ENGLISH SUMMARY

Background

Acute malnutrition remains a public health concern with mortality still over 30% for those affected by the severe acute malnutrition (SAM) admitted for in-patient care. Poor intestinal function may contribute to increased morbidity and mortality among these children. The intestinal mucosa in children with SAM is characterized by villus blunting, hyperplasia of the crypts of Lieberkün and infiltration of the lamina propria with inflammatory cells. Improving gut function and its methods of assessment other than invasive intestinal biopsies would probably contribute to reduction in intestinal inflammation and intestinal permeability, improved mucosal repair and also enable researchers obtain larger sample sizes during research involving the gut. Recent studies have identified simple and non-invasive biomarkers for assessment and monitoring gut function however it is not known whether these biomarkers can be used for the assessment of gut function in children with SAM given the physiological and metabolic changes that occur in these children as result of reductive adaptation. Additionally, it is not known whether probiotics could contribute to improving gut function in children with SAM as observed in well-nourished individuals.

The studies presented in this thesis assessed the correlates of gut function among children with SAM using blood and fecal biomarkers and evaluated the predictors of change in the biomarkers during nutritional rehabilitation. One of the studies presented here also evaluated one of two approaches recommended by World Health Organization (WHO) for the direct transition from F-75 to RUTF therapeutic feed during nutrition rehabilitation.

Methods

The papers presented in this thesis were sub studies of a randomized clinical trial (ProbiSAM) conducted in Mwanamugimu Nutrition unit, Mulago Hospital, Uganda among 400 children aged 6-59 months with complicated SAM and 30 community controls recruited from March 2014 and October 2015. A cross sectional study design was used in paper I to investigate the correlates of gut function among children hospitalized for SAM. Biomarkers; plasma citrulline, fecal myeloperoxidase (MPO) and fecal neopterin (NEO), fecal alpha 1 antitrypsin, blood concentrations of 16S rRNA and ITS fragment were used to assess for enterocyte mass, intestinal inflammation, intestinal permeability and microbial translocation respectively. Paper II and III used cohort study designs. In paper II, we assessed for the
predictors of change in the biomarkers of gut function during the in-patient phase and outpatient phase and compared the concentrations of the biomarkers at completion of 8 weeks follow up in OTC with that in the community controls. In paper III, we assessed an approach of direct transition from F-75 to RUTF where we provided half of the energy requirements from RUTF and the other half from F-75 and then gradually increased to RUTF as only energy source. We then evaluated the correlates of failed transition.

**Results**

Compared to controls, the median plasma citrulline was markedly lower in children with SAM while that of fecal MPO and NEO were raised in children with SAM. No significant difference was observed in blood concentrations of 16S rRNA and ITS fragment. Children with oedema, dermatosis, diarrhoea and CRP >10mg/l had a lower plasma citrulline. Among the children with SAM, elevated monocyte and neutrophils count and symptoms of fever and cough positively correlated with fecal NEO while MUAC, WHZ, oedema and dermatosis negatively correlated with fecal NEO. During nutritional rehabilitation, plasma citrulline markedly increased reaching near normal levels. Fecal MPO decreased while fecal NEO increased during ITC and by 8 week follow-up in OTC, there was no difference all biomarkers among children with SAM compared to the community controls. Probiotics did not have an effect on gut function during nutritional rehabilitation.

Majority of the children successfully transitioned directly from F-75 to RUTF on first attempt using this approach however children that were severely wasted, HIV positive and had diarrhoea on admission were more likely to fail.

**Conclusion**

Based on the biomarkers, gut function in children with complicated SAM seems to be impaired characterized by reduced enterocyte mass, increased intestinal inflammation and microbial translocation. Majorly, enterocyte mass improved during nutritional rehabilitation while intestinal inflammation and permeability persisted after completion of 8 weeks in outpatient therapeutic care. Further research on intestinal function using the same biomarkers is encouraged and should include evaluation of other amino acids given that protein synthesis among other metabolic processes are impaired in children with SAM.