adults. It is also becoming clear that individual amino acids within a food protein have different digestibility. Methods to determine amino acid digestibility in humans include the indicator amino acid oxidation technique and the dual isotope method. Furthermore, there appear to be differences in digestibility among individuals and in different environments. Therefore, we need to consider whether digestibility is an “intrinsic” protein quality or whether diverse conditions also need to be considered. Finally, the indispensable amino acid requirement pattern for children is still speculative, as it is based on a factorial model derived from adult requirements. Amino acid patterns for catch-up growth and other contexts are needed.

Dietary protein quality is an important factor in growth and nutritional status. However, determination of the protein quality of foods and diets is still imprecise and complex. We need more data on two fronts: 1) We must ensure that the indispensable amino acid requirements for children are appropriate and accurate in “ideal” and “non-ideal” settings; and 2) We need more human ileal digestibility data in varying ages and contexts. Finally, we need further research into the role that protein quality plays in specialized nutritious foods and other interventions to prevent and treat child malnutrition.

Table 3: Methods and Challenges in Assessing Protein Quality

<table>
<thead>
<tr>
<th>Method</th>
<th>Challenges</th>
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<tr>
<td>Protein digestibility corrected amino acid score (PDCAAS)</td>
<td>PDCAAS is a composite of a protein’s (fecal) digestibility and the amino acid score (how well the amino acid profile meets the requirement). Human digestibility data is limited. Debate of truncation of the AA score persists.</td>
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</table>
| Digestible ileal amino acid score (DIAAS)       | DIAAS is a newer measure which uses ileal digestibility (instead of fecal) of each amino acid. Ileal digestibility data for humans is even more limited than PDCAAS. Methods for obtaining ileal digestibility data include:  
  - Indicator amino acid oxidation method for digestibility; and  
  - Dual isotope method.  
  Digestibility values to be used, listed in order of accuracy:  
  1. Human true ileal digestibility values;  
  2. Growing pig - True ileal amino acid digestibility values;  
  3. Prediction equation: human values from growing pig values;  
  4. Growing lab rat - True ileal amino acid digestibility values; and  
  5. Fecal protein digestibility values. |
IV. CONCLUSIONS AND RECOMMENDATIONS

The use of anthropometric Z-scores alone to measure child malnutrition may lead to an underestimation of the extent of problems to be addressed. Because of this, the range of actions required to provide effective treatment should be reexamined. This Symposium outlined three measures which potentially add important information to the context of malnutrition.

First, during growth and treatment of malnutrition, body composition gives important information about lean versus fat mass accretion, which has implications for future under- and overnutrition. Second, in the context of EED, food-based strategies alone may not be enough to overcome the effect of chronic, subclinical infections/inflammation associated with malnutrition. Third, protein quality, not just quantity, should be considered in dietary evaluations and food-based interventions due to its important role in growth and development. A summary of the research priorities, policy implications and programming guidance from this symposium can be found in Table 4.

While technology currently exists to assess these three measures, the methods are still expensive, sometimes difficult to use in the field and lack universally agreed upon “gold standards” of measurement. While further research is needed, we can and should use what we know about these three measures in current programming and evaluation of interventions. We also need to focus efforts on promoting the acceptance of these new measures and understanding how they should be interpreted. Finally, these new measures should not be used on their own but used in combination with several indicators and a broader contextual view in order to enhance our understanding of child malnutrition and health outcomes.

V. ACKNOWLEDGEMENTS

This Symposium would not have been possible without the support of the USAID Office of Food for Peace and their ongoing commitment to improving Title II programming in order to address food insecurity in vulnerable populations. The time and support offered to the Food Aid Quality Review by Title III awardees, both headquarters and field staff, as well as Food for Peace Officers abroad and in Washington, D.C. and the Policy and Technical Division of FFP headquarters were also invaluable to informing this study. The authors thank Patrick Webb and Kristine Caiafa for their assistance in planning and executing this Symposium, and the presenters for their participation in the Symposium.
<table>
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<th>Table 4: Summary of Research, Policy and Programming Recommendations</th>
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<td><strong>Research Priorities</strong></td>
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<td><strong>Overall</strong></td>
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<td><strong>Body Composition</strong></td>
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<td><strong>Environmental Enteric Dysfunction (EED)</strong></td>
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<td><strong>Protein Quality</strong></td>
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VI. RESOURCE AND GUIDANCE DOCUMENTS

Body Composition

Environmental Enteric Dysfunction (EED)

Protein Quality
VII. REFERENCES CITED


