Children with severe acute malnutrition
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Chapter 1

General Introduction and Outline of the Thesis

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CHILDHOOD MORTALITY IN THE WORLD

Every day, 15000 children under the age of 5 years (under-5) died in 2016. (1) Eighty percent of these deaths occur among children living in sub-Saharan Africa or Southern Asia (Figure 1), (1) Furthermore, more than half of these deaths could be prevented when access to simple, affordable interventions were available. (2) In 2015, the 17 Sustainable Development Goals (SDGs), otherwise known as the Global Goals, were formulated with the aim to: “end poverty, protect the planet and ensure that all people enjoy peace and prosperity”. (3) The third goal (“good health and well-being”) aims to: “end preventable deaths of newborns and children under-5, with all countries aiming to reduce neonatal mortality to at least as low as 12 per 1,000 live births and under-5 mortality to at least as low as 25 per 1,000 live births” by 2030.

Childhood Undernutrition in the World

Nearly half (45%) of worldwide deaths in children under-5 is attributable directly or indirectly to poor nutrition. (3, 4) It was estimated in 2016 that on a Global scale 52 million children under-5 were wasted (a child who’s weight is too low for his or her height) of which, 17 million were severely wasted (Figure 2). (5) As a consequence, two of the targets of the second SDG goal (‘zero hunger’) are to: “end hunger and ensure access by all people, in particular the poor and people in vulnerable situations, including infants, to safe, nutritious and sufficient food all year round” and to: “end all forms of malnutrition, including achieving, by 2025, the internationally agreed targets on stunting and wasting in children under 5 years of age, and address the nutritional needs of adolescent girls, pregnant and lactating women and older persons” by 2030. (3) It is important that these
goals have been formulated, but it is also important to realize that up to date healthy and sufficient nutrition has been a neglected area of global health and development, accounting for less than only 1 percent of global foreign aid. This is largely due to the underlying and often hidden role malnutrition plays in childhood illnesses and deaths. (6) As a consequence, in order to reduce under-5 mortality, it is of great importance to better understand malnutrition and its causes in order to develop better preventive, diagnostic and treatment strategies.

DEFINING SEVERE ACUTE MALNUTRITION

Different concepts and gradings of undernutrition are in use, but the World Health Organization (WHO) has defined severe acute malnutrition (SAM), which is used by most researchers and clinicians, as any of the following (Figure 3):(7)
- Non-edematous SAM/marasmus: a weight for height (W/H) below -3 standard deviation (SD), OR a mid-upper arm circumference (MUAC) of less than 115 mm
- Edematous SAM/kwashiorkor: the presence of bilateral nutritional edema
- Marasmic kwashiorkor: a combination of the two above

TREATMENT AND PROGNOSIS OF CHILDREN WITH SEVERE ACUTE MALNUTRITION

Children with SAM are normally treated as outpatients, and receive WHO recommended rehabilitation feeds outside a hospital setting.(8) However, when they have clinical complications such as signs of severe or systemic illness and/or poor appetite, they are considered children with complicated SAM and require inpatient treatment.(8) Despite adherence to WHO and National treatment protocols the case fatality rate in children with SAM, and especially those with complicated SAM, is still unacceptably high (up to

Figure 2. Number of children under-5 who are wasted by region. Source: UNICEF-WHO-The World Bank(5)
35%.(3,4,9–12) In addition, mortality remains high after hospital discharge, which may also indicate deficits in the effectiveness of current long term management.(13,14) The above figures indicate the urgency to better understand the malnutrition ‘syndrome’ in order to improve the current SAM management and being able to identify the SAM children who are at risk of clinical deterioration and death at an early stage.

SEVERE ACUTE MALNUTRITION AND THE EXOCRINE PANCREAS

The pathophysiology of children with SAM is complex, multifactorial and it results in many different physiological abnormalities (Figure 4).(11)
One of the problems children with SAM often suffer from is severe diarrhea, which greatly increases mortality.(11,15–17) This diarrhea may be caused by: infections, intestinal epithelial dysfunction relating to malabsorption, impaired digestion or a combination of the above.(18,19)
The exocrine pancreas plays a significant role in nutrient digestion by secreting enzymes (e.g. amylase, lipase, trypsinogen, etc.) that digest all macronutrients: fat, protein and carbohydrates.(20) Exocrine pancreatic insufficiency (EPI) is defined as a lack of digestive enzyme production, which can lead to impaired weight gain and growth due to protein and lipid malabsorption.(21) Its main clinical symptom is steatorrhea (the presence of excess fat in feces), caused by the inability to digest fat.(20,22) EPI is a known common complication of conditions such as Cystic Fibrosis (CF), Shwachman-Diamond syndrome, and HIV.(23–25) In children with CF, pancreatic function is an important predictor of
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long-term survival.(26) In high income countries it is standard clinical practice to start pancreatic enzyme replacement therapy (PERT) in patients suffering from EPI with the aim of restoring nutritional status by improved digestion.(21,27) It is not well known if EPI may also be of benefit for children suffering from SAM in low-income countries.

SEVERE ACUTE MALNUTRITION AND GUT INFLAMMATION

Children with SAM have intestinal pathology that is thought to result from a combination of increased exposure to microbial pathogens and poor nutrition. (11,18,28–30) A significant feature of this so called ‘enteropathy’ is gut inflammation that persists despite management. (31,32) The inflammation has similarities to that which occurs in non-IgE mediated food allergy (hereafter “food allergy”; e.g. due to cow’s milk protein) and Crohn’s disease, which raises the intriguing possibility that treatments which reduce gut

Figure 4. Organ system involvement in severe malnutrition.
Severe malnutrition can affect several organ systems. The functional impairments in these systems have been characterized, but the underlying mechanisms have not been fully elucidated. Source: Bhutta et al.(11)
inflammation in food allergy and Crohn's disease may also benefit children with SAM. (33–35) In food allergy, the intestinal inflammation responds well when the causal antigen, if known, is excluded from the diet (e.g. cow's milk protein) or, when the concerning antigen is not known, a hypoallergenic, elemental feed composed of single amino acids is proven to be effective both clinically and in reducing the intestinal inflammation. (35) In pediatric Crohn’s disease, first-line therapy consists of exclusive enteral nutrition, where either an elemental formula or polymeric formula is given for 6-8 weeks, while all other foods are excluded. (35–38) In limited previous research, hypoallergenic and elemental feeds were well tolerated in children with malnutrition, but evidence of benefit was limited. (39,40) If the gut inflammation in children with SAM would respond to existing treatments already being used in high income countries, this could mean a big step forward in the management of this problem that currently has not been resolved and contributes greatly to the high mortality rates of children with SAM.

**SEVERE ACUTE MALNUTRITION AND BIO-ELECTRICAL IMPEDANCE ANALYSIS**

Children with SAM are diagnosed, as described above, by measuring W/H and MUAC, and by physical examination to identify bilateral nutritional edema. These ‘anthropometric’ measurements do not provide any information on body composition (the proportion of fat mass and fat-free mass in the body). Altered body composition (in malnutrition: loss of fat-free mass) is linked to poor clinical outcome, and can be estimated by bio-electrical impedance analysis (BIA). (41) Over the past two decades, bioelectrical impedance analysis (BIA) has proven to be a non-invasive and inexpensive method for estimating body composition, and is widely used in various clinical situations both in adults as well as children. (41–45) Body composition is not quantified directly by BIA but is calculated from body reactance and resistance measured by changes that occur in a small alternating electrical current, as it passes through the body. (46,47) Reactance arises from cell membranes, and resistance from extra- and intracellular fluid, and their combination is called ‘impedance’. (43) It provides a reliable estimate of total body water and fat free mass in healthy individuals, but requires population and disease-specific equations. (48) Although prediction equations have been recently developed for children, they have not been validated for the African pediatric population, let alone for malnourished children. (49–51)

With differing phenotypes and hydration status in SAM (i.e. non-edematous SAM versus edematous SAM), knowing how BIA changes with nutritional rehabilitation in children with or without edematous severe acute malnutrition (SAM) during nutritional rehabilitation might help the clinician. In addition to this it would help to know if BIA adds a prognostic value to clinical outcome when combined with ‘classic’ anthropometry.
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SEVERE ACUTE MALNUTRITION IN MALAWI

Malawi is a landlocked, small country in southeast Africa with an estimated population of 18 million people (Figure 5).(52) It is amongst the world’s least developed countries, with a gross domestic product per capita of $301. The economy is mostly based on agriculture, and foreign aid. There is a high prevalence of HIV (1 million people), 24000 adults and children die of AIDS annually and life expectancy is low (males: 57 years, females: 60 years).(53,54) Under-5 mortality rate in Malawi has dropped over the past 20 years, but remains among the highest in Africa with 55.1 per 1000 live births.(55) In Malawi malnutrition is also a major contributor to under-5 mortality. Around 46 percent of children under five are stunted; 21 percent are underweight; and four percent are wasted.(56) The Malawian government has put tackling the malnutrition problem high on their agenda. As a consequence the ‘Malawi guidelines’ on treatment of malnutrition have been recently revised.(57) In these guidelines, community based management is encouraged, but complicated cases and children with complicated SAM should be treated in an inpatient setting on, so called, Nutritional Rehabilitation Units (NRU), as is similar to the management of children with complicated SAM in other low income countries. The largest NRU of Malawi is ‘Moyo’ NRU in the pediatric department of Queen Elizabeth Central Hospital in Blantyre.Moyo NRU, with a yearly admission rate of around 750 SAM children, is where the observational and intervention studies in this thesis (Chapters 3-6) have been conducted between 2013-2017.

Figure 5. Malawi.
Map of Malawi. Source: onestopmap.com; Openclipart.org
OUTLINE OF THE THESIS

This thesis outlines the improvement of diagnosis and management of children with complicated SAM through improved insight into the malnutrition ‘syndrome’ and through exploring new strategies.

**Chapters 2-4:** assessing the prevalence and treatment of EPI in children with SAM.

In **Chapter 2**, a systematic review, we systematically synthesize current evidence concerning the relation between EPI and malnutrition in children.

In **Chapter 3** we describe the results of an observational study to assess pancreatic function in children with SAM. We aim to assess whether pancreatic function: 1) is impaired in children with severe acute malnutrition (SAM), 2) is different between edematous versus non-edematous malnutrition, and 3) improves by nutritional rehabilitation.

In **Chapter 4** we perform a randomized controlled trial to assess the benefits of pancreatic enzyme replacement therapy in children with complicated SAM. We look at weight gain, pancreatic function and clinical outcome after 28 days of pancreatic replacement therapy.

**Chapter 5 and 6:** Gut inflammation and BIA:

In **Chapter 5** we evaluate whether therapeutic feeds that are effective in treating intestinal inflammation in food allergy and Crohn’s disease may also benefit children with SAM. With an open randomized controlled 3-arm intervention trial we evaluate the efficacy, tolerability and safety of a hypoallergenic and an anti-inflammatory therapeutic formula in children with complicated SAM.

In **Chapter 6** our focus is on the diagnostic and prognostic value of BIA in children with SAM. We aim to assess if bio-electrical impedance parameters: 1) change with nutritional rehabilitation in children with or without edematous SAM; 2) add a prognostic value to clinical outcome when combined to classic anthropometry.
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REFERENCES


